FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC) AND THE OBSTETRICS, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE (ORUDAC)

Virtual Meeting

Day 2

Wednesday, May 10, 2023

9:30 a.m. to 1:48 p.m.

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C O N T E N T S

AGENDA ITEM	PAGE
Call to Order	
Maria Coyle, PharmD, FCCP, BCPS, BCACP, CLS	13
Introduction of Committee	
Moon Hee Choi, PharmD	13
Conflict of Interest Statement	
Moon Hee Choi, PharmD	21
Open Public Hearing (continued)	25
Statement by FDA	
Karen Murry, MD	31
Clarifying Questions (continued)	32
Charge to the Committee	
Pamela Horn, MD	82
Questions to the Committee and Discussion	87
Adjournment	186

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

DR. COYLE: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Jeremy Kahn. His email is currently displayed.

My name is Maria Coyle, and I will be chairing this meeting. I will now call Day 2 of the May 9-10, 2023 Joint Meeting of the Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee to order. Dr. Moon Hee Choi is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi. I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Baron?

DR. BARON: Good morning. Elma Baron from Cleveland, Ohio. I'm professor at Case Western Reserve University and serve as chief in dermatology at the VA of Northeast Ohio.

DR. CHOI: Dr. Coyle?

DR. COYLE: Good morning. Maria Coyle, associate professor of pharmacy at the Ohio State University College of Pharmacy in the Wexner Medical Center.

DR. CHOI: Dr. Pisarik?

DR. PISARIK: Paul Pisarik, family medicine, working at Archwell Health in Tulsa, Oklahoma.

DR. CHOI: Dr. Roth?

(No response.)

DR. CHOI: Dr. Roth, you are on mute.

DR. ROTH: Good morning. I'm Katalin Roth. I'm a professor of medicine at George Washington University, specializing in general internal medicine, geriatrics, and palliative care. Thank you.

DR. CHOI: Dr. Walker-Harding?

DR. WALKER-HARDING: Hello. I'm Leslie Walker-Harding, chair of the Department of Pediatrics, University of Washington, and chief academic officer at Seattle Children's, and I'm an adolescent medicine doctor by specialty.

DR. CHOI: Dr. Dato?

DR. DATO: Mark Dato. I'm the industry rep for the Nonprescription Drug Advisory Committee and pediatric pulmonologist by training, and retired.

DR. CHOI: Dr. Gass?

(No response.)

DR. CHOI: Dr. Gass?

(No response.)

DR. CHOI: Dr. Gass, you might be on mute.

(No response.)

DR. CHOI: We can go back to Dr. Gass.

Dr. Shaw?

DR. SHAW: Good morning. My name is Pamela Shaw. I'm senior investigator of biostatistics at the Kaiser Permanente Washington Health Research Institute.

DR. CHOI: Dr. Fox?

(No response.)

DR. CHOI: Dr. Fox, you may also be on mute.

DR. FOX: Hi. Michelle Fox. I'm an OB/GYN and the industry representative for the Obstetrics, Reproductive and Urologic Drug Committee.

DR. CHOI: Dr. Armstrong?

DR. ARMSTRONG: Hi. I'm Deb Armstrong. I'm a medical oncologist at Johns Hopkins in Baltimore, Maryland. I specialize in breast and gynecologic cancers and cancer genetics. I'm professor of oncology and of gynecology and obstetrics, and I am a prior member and chair of the Oncology Drugs Advisory Committee for FDA.

DR. CHOI: Dr. Baur?

DR. BAUR: Hi. I'm Cynthia Baur. I'm director of the Horowitz Center for Health Literacy at the University of Maryland School of Public Health.

DR. CHOI: Dr. Berenson?

DR. BERENSON: Hi. I'm Dr. Abbey Berenson. I'm a professor of obstetrics and gynecology at the University of Texas, where I direct the Center for

Interdisciplinary Research in Women's Health. Good morning.

DR. CHOI: Dr. Berlan?

DR. BERLAN: Hi. Good morning. I'm Dr. Elise Berlan. I'm an adolescent medicine physician. I am professor in the Department of Pediatrics at The Ohio State University College of Medicine and a faculty physician at Nationwide Children's Hospital.

DR. CHOI: Thank you.

Can we go back to Dr. Gass?

Dr. Gass?

DR. GASS: Hello. I'm an obstetrician/gynecologist, retired professor emeritus from the University of Cincinnati.

DR. CHOI: Thank you.

Dr. Catlin?

DR. CATLIN: Good morning, everyone. I'm Jesse Catlin, professor of marketing at California State University Sacramento, and my expertise is in the area of consumer behavior.

DR. CHOI: Dr. Curtis?

DR. CURTIS: Good morning. I'm Kate Curtis. I'm an epidemiologist in the Division of Reproductive Health at the Centers for Disease Control and Prevention.

DR. CHOI: Dr. Espey?

DR. ESPEY: Good morning. I'm Eve Espey. I'm a professor of obstetrics and gynecology at the University of New Mexico and chair of the department, and specialize in complex family planning.

DR. CHOI: Ms. Everhart?

MS. EVERHART: Good morning. I'm your patient representative. My name is Sabrina Everhart. I'm out of Charlestown, Indiana. Thank you.

DR. CHOI: Dr. Haun?

DR. HAUN: Good morning. My name is Dr. Jolie Haun. I'm a supervisory research health scientist at the James A. Haley Veterans Hospital and Research Service in Tampa, Florida. I am also an adjunct associate professor in the Division of Epidemiology and the Department of Internal

Medicine at the University of Utah in Salt Lake City, Utah. Thank you.

DR. CHOI: Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I am the founder of MedShadow Foundation and the executive director of DES Action. I'm the consumer rep. Thank you.

DR. CHOI: Thank you.

FDA, Dr. Stein?

DR. STEIN: Peter Stein, director of the Office of New Drugs, CDER, FDA.

DR. CHOI: Dr. Murry?

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs, FDA.

DR. CHOI: Thank you.

Dr. Horn?

DR. HORN: Pamela Horn, director, DNPD II, Office of New Drugs.

DR. CHOI: Dr. Nguyen?

DR. NGUYEN: Good morning. Christine Nguyen, deputy director, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine.

DR. CHOI: Dr. Gassman?

DR. GASSMAN: Audrey Gassman, deputy director, Division of Urology, Obstetrics, and Gynecology at the FDA.

DR. CHOI: Ms. Cohen?

MS. COHEN: Good morning. Barbara Cohen, social science analyst, DNDP II, FDA.

DR. CHOI: Dr. Jacob?

DR. JACOB: Good morning. Jeena Jacob, medical officer, Division of Nonprescription Drugs II, FDA.

DR. CHOI: Dr. Kotak?

DR. KOTAK: Good morning. Anandi Kotak, medical officer, Division of Urology, Obstetrics, and Gynecology, FDA.

DR. CHOI: Thank you.

DR. COYLE: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for the discussion of these issues and that individuals can express their

views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. 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 are 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 topics during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's Joint Meeting of the

Nonprescription Drugs Advisory Committee and the Obstetrics, Reproductive and Urologic Drugs Advisory Committee. With the exception of the industry representatives, all members and temporary voting members of the committees 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 at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

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

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

Today's agenda involves the discussion of supplemental new drug application, sNDA, 017031/S-041, for Opill, norgestrel, Tablet, 0.075 milligram, submitted by Laboratoire HRA Pharma. Opill is proposed for nonprescription use

as a once daily oral contraceptive to prevent pregnancy. This is a particular matters meeting during which specific matters related to Laboratoire HRA Pharma's sNDA 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 product at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Mark Dato and Dr. Michelle Fox are participating in this meeting as non-voting industry representatives, acting on behalf of a regulated industry. Dr. Dato's and Dr. Fox's role at this meeting is to represent industry in general and not any company. Dr. Dato is retired and Dr. Fox is employed by Merck Research Laboratories.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

Open Public Hearing (continued)

DR. COYLE: Before we proceed with today's agenda, during the open public hearing session from Day 1, speaker number 33's slides did not appear, and thus we will go back to open public hearing speaker number 33 so that they are able to speak with their slides. I will reread the statement from yesterday.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at

the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in this 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 for 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 chairperson. Thank you for your cooperation.

Speaker number 33, please unmute and turn on your webcam. You may begin and introduce yourself by stating your name and any organization that you are representing for the record.

DR. DHAR: Good morning, and happy to be with you again today. My name is Dr. Cherie Priya Dhar, and I'm a board-certified adolescent medicine physician, here today representing the Society for Adolescent Health and Medicine or SAHM. SAHM is a non-profit, multidisciplinary professional society

of 1200 members committed to the promotion of health, well-being, and equity for all adolescents and young adults. I have no relevant financial disclosures today.

Yesterday, you heard from several prominent clinicians representing themselves and various medical societies, and heard the powerful voices of young adults sharing their experiences and advocating for access to evidence-based reproductive health care. This morning, I would like to echo the voices you heard yesterday and talk with you about Valerie, the 16-year-old patient that I never saw. She lived over an hour away and was told our clinic was the closest that provides birth control to adolescents. Valerie couldn't get to her appointment, as is the case with many teens.

SAHM endorses making Opill available over the counter with no age restriction. Let me share with you how this could positively impact our adolescent patients such as Valerie. Oral contraceptive pills, abbreviated as OCPs, are

available without prescription in more than 100 countries and have already been used safely by millions of people around the world. OCPs are also the most common contraceptive used by my patients, adolescents. Adolescents have unique barriers to contraceptive access, including those related to transportation, appointment availability, and cost associated with healthcare visits.

Like Valerie, in our recent national survey, the overwhelming majority of respondents reported facing at least one barrier to obtaining contraception as a teen or young adult, and because of this, were unable to obtain that prescription. Minoritized adolescents have even more barriers to accessing care. These groups include black, indigenous and people of color, recent immigrants, LGBTQ youth, youth with disabilities, and those in more rural neighborhoods. An over-the-counter contraceptive would reduce inequities for these young people.

This pill is more effective at preventing pregnancy than other over-the-counter options

currently available. Furthermore, per the CDC, for healthy women, no exam nor tests are needed before starting progestin-only pills, and mandating such only reduces access to care, as it has for our patient, Valerie.

This medication is safe, making over-the-counter status the appropriate way to make it available to the public. In fact, absolute contraindications for progestin-only pills are exceedingly rare in adolescents. Early studies show that many adolescents can understand the Drug Facts Label for this oral contraceptive and that adolescents can self-select for use.

Today, as members of the FDA advisory committee, you can make a public health impact in increasing access to this safe contraceptive, and on behalf of SAHM and Valerie, I urge you to make this pill available with no age restriction. Thank you for the opportunity to testify again today.

DR. COYLE: Thank you.

Before we move on to the charge for the committee, I would like to call on Dr. Karen Murry.

This is a representative of the sponsor, and they have asked FDA to address a question.

Dr. Murry?

Statement by FDA - Karen Murry

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs, FDA. I wish to clarify something that appears to have caused a misunderstanding.

We heard after yesterday's meeting that some people interpreted an FDA statement as saying that FDA did not review the applicant's protocol for ACCESS. That is not correct. We did review the extensive protocol document in detail; however, with respect to the applicant's unusual way of counting selectors, that was not flagged, was not in keeping with with FDA guidance, and we did not agree to it.

We have gone back to the actual protocol, and the applicant's brief mention of this approach is confusingly worded and open to interpretation; however, we did want to make it clear the FDA did review the protocol in detail.

Clarifying Questions (continued)

DR. COYLE: Dr. Murry, thank you.

We will now move on to take some additional clarifying questions from Day 1. We will start with the remaining clarifying questions from panel members that did not get a chance to ask their clarifying questions to HRA Pharma, and then at the conclusion, we will go back to the panelists that did not get a chance to ask their clarifying questions for FDA.

I'm going to start with Dr. Haun. Just as a reminder, Dr. Haun, please state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And as a gentle reminder, please acknowledge the end of your question with a thank you, and any follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

Dr. Haun?

DR. HAUN: Good morning. My name is

Dr. Haun. I have three questions. My first question is for the ACCESS trial representative.

During the consenting process, were the participants informed of the intention to make this medication over the counter as a part of this trial?

DR. LAURORA: Yes, they were informed, actually, from the beginning, including all the recruitment materials made it clear.

DR. HAUN: Thank you very much.

DR. COYLE: And could you state your name for the record, please, HRA?

DR. LAURORA: Yes. Irene Laurora, HRA Pharma.

DR. HAUN: For my second question, this is for the representative that would be supporting the label development. I noticed on the label that it says take one time a day. If you'd like to show the label, you're welcome to put that up on the screen so that I can be clear in the language.

DR. LAURORA: Yes.

DR. HAUN: So it says take one tablet at

same time every day. May I ask, did you consider the terminology, "Take one tablet by mouth at same time every day?" Was this considered for the label, and was there a reason that you did not include the term "by mouth?"

DR. LAURORA: I don't recall that we considered that exact wording, but of course we're open to discussion on topics about how to convey the information on the label.

DR. HAUN: I do recommend that you consider this terminology for the directions, as there have been cases where individuals have been instructed to take a medication and have not taken it appropriately. For example, take one tablet at same time every day, there is a possibility that an individual could think, okay, maybe I should put this, for example, in my vaginal area; or, for example, we do know that for suppositories, individuals have said to take a suppository as needed, and they have actually taken them by mouth instead of putting them in the appropriate place. Please consider.

Also, for the individual representing the use of the REALM, I would like to know were you aware that the REALM is actually not considered a multidimensional construct measurement of health literacy, and that it is mostly for a measurement of pronunciation and literacy, not comprehension? Have you considered that your estimations of low literacy in this sample were actually underreported, based on more complex measures of health literacy? Please respond, and thank you.

DR. LAURORA: Yes. I'd like to ask Dr. Bradford to address that.

DR. BRADFORD: Thank you, Dr. Haun. Russell Bradford from PEGUS Research. Indeed, as you note, the REALM simply measures one very limited aspect of literacy; however, it is widely used in prescription-to-OTC switch programs and recommended in FDA guidance. It's been the industry standard, and in fact was used by FDA in their own label comprehension for OTC naloxone.

Having said that, the point that you make is very poignant because, indeed, we expect that our

estimations of low literacy based on the REALM likely underestimate actual limited literacy and, as you note, there are many elements that comprise literacy, and therefore our estimates of low literacy are likely low compared to a more extensive evaluation.

DR. HAUN: I would like the committee to please note that there are published research documents that do indicate that the REALM does significantly, at least compared to other measures, underestimate low literacy in diverse populations. Thank you for your time.

DR. COYLE: Thank you, Dr. Haun.

I'd like to move on to Dr. Shaw. Did you have an additional clarifying question for HRA Pharma?

DR. SHAW: No. My questions were answered. Thank you.

DR. COYLE: Thank you.

I will then move on to Dr. Dato to offer you an opportunity for any further clarifying questions for HRA.

DR. DATO: Thank you. Mark Dato here. Once again, to the sponsor, yesterday I believe Dr. Shaw had asked the FDA about the self-selection analyses used. I'm curious what was your rationale for differing with the agency. I appreciate Dr. Murry's comment at the beginning, but I'd also like to understand what communications went between you and the agency to align on that. That's question one.

Second question, my last question is, yesterday, there was a lot of discussion about 30 percent overreporting improbable use, and users somehow impugning the data on the 70 percent that did not overreport. My question is, is there existing data that lends to that hypothesis or is this just a general concern based on that? I'll also note the Office of Scientific Investigations found source data matching existent data.

Those are my questions. I look forward to your response. Thank you.

DR. LAURORA: Thank you. Our self-selection endpoint definitions and the planned analysis were

prespecified in our protocol and in the statistical analysis plan to include both the self-selection and purchase question. Detailed study methodology, including the definitions and statistical analysis plan for all endpoints, was submitted via the 2019 Type C meeting, which occurred before study execution.

This is our specific comment that I'm showing you, where we asked the FDA for feedback. This excerpt from the briefing document highlights both our definition of a selector and our efforts to elicit feedback from FDA. Please note that CHOICE was the name of our actual use study before it was renamed to ACCESS.

The responses from FDA did not include any discussion or recommendations regarding the prespecified definition of a selector, or regarding the prespecified physician review of appropriate for use, so I'd like to ask Dr. Bradford to discuss why we chose this information.

DR. BRADFORD: Russell Bradford from PEGUS Research. The FDA selection guidance states that

analyses should be done based on responses to the self-selection question. It also states that the purchase question can be informative and should only be asked after the self-selection question, which is what we did.

I have decades of experience doing these studies, but you really don't have to observe very many self-selection interviews to understand that the okay or not okay response to the self-selection question alone is not sufficient to understand if a participant is indeed a selector.

I showed you some examples of this yesterday, and many interpret the selection question as if it's asking about likeability of the product. Therefore, to fully understand, we define a participant as a selector based on verbatim responses to the selection question, the purchase question and, importantly, the reasons given for those responses. Indeed, the reasons are critical for clarifying selection intent.

As you heard, we prespecified this approach, and further, it is not unique. I've personally

been involved with a number of self-selection studies beginning at least 10 years ago, which have followed this self-selection classification approach with protocols reviewed by FDA.

DR. LAURORA: Dr. Dato, you had a second question. Your second question was in relationship to the validity of the people who were -- or reliability of the data from the non-overreporters, and I'd like to ask Dr. Stone to address that for you.

DR. STONE: Arthur Stone, University of Southern California. I want to reinforce the point that overreporting in published adherence studies is known to occur, and we simply do not know what causes overreporting. However, in terms of the non-overreporting group, we can exclude a number of causes of overreporting. It was not related to the e-diary use or the e-diary recall period.

My review indicates that the overreporting was actually a decision made by certain individuals for individual reasons. Thus, in my view, there's no reason for questioning the data from the

non-overreporters, and their data should be considered informative. If we were to throw out the group of non-overreporters in this case, we are really questioning all previous studies based on self-report data, and I just don't think that's justified. Thank you.

DR. DATO: Thank you. No more questions.

DR. COYLE: Thank you.

I see that, Dr. Espey, you have your hand raised. I'd like to give you the floor.

DR. ESPEY: Thank you. Eve Espey, University of New Mexico. This was a question for Dr. Stone, actually very similar to the one that was just asked because it does seem that the concerns about overreporting improbable dosing are key to the concerns with the data, to the point of essentially negating the reliability of the study. And the FDA has mentioned that the design and interpretation were extremely different from the norm.

So my question for Dr. Stone, who appeared to feel that that was not the case, is on what do

you base your thought that this is so different from the way that the FDA interpreted this?

DR. LAURORA: Dr. Stone?

DR. STONE: Arthur Stone, USC. I have about 45 years of experience working with diary studies and momentary studies, so when I looked at the ACCESS trial and tried to understand what was going on with the overreporting, I asked myself the question, is there anything special about the design of ACCESS that would encourage overreporting, anything special over and above what happens in most diary studies that I know of, and I could find nothing in particular. And I would also mention that the root cause analysis indicated that there was nothing operationally wrong about how the diary study was conducted. So for those reasons, I have confidence in the non-overreporting set of data.

DR. ESPEY: Thank you. My question is answered.

DR. COYLE: Thank you.

I would like to acknowledge Dr. Horn from

FDA.

DR. HORN: Thank you. Pamela Horn, FDA. I'd like to give Barbara Cohen an opportunity to respond to some of the comments.

MS. COHEN: Thank you, Dr. Horn.

I'm requesting the slide be put up where you had the excerpt of the communication with FDA. Could you put that back up?

DR. LAURORA: Yes.

MS. COHEN: Thank you.

I just want to point out this is a very complicated study logistically. There were many, many moving pieces to this, and a chart of the process of this study would take up more than one screen.

The line, "subjects who do not eventually complete the purchase dispensing," we interpreted in a different way than apparently the sponsor meant it. That's all I wanted to say. We thought that that was much further in the process maybe for people who had to be excluded, and they were looking at why they said they wanted to purchase.

But we did not interpret that -- it was vaguely worded, so we did not interpret it in that way. These things sometimes happen when things are not clear.

The other two points I wanted to make was, one, I think we need to remember that even before our reanalysis, the deselection endpoint was 75 percent, which was already considerably below the 90 percent threshold. And I also want to state that -- I'm not going to go through all the examples that the sponsor gave, but just for one of them, he gave an example of why would women who couldn't bear children say that they were appropriate to use the product?

Well, actually, if you look at the verbatims, they said that because they didn't want to use the product for contraception; they wanted to use it to regulate their periods, so they did think it was appropriate to use. Again, I just wanted to add that clarification, and thank you very much for giving me this opportunity.

DR. COYLE: Thank you.

I'm just taking a scan among our participant list. I don't see any other hands raised. If our panel members have any clarifying questions for HRA Pharma, we do have a minute or two to address those right now.

Dr. Baur, please go ahead.

DR. BAUR: Thank you. Cynthia Baur, University of Maryland, and a question for the sponsor. The briefing document references 7 years and 14 consumer studies. I couldn't find dates over which those studies were conducted, so if I could get a sense of the time span for those 14 consumer studies.

DR. LAURORA: Yes. I'll have Dr. Guillard address that.

DR. GUILLARD: Yes. Helene Guillard. Let me show you the different studies that we did to test the label. This in fact includes the label comprehension study that we did on the DFL and on the CIL, as well as the main AUT and the final combined study. So it does not include the full 14, but you can see still many of them, and that

started in 2015. So many studies on the label comprehension study for the DFL were done between 2015 and 2017, while we also conducted the CIL development in '16 and '17, and the ACCESS study was conducted between 2019-2021, and the final study in '21.

DR. BAUR: If you could just clarify that between 2015 and 2017, all of those were just trying to clarify the language to enhance comprehension.

DR. GUILLARD: Exactly.

DR. BAUR: So that was iterative; like each round was trying to improve on the one before.

DR. GUILLARD: Exactly. That was really the exact process to the label.

DR. BAUR: And your briefing document references that FDA gave feedback on your consumer materials. Could you characterize what the nature of that feedback was?

DR. GUILLARD: During those years, you mean?

DR. BAUR: I don't know. The briefing document just references that FDA gave feedback on

the label and on the Consumer Information Leaflet, so I was just wondering if you could characterize what the nature of that feedback was.

DR. GUILLARD: Yes. We received in our early studies responses to the label that we initially suggested, and in fact while we were finishing the ACCESS actual use study, we received feedback from FDA to incorporate a number of additional renditions on the label, and this is also why we amended the final label that we tested in the final pivotal DFL LCS.

For instance, FDA asked us that we modify the warning on the breast cancer as a do not choose that is very specific for breast cancer. We also changed the drug-drug interaction so that the list of specific medications only appear on the CIL and not on the DFL. We had also rewording about the vaginal bleeding information, and they also asked us to change some headings for the situations that required immediate medical attention. They wanted us to ask a specific section about when to use a condom. Those are examples.

DR. BAUR: Great. Thank you very much.

I'm not sure if we save this for the questions that will be presented to us, but I think it's very interesting if FDA then gave you feedback on a couple of the items that proved to be the most challenging from a comprehension perspective, because it was the cancer information and the vaginal bleeding that showed up as being particularly difficult to comprehend.

Am I remembering correctly from yesterday's presentation?

DR. LAURORA: Well, ultimately, we believe the cancer warning was very well understood, but yes, there is always iterative back and forth with FDA, and of course we're still very open to further discussions on proposed labeling.

DR. BAUR: Alright. Thank you.

DR. COYLE: Thank you.

I'd like to call on Dr. Shaw. Please go ahead.

DR. SHAW: Hello. Pamela Shaw. I'd like to ask a question of the person -- I'm sorry I forgot

your name -- that responded about the quality of the self-report and the overreporting. It was just on maybe 5 or 10 minutes ago, talking about how the overreporting in this study is similar to many other studies in the 45 years of his experience.

Do people know who I mean? Sorry.

But my question is this. My understanding is in this study, ACCESS, it was e-diaries that people were using, and those are relatively new and have their own set of problems. And my understanding is there were issues with the reminder structure in the sense that people could be reminded to enter their information up to 10 days -- let me say this differently. They would be reminded to enter their information even if they had already done it. It was sort of automatic reminders. So that's the first question. I'm really trying to understand how many times people could be reminded.

Specifically, I think there were 10 days they could go back and enter. So my second question is not only how many times they're being

reminded, but when they say they hadn't used the app in 10 days and they're going to go enter, did they have to enter each of the previous days that they missed; and therefore how to remember quite a number before they could try to enter the current day?

I know we have a lot to discuss today, so just some clarity on how many times people could be reminded and if they were required to enter days that they missed, or at least to bypass those days in order to enter a current day.

DR. LAURORA: I will address the clarifications about the operational details of the study, and then of course I'll bring Dr. Stone up to address his experiences in looking at these studies and oral contraceptive studies.

So the reminder was a standardized reminder. Everybody received the reminder every 4 days. It was a reminder to complete the diary, not to fill out to take your medication. The purpose of the reminder was to decrease missing data. And yes, when people did not complete their diary on any

day, when they did open it to complete it, they were asked to go back to the previous days. And as you heard, about 80 percent of the days were reported within 3 days of taking the medication.

Also, the diary was very specific as to what day and date they were entering, and they had the pill pack in front of them as well, which also has -- well, they have the pill pack as assistance to remind them if they needed it on what they did on any particular day.

Dr. Stone?

DR. STONE: Arthur Stone, USC. I think that we have to remember the context of this trial. This was not an efficacy trial with all kinds of controls and reminders. A study I would typically do might remind people every day to put in their data, and if someone missed it, I would get on the phone with them and get them to put it in. This was an AUT trial, so a bunch of compromises were made in order to accommodate this kind of trial.

One of the things that was done was to use the electronic diary, and if people hadn't entered

data into the diary for a few days, they could enter past days. Now, the issue there is how much recall is too much for this kind of data? And I want to point out in this slide, which I believe was shown earlier, that most of the data, 80 percent of it, was reported within 3 days, and in my experience, that seems to be a reasonable amount of time for reporting information about taking a pill or not. Relatively little data was reported at the extremes, as you can see in this distribution. So I think this all had to do with the compromises that were made for an AUT trial.

DR. SHAW: Okay. Thank you. No further questions.

DR. COYLE: Thank you.

Dr. Roth, I do see your hand up, but before I call on you, I'm going to ask Dr. Horn to step in to respond to an earlier question.

Dr. Horn?

DR. HORN: Thank you. Pamela Horn, DNPD II, FDA. I'd like to ask Dr. Michele to respond to a previous question.

DR. MICHELE: Hi. Thank you. Theresa Michele, director, Office of Nonprescription Drugs.

I just wanted to circle back to this question of overreporting and, again, I think it's been brought up several times now whether this is something that is just a normal course of events that we expect for every study. I want to emphasize again that while you may have an occasional overreporter in a study, the thing that is particularly unique about this study is the extent of the overreporting. I can't think of a study that has 30 percent invalid data. That really just does not occur in any kind of a study, much less a consumer study of this nature, so it's really very extraordinary.

The other thing that I wanted to note is that we went back and asked the sponsor to look for a root cause of this, and they didn't find one. So there was not some systemic issue with data in the study that we could point to, and therefore go in and say, okay, these data were bad for this reason but we know the other data were good; instead we're

left with this ambiguity. So those are the things that I wanted to just make sure that we had clearly on the table, and I'll stop there. Thank you.

DR. COYLE: Thank you, Dr. Michele.

Dr. Roth, please go ahead with your question.

DR. ROTH: My question is we're talking about birth control pills.

DR. COYLE: Would you please state your full name, for the record?

DR. ROTH: Sorry. This is Katalin Roth, George Washington University.

We're talking about birth control pills, which come in a package labeled day 1 through day 28, and people when they're taking these pills can look at the pills and see if they took the pills. So the statistical problem that we're talking about is not about reporting adverse effects, it's not about reporting unintended pregnancies, it's only about whether the women in the study accurately reported or overreported whether or not they took the pills. Is that

correct?

I guess, let me just follow up by saying that I really appreciated Dr. Shaw's comment because I personally participated in a vaccine trial in the last few years, and I found the electronic reminders extremely difficult to use. I think as a physician, I would be a relatively sophisticated user. I use a lot of apps on my phone, but I could imagine many ways in which overreporting could occur in an effort to try and comply with this study.

That's all I wanted to say, but I would appreciate clarifying exactly what it is we are spending time about. Thank you.

DR. LAURORA: The question has been raised about the validity of the data because of overreporting, and as Dr. Michele told you, there was no systematic problems in the study, and if you choose to exclude anybody who did overreporting, we shared that analysis with you, and I will show that to you again right alongside our primary analysis, which showed you that people do understand how to

take one pill a day and that they follow the label directions.

Dr. Stone can address, as well, your question.

DR. STONE: Arthur Stone, USC. I agree with the statement that this amount of overreporting is not usually seen in such trials; there's usually a little bit of overreporting. But the reason that there's more overreporting in ACCESS is because the very rare conditions to allow for overreporting of this time existed, and that is that the sponsor allowed people to continue to use the diary when there weren't any pills available to them. That's an extraordinary circumstance that happened. It's happened a few times in the past. The Oxytrol trial was one example of that. So when the conditions are right, people do this kind of overreporting, but it is rare, and it's rare because the conditions do not exist for it to be seen very often.

DR. ROTH: Can I follow up my question?

DR. LAURORA: Yes, and you are correct.

There is no safety issue being assessed.

DR. ROTH: So is it possible that these women were able to secure additional pills? All of the overreporting, did it all occur after they finished the study or between the times that they were picking up the pills at the designated sites when they may have not had any available pills? Can you tell whether the overreporting occurred at times when the participants did not have pills available to them? And that concludes my question. Thank you.

DR. LAURORA: We did look into what happened at the sites, and the drug accountability at the sites was correct, so we do not think that people got additional pills. Importantly, let me show you again the sensitivity analysis where we use a revised stop date. This is the information we have on when people may have reported to the nurse interviewer or otherwise indicated that they had stopped taking the drug. So the diary may have remained open, but they had indicated that they had stopped taking the drug.

So now, if we were to look at any restrictions on reporting in the diary based on drug availability, this is what you would see, as the results indicating adherence is very high.

DR. COYLE: Thank you.

Dr. Roth, does that address your question?

DR. ROTH: It's helpful. Thank you very much.

DR. COYLE: Thank you.

I don't see any further hands raised from our panelists, but I do want to offer an opportunity for HRA Pharma. I think they did have some responses to some of the clarifying questions from Day 1, so I would be interested to hear from our sponsor which clarifying questions they wanted to address. We have just a few minutes, so perhaps if there are one or two that are more pressing, and then you can maybe share that information with the panelists.

DR. LAURORA: Yes, we had some clarifying questions. I think it first was about our interactions with FDA during the course of the

development, and that was clarified, but I'd like to ask Dr. Glasier also to clarify what we know about real-world use of oral contraceptives.

DR. GLASIER: Thank you. Dr. Glasier from Scotland. A question was asked yesterday about what a woman who has been prescribed an oral contraceptive understands about adherence when she leaves a prescriber's office. There are no data specifically on what U.S. women understand, but there are data on how they behave.

Two studies present daily diary adherence data detailed by cycle. Dr. Fox and colleagues in 2003 found that in over 3 months of treatment, only 50 percent of subjects were 100 percent adherent, and cycle 3, 18 percent missed three or more pills despite being sent daily email reminders. And a study done in 1996 by Potter and colleagues found similar variability and levels of non-adherence. And it's this level of non-adherence in the prescription setting that you need to use to put in context the data from the ACCESS study. Thank you.

DR. LAURORA: No other clarifying

statements.

DR. COYLE: Thank you. I appreciate that.

We will move on to follow up with a few additional clarifying questions for FDA. These are questions that we did not get to yesterday in our discussion, and if we have a few minutes, we will open it up for further clarifying questions, so please use the raise hand icon if needed, and also remember to state your name for the record before you speak; to direct your question to a specific presenter, if possible, including a specific slide, if you have that information; and please to acknowledge the end of your question with a thank you so that we can move on to the next panel member.

We will begin with Dr. Curtis.

DR. CURTIS: Good morning, and thank you. I have two questions left over from yesterday. One is, can FDA help us think about how to interpret the comprehension and actual use data in the over-the-counter setting? For example, is it typical that all subgroups would meet or approach

the thresholds or is it mainly the overall study population that we would expect to meet the thresholds? Of course, it's important to work hard to make sure all the subgroups meet those thresholds, but I'm wondering what's typical for approval.

DR. HORN: Thank you for the question, Dr. Curtis. This is Pamela Horn, DNPD II, and I'd like to ask Dr. Levenson to take that question.

DR. LEVENSON: Hello. This is Mark Levenson, Office of Biostatistics, CDER, FDA. Typically, when we look at subgroups, we don't expect them all to meet the threshold, but we're looking for consistency, and we want to ensure that no subgroup is particularly worse.

Does that answer your question?

DR. CURTIS: Yes. Thank you.

Then my second question is a follow-up point made yesterday about comparisons for the comprehension and actual use findings with what we know about the prescription setting, and Dr. Glasier actually just addressed this issue as

well, but I wanted to give FDA the chance to address that also. It sounds like we don't have much of that information, but I do think it's important to consider the thresholds that we're using and where they came from.

It was pointed out yesterday that current POP users in the U.S. are a select group, so if we had data from them, they probably wouldn't be representative of those who might be using Opill over the counter, but we do have some data, as Dr. Glasier just mentioned, for combined oral contraceptives and that the use instructions are fairly similar. And I believe that the 85 percent threshold for taking pills every day in the ACCESS study was based on the typical adherence for combined oral contraceptives.

So my question is, are there other comparative data that were used or that exists, especially for adolescents? And if not, then I think it is important to consider that we don't really know whether the data that we're reviewing today reflect comprehension and behavior that would

be better, worse, or similar to what's seen in the prescription setting. Thank you.

DR. HORN: Thank you, Dr. Curtis. Pamela Horn, DNPD II. I'd actually like to invite HRA Pharma to comment on if there were other considerations that they took into account, or other data to support the threshold that they chose, and also to ask them to comment on what considerations they used for the adolescent consumers that they were going to be enrolling, and how they applied the 85 percent threshold to them.

DR. LAURORA: Adherence to all types of daily medications is less than what we would want it to be, as we hoped people would take it, so we look very carefully at all the data on adherence, and the main data on adherence using diary studies was presented to you by Dr. Glasier, but there were other studies that we looked at, and they found very similar data showing that people are missing at least one pill a week in their current daily oral contraceptives.

Importantly, we also consider the benefit in

deciding whether or not this type of adherence would still maintain a significant benefit in the potential OTC setting, and we feel very strongly it will. And we really would like to discuss specifically the benefit in adolescents and how we considered the potential barriers that they have to access as well.

Dr. Wilkinson?

DR. WILKINSON: I'm Dr. Tracey Wilkinson. I'm pediatric faculty at Indiana University School of Medicine and a practicing general pediatrician. I would like to remind the panel about the data that we saw about adolescents' use of contraception before entering the study, and how 60 percent of them were using no contraception and 26 percent were using the least effective form of contraception.

We know that adolescents face significant barriers to access and have significant unintended pregnancy rates, and that 30 percent of first births in the United States occur during teenage years. I also would like to note that this

medication is FDA-approved currently without any age restrictions or length of use. Having over-the-counter access to an effective form of contraception would significantly improve access for adolescents.

DR. COYLE: Thank you.

Dr. Horn, can I ask you to step back in to the conversation?

DR. HORN: Yes. Thank you. Pamela Horn, DNPD II. I'd like to ask Dr. Nguyen to also provide a response to Dr. Curtis' question.

DR. NGUYEN: Hi. Christine Nguyen, CDER, FDA. Thank you for that question, Dr. Horn.

I'd like to just point out a couple of very important differences. I understand Dr. Glasier had quoted some literature about adherence with combined birth control pills, and as Dr. Kotak mentioned yesterday, the progestin-only pill is less forgiving for the reasons that were discussed. It's once daily, and at the same time allowing for a 3-hour window, and obviously, the side effects when adherence is not stringent is an unintended

pregnancy. So missing a pill with COC versus a progesterone-only pill may differ as far as the risk for an unintended pregnancy.

Another consideration I'd like to raise that we haven't really discussed is unlike condoms, when you don't use them, you're clearly at risk for pregnancy, and you can choose to use emergency contraception in a timely manner. If one is taking a pill every day but not taking it at the same time every day, that risk of pregnancy may not be self-evident, and there is missed opportunity to take emergency contraception in a timely manner. So for adolescents, I think that's particularly important to consider. Thank you.

DR. COYLE: Thank you.

Dr. Curtis, did that address your questions?

DR. CURTIS: Yes. Thank you very much.

DR. COYLE: Thank you.

I'd like to move on to Dr. Baur. I believe you had questions from yesterday.

DR. BAUR: Thank you. Cynthia Baur, University of Maryland. My question is to the FDA

team. The question that you posed to the committee members is really based on the consumer information that they would have to make this decision.

My question is, as part of our deliberations, are you looking for us to make recommendations about changes, specific changes to the consumer information, or whether that's on the label, or the leaflet, or anything else, or are you really asking us to consider what's been presented by the sponsor as is, and just consider whether the current versions are adequate for informed decision making?

DR. HORN: Thank you for that question. This is Pamela Horn, DNPD II. I just wanted to remind the committee that one of the points I made yesterday is that the proposed labeling, if it were to have major changes made to it, we would expect that those changes would need to be tested again prior to approval. So we do want the committee's input on what they think of the labeling and its adequacy, but I just wanted to make that point about the need for any changes that are substantive

to be tested prior to approval.

I want to invite Dr. Murry to also add on to that if she has additional comments.

DR. BAUR: And could you both clarify what you mean by substantive changes? That would help us understand what those parameters are.

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs. As an overall matter, we would ask the committee to consider the labeling as it already stands and has already been tested.

If the committee feels that changes are necessary to the labeling in order to ensure safe and effective use in the U.S. nonprescription environment, we would expect that the committee would then be stating that the application as presented is inadequate, and that the sponsor would need to go back, change the labeling, retest, and resubmit an application. That's what we would expect, so please consider the application and the labeling as it already stands and has already been tested.

DR. BAUR: Okay. I think it would be really helpful just to make sure that the committee knows exactly which versions we're looking at because I found a different version in the briefing materials versus on the slides yesterday. So I just want to make sure that we're looking at the correct ones when we consider those things.

One other follow-up question is I noted that FDA held a workshop on June 9, 2021 to consider updates to the Drug Facts Label, and there were a number of experts who testified about improvements, and specifically some of the issues that are being discussed today in the sponsor's application. I'm just wondering was any of that information from the workshop part of your discussions with the sponsor before, and leading up to today's committee meetings?

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs. No, it was not, and the reason for that is because the vast majority of the interactions that we had with the sponsor regarding this occurred prior to that

meeting.

We've been meeting with and giving advice to the sponsor on this since at least 2016. We met with them and sent advice letters to them on at least 13 occasions with many, many pages of advice. But no, we did not give them specific advice related to future iterations of what Drug Facts labeling might look like overall. They were working within the construct of what is currently in regulation.

DR. BAUR: Great. Thank you very much.

DR. COYLE: Thank you, Dr. Baur.

I will call on Dr. Baron.

DR. BARON: Hi. Elma Baron here. My question is actually in a different aspect of the study. Yesterday, we heard from one of the FDA presenters that this study had a very high attrition rate. I think it was 46 percent broken down into 21 percent withdrawal and 25 percent lost to follow-up.

Can someone elaborate on this and potential reasons? As a clinical investigator, to me that's

a little concerning. Of course, there is no set -- like I cannot give a specific number as to what is considered appropriate as far as attrition rate. It depends on the study design, the condition being studied, and all that but, in general, when we see attrition rate higher than 20 percent, we would like to know further what caused that. Thank you very much.

DR. HORN: Thank you, Dr. Baron. This is Pamela Horn, DNPD II.

Could you please bring up slide 129?

Dr. Baron, is this the slide you were referring to?

(Pause.)

DR. HORN: Just waiting. Is this the slide you were referring to, Dr. Baron?

DR. BARON: Yes, it is. I believe this is it --

DR. HORN: Okay. Thank you.

DR. BARON: -- the 1 percent withdrawal and 25 percent lost to follow-up.

DR. HORN: Okay. I'm going to ask Dr. Jacob

to comment on the disposition for ACCESS.

DR. JACOB: Thank you. Jeena Jacob, medical officer, Division of Nonprescription Drugs II.

As we can see from the slide, 25 percent were lost to follow-up. We do not know why those participants did not complete the study. In terms of the 21 percent that withdrew from the study, 60 percent provided the reason that they withdrew due to the subject deciding they wanted to discontinue use of the product.

There were a significant number of the participants who were in that category who did discontinue due to adverse events, and then another 24 percent provided the reason of discontinuation due to adverse events. All of the adverse events that were reported in the subgroup that decided to withdraw due to decision to discontinue, as well as withdraw to an adverse event, were accounted for in the overall discontinuations of the study, and that made up 7 percent of the user population that discontinued the study drug due to an adverse event.

In terms of the remaining participants that withdrew from the study, five cited reasons due to COVID-19, and we don't have any more information regarding that; 11 withdrew consent; two withdrew due to their own personal physician basically making the decision, in conjunction with the participant, that the participant needed to withdraw from the study; 8 provided the reason of withdrawing because they were pregnant; and four had a protocol violation as the cited reason.

DR. HORN: Thank you, Dr. Jacob.

I just want to call your attention, Dr. Baron, to the last row, where there were only 46 percent of participants who had a known end-of-study home pregnancy test result. I think that that was concerning to us in terms of there being a lot of missing information about what we knew about pregnancy outcomes from this study, and combining that with the concerns that we had with the self-report data, I think it does raise a lot of concern for us about what we know about the outcomes from this study.

In terms of actual use study dispositions, in general, there are definitely examples of actual use studies where there's much higher completion rates and much less dropout than what we saw in this study, but the actual use studies span a wide range of different conditions and indications, so it's kind of hard to make much comparison in that way.

I can invite my colleagues to talk about completion rates and discontinuation rates in contraceptive efficacy studies, so I'll send that over to Dr. Gassman.

DR. GASSMAN: Audrey Gassman, deputy director in the Division of Urology, Obstetrics, and Gynecology. Although we have not had a recent large contraceptive trial, probably the most recent comparator for dropout rate in a contraception would be that of Slynd, which is a progesterone-only product, where I believe at one year, the discontinuation rate was 26 percent.

We do know that there is a dropout rate, as women may move on to different insurances and are

able to select different pills, or may move, or have other reasons why they want to discontinue contraception. So I think it's difficult to look at an individual rate of discontinuation in a contraceptive trial to, unless you have detailed information, really try to make a conclusion on that. Thank you.

DR. LAURORA: I can provide some additional information that we do have from this study. Remember, the study was designed to mimic the OTC setting, so it's not typical to what you would expect in a clinical trial assessing efficacy of a contraceptive.

DR. COYLE: I'm sorry to interrupt you, sponsor. Could you just at least state your name for the record so we know who's speaking? Thank you.

DR. LAURORA: My apology. Yes. Dr. Irene Laurora. I'd like to show a slide. Okay. We might not be able to.

This study was designed to simulate an OTC setting, where people may choose to start a

contraceptive and they may choose to stop a contraceptive. This is the data that shows a continuation rate in ACCESS, and after about 6 months of use, we had about 50 percent of participants who were still taking the product. I'm sorry.

This is the reasons why people discontinued, and the most common reason was because they ran out of pills, and they couldn't get back to the pharmacy sites to get the pills, and that is precisely, again, the reason why OTC access is so important for continuation of contraceptive use, and therefore contraceptive efficacy, and pregnancy.

Oh. I'm sorry. One more clarification is we had pregnancy outcomes, pregnancy tests in 73 percent of participants by the end of their participation in the study.

DR. BARON: Thank you to our sponsor for responding, and as just a matter of procedure, please raise your hand so that I know to call on you. Thank you.

I'd like to move on to Ms. Robotti.

MS. ROBOTTI: Hi. Thank you. It's actually a follow-up, one on slide 129 --

DR. COYLE: Please state your name for the record, the full name.

MS. ROBOTTI: I thought I already did. It's Suzanne Robotti. [Indiscernible - audio garbled] adverse events withdrew from the study, 50 percent of about half of 21 percent.

Could we get more information on what those adverse events were?

DR. HORN: This is Pamela Horn, DNPD II. Thanks for that question. Yes, I'm going to ask Dr. Jeena Jacob to respond.

DR. JACOB: Thank you. Jeena Jacob, medical officer, Division of Nonprescription Drugs II. The most common adverse events that led to drug discontinuation were due to bleeding abnormalities, including menorrhagia, metrorrhagia, and there were several preferred terms that were included in that category, but most of them were due to bleeding abnormalities.

DR. COYLE: Sponsor, would you like to add some information to that question?

DR. LAURORA: I'd like Dr. Sober to address your question.

DR. SOBER: Stephanie Sober. In the study, there were 7 percent of participants who discontinued due to an adverse event, and of those, less than 5 percent discontinued due to any bleeding changes.

DR. COYLE: Thank you.

Did that address your question, Ms. Robotti?

MS. ROBOTTI: Oh. What were the adverse events? Was it nausea, cramps, any [indiscernible] there? Were there hospitalizations?

DR. LAURORA: Yes. Dr. Sober?

DR. SOBER: Stephanie Sober. I can show you in just a moment, as soon as I have the slide, the list of the most common adverse events reported during the study.

As you can see here, this is the list of the most common adverse events reported, and the most frequent events were changes in menstrual bleeding,

which is expected and consistent with the known side effect profile of the product, and the most frequent of those was still only reported at about 5 percent of the population.

In terms of other adverse events --

MS. ROBOTTI: Please -- [indiscernible].

DR. SOBER: Okay. Thank you.

MS. ROBOTTI: Sure. I guess what I heard, and perhaps I heard incorrectly, was that 21 percent withdrew, and 3 percent of those who withdrew, it was because of adverse events. It sounds more like a third of those withdrew had adverse events.

DR. LAURORA: I'm sorry. Did we not answer your question? Can you please ask it again?

MS. ROBOTTI: No. I just wanted to clarify why I was asking the question. In slide 129, my understanding was that of the 21 percent who withdrew, half of those withdrew because of adverse events, so 7 percent would reflect a third of them. So I'm just trying to clarify was it a half, was it a third? It's a small differential, and I'm

probably splitting a hair there, so I'll let it go. Thank you.

DR. COYLE: Thank you, Ms. Robotti.

I'm going to call on Ms. Everhart as our last question for this section.

MS. EVERHART: Thank you. Sabrina Everhart. My question is, of those who withdrew or were lost, is there an age breakdown of those percentages? And if there is, could you please provide that? Thank you.

DR. HORN: This is Pamela Horn, DNPD II. I just want to restate the question. Thank you for that. The question, if I understood it correctly, was do we have the discontinuations in the study broken down by age group?

MS. EVERHART: Yes.

DR. HORN: We could ask HRA if they have a slide handy to give the breakdown by age, we'd invite them to put that up.

MS. EVERHART: Thank you. I have no more questions.

DR. LAURORA: Yes. I have that data, and

this is what we look at in the continuation rate by age. You can see the progression of people through the study based on age, and we really didn't see that there were significant differences by age.

DR. COYLE: Thank you. Thank you to both FDA and the sponsor for indulging those additional questions and helping us understand the data before us, to an even greater degree. We appreciate that very much.

Dr. Horn, did you have any final comments?

DR. HORN: Yes. Thank you, Dr. Coyle.

I just wanted to respond to a question from Dr. Baur earlier, asking us to point her and the rest of the committee to the proposed label submitted. I can refer you to page 77 of the briefing document, the FDA briefing document, which has that information for you to use.

Then also, I wanted to respond to a question from yesterday that we didn't have a full answer to from Dr. Walker-Harris [Harding] about previous contraceptive use in adolescents in the ACCESS study, so I want to invite Dr. Jacob to add to our

response from yesterday with respect to that.

DR. JACOB: Thank you. Jeena Jacob, medical officer from the Division of Nonprescription Drugs II. In response to Dr. Walker-Harding's question yesterday regarding prior oral contraceptive use, prior to the start of the ACCESS study, we would like to note that 16 percent of the participants in the 12 to 14 age group and 34 percent in the 15 to 17 age group had a history of prior oral contraceptive use.

DR. HORN: Thank you. That's all from us.

DR. COYLE: Thank you, Dr. Horn.

So we'll now proceed to the charge to the committee, so I will invite Dr. Horn back to the stage.

Charge to the Committee - Pamela Horn

DR. HORN: Thank you.

I'm going to give the charge to the committee now, and ask the committee to discuss the questions and the vote. I once again want to emphasize that we recognize the many challenges that women of reproductive potential face in

accessing contraception in the U.S. currently, and the importance of making decisions that will enhance women's Health. The public hearing yesterday was filled with courageous, compelling stories testifying to these challenges. We support women's autonomy and empowerment in making their own decisions with the best information available.

When an applicant applies to change a drug's available prescription to nonprescription, the applicant is required to provide data to demonstrate that the benefits of the drug will continue to outweigh the risks, and we owe it to women of reproductive potential in the U.S. to ensure that the data the applicant provided is sufficient to support the likelihood of safe and effective use without interaction with the healthcare provider, and that the data demonstrate that labeling has been optimized to support this use, and that is our charge to the committee this morning as well.

So having said that, our first discussion question for the committee is to discuss whether

consumers are likely to use norgestrel tablet in a safe and effective manner, considering the possibility of unintended pregnancy with incorrect use, and we'd specifically like the committee to talk about the need to adhere to taking the tablet at the same time of day, based only on the nonprescription labeling without any counseling or advice from a healthcare professional.

We'd like the committee to specifically talk about the general population that's targeted, as well as what we know from the application about the likelihood for this safe and effective use in adolescents and in consumers with limited literacy. Then we'd also like the committee to discuss specifically the implications of potential use of norgestrel along with concomitant drugs that may interact and reduce efficacy of norgestrel.

Our discussion question 2, it pertains to actual use study design, and we've talked extensively about the findings of the ACCESS study. We would like the committee, if they have thoughts or recommendations on actual use study design in

this therapeutic area, to please comment on the following different aspects of study design for actual use studies: the e-diary design; the e-diary recall period that's allowed; compensation structure for participants; methods to ensure that the entry instructions for an e-diary in a study are adequately comprehended; and the potential to incorporate a pathway to allow participants to talk to a healthcare provider before deciding about a drug purchase; and study questions to determine the timing of when participants spoke to a healthcare provider to inform assessment of endpoints that include assessment of that action and behavior by participants.

Our third discussion question is targeted on safety. We would like the committee to discuss whether there's sufficient information to conclude that consumers with a history or current diagnosis of breast cancer, or other progestin-sensitive cancer, would deselect from use; and whether consumers with abnormal vaginal bleeding of undiagnosed etiology would take the appropriate

action based on the messages in the DFL; and whether consumers who are using other hormonal contraceptives would take the appropriate action based on the DFL messages.

Then finally, our voting question, we would like the committee to vote as to whether they think that there's adequate information to conclude that consumers will be likely to use norgestrel tablet properly, such that the benefits of making this product available without a prescription and without the need to interact with the healthcare professional exceed the risks, and paramount among those risks are the risk of inadequate adherence leading to contraceptive failure and unintended pregnancies; the risk of use of the medication by consumers with a contraindication to its use and the failure to see a healthcare professional when appropriate.

If you vote no, we'd like you to explain your vote and what additional data would be necessary to support approval, and if you vote yes, we'd like you to explain why you think the benefits

outweigh the risks and are likely to continue having the benefits outweighing the risks in the nonprescription setting.

If possible, we'd like you to not change the wording of our questions and try to respond to the questions as they are worded, and address the specific issues that we have outlined in these questions. Thank you.

Questions to the Committee and Discussion

DR. COYLE: Thank you, Dr. Horn.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. As we begin to proceed with the questions to the committee and the panel discussions, I'm going to provide just a short logistic update.

We do have a number of questions, including a voting question to address, so I want to make sure that we get through at least the first question before we break for lunch, and we may take just an abbreviated 30-minute lunch, and then we

will return after that time frame, also moving through the remaining questions and allowing sufficient time for the voting question.

So we will further be keeping an eye on timing here, but I do want to encourage all members, including those who maybe have not spoken up yet, to share their thoughts and concerns as we work through these questions today.

I'd like to remind public observers that while this meeting is open for observation, public attendees may not participate, except at the specific request of the panel. As we go through these questions, I will read each question, and then we will pause for any questions or comments concerning its wording specifically. After that time, we will then open the question for discussion.

Let me begin by reading the question and asking for any clarifications or comments as to the wording.

Discuss whether consumers are likely to use norgestrel tablet in a safe and effective manner,

considering the possibility of unintended pregnancy with incorrect use. Specifically discuss whether consumers are likely to adhere to taking the tablet daily at the same time of day, based solely upon the nonprescription labeling without any assistance from a healthcare professional.

Then please discuss for the following consumer populations: the general population of females of reproductive potential; adolescents; those with limited literacy; and those using concomitant products, for example, anticonvulsant drugs that may interact with and reduce efficacy of norgestrel tablet.

Are there any questions about the wording of the question?

(No response.)

DR. COYLE: Seeing none, I will open up for comments. I'm going to suggest that we deal with these in subparts, so any comments related to the discussion question around the general population of females of reproductive potential from our panel.

Yes. Dr. Armstrong?

DR. ARMSTRONG: This is Deb Armstrong from Johns Hopkins. So I'll break the ice a little bit. I think the data that we have been presented from the use of Opill is that there certainly can be some unintended pregnancies, but if one looks at the data that we have, and that was presented for other options for patient-generated use for contraception, such as the condoms, diaphragm, et cetera, that the incidence of unintended pregnancies is certainly lower.

It certainly may not be as good as what was called the moderately effective agents, such as oral contraceptives provided under a healthcare provider -- patches, rings, injectables, et cetera -- but I think it certainly is better than what's available right now, overall, for the general population.

I just wanted to break the ice and say that was my thoughts with regard to the general population.

DR. COYLE: Thank you.

Dr. Curtis?

DR. CURTIS: Thank you. Kate Curtis, CDC. I'm thinking that we were presented a lot of data, and I echo Dr. Shaw's comment yesterday that it's a little difficult to take all of the disparate sponsor and FDA analyses into account. But I think looking over all of the general population, looking over both actual use and the comprehension data, and looking at the key endpoints on taking the pill every day, taking it the same time every day, and especially factoring in the mitigating behavior, I think we can say for the general population that at least the pill taking behavior and comprehension are good.

I did want to make a comment about the Delayed Pill Study presented by the sponsor. To me, those data are reassuring. I agree with the FDA that there's certainly not enough data to expand that 3-hour window, but I do think measuring cervical mucus and ovulation are standard measures of proxies for pregnancy risk when pregnancy isn't feasible to measure, so those data were reassuring

to me. Thank you.

(Pause.)

DR. COYLE: I apologize.

Dr. Berenson?

DR. BERENSON: Thank you. Abbey Berenson, University of Texas, Medical Branch. I would just like to repeat a comment that was made earlier, I believe, by Dr. Curtis that we have to think about if people take the pill the same time every day when they do see a provider. I think all of us that have had experience taking care of adolescents and adult females realize that it is very difficult for people to long-term take even birth control pills when they see a provider the same time every day. So I just think that we should think about the big picture and not just the over-the-counter use. So given what's been presented, I feel that it is as safely taken without a prescription as it is with a prescription.

DR. COYLE: Thank you.

Dr. Shaw, please go ahead.

DR. SHAW: Yes. Pamela Shaw. I'd just like

to add that I agree with the statements that were just made by Dr. Curtis and I believe Dr. Berenson. I agree and think for the general population of females with reproductive potential, I believe it's going to be used generally in a safe and effective manner. I looked at similar questions that were mentioned, the daily use.

Also, in terms of the disparate analyses, I focused my evaluation on the FDA analysis because I did agree with the FDA that there was concerning re-categorization, but looking at the FDA analysis, such as this overall selector analysis of ACCESS, table 7, I saw that 85 percent threshold was being met in terms of appropriate selection, at least in the point estimate, and closely, the lower bound; not quite, but close.

So overall, taking into account the safety of the progesterone-only pill that has been established, I would agree that it would be safe and effective.

DR. COYLE: Dr. Haun, what would you like to add?

DR. HAUN: I would like to voice my agreement with my advisory committee members. I do believe that we can all agree that when a physician prescribes birth control pills, these are typically done on an annual basis, if not less than that, and that individuals who are prescribed those pills are left to their own vices to take it regularly, as instructed, and a prescription will not prevent or support the use of this medication appropriately for these targeted populations on the slide. I also believe that this is a viable option to support ACCESS and will support the prevention of unintended and unwanted pregnancies. Thank you.

DR. COYLE: Dr. Espey, you could go ahead.

DR. ESPEY: Thank you. Eve Espey, University of New Mexico. I agree, and would just add that I'm not sure, in my mind, that there's a big difference between these different categories for the reasons that have been stated before, and that is that this is a medication that's been approved for quite some time, so it doesn't seem like the effectiveness is really what we should be

considering here, but the focus should be on safety.

I don't think we can think about this question outside of the context of what else is available to patients. And all of these groups, the subgroups, face incredible barriers to being able to access contraceptive care. So if we agree that the major harms of this medication are very limited, and we also don't have evidence that when a patient accesses their caretaker [indiscernible] or provider, that it is much safer than it is through self-use and looking at the label, that I agree that the data would support that it can be used in a safe manner. Thank you.

DR. COYLE: Thank you.

I will call on Dr. Roth with perhaps encouragement to consider points that have not yet been discussed, or haven't been discussed in the depth that you would like around the general population in particular.

DR. ROTH: I'll try. For 20 years, I was a primary care doctor and a primary care program

director before going into geriatrics and palliative care, and I think that the safety profile here is very well established. I am very skeptical that most women who get prescribed birth control pills in a clinic or doctor's office setting, get very much counseling about how to take the pills, and on repeat prescriptions, that probably doesn't happen almost at all.

So I think that it's really an access issue. We know there's a need. We know that access is even worse than it used to be given a number of socioeconomic factors and disparities, and I don't see why the general population of women cannot safely have this medication available over the counter.

Patients who have medical conditions, I hope, like breast cancer and anticonvulsant therapy for epilepsy, are getting medical care, and are getting counseling regarding such issues as contraception. So I think that making it available over the counter is the right thing for women. I'm going to stop there, but I appreciate Dr.

Berenson's remarks also about what really happens in the renewal of birth control pills, in the office.

DR. COYLE: Thank you, Dr. Roth.

Dr. Baur, what can you add to the conversation, especially regarding the general population?

DR. BAUR: Sure. Cynthia Baur, University of Maryland. So I'm looking at the label itself, which is labeled, I guess, version H, and I wanted to recommend that we consider Dr. Haun's suggestion about adding "by mouth" because I think that would apply to audiences A, B, and C. That would be helpful, so take one tablet by mouth at the same time every day. And if it were considered a substantive change, I would not suggest this, but I would consider also adding the word "only," take one table only by mouth at the same time every day because one of the issues Dr. Haun raised is there's a lot of confusion around directions. People may not always know how a pill might be taken.

We also, within health literacy research, know that people sometimes think taking more is better, so sometimes it's really important to clarify that only one pill should be taken and not multiple; multiple is not better. So I think that for populations A, B, and C, those additions might be really helpful as part of the labeling.

DR. COYLE: May I ask FDA to comment to what extent some of the potential upcoming revisions to drug facts labels might impact this product, or really any product, out in the over-the-counter market? In other words, is there going to be an opportunity to further refine the Drug Facts Label for all products in the short term, or is that more of a long-term process?

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs. That opportunity would not be available in this approval cycle because the PDUFA goal date for this is coming up very quickly. So I wouldn't consider that to be something that would be an option for consideration about whether the product is appropriate for

approval in this cycle.

DR. BAUR: Could I ask, FDA, if --

DR. COYLE: Thank you.

Dr. Baur?

DR. BAUR: Well, I was just going to say, would they consider the addition of "only" and "by mouth" to be substantive changes requiring retesting? Because otherwise, I think that impacts my recommendation.

DR. COYLE: FDA, can you comment on that?

DR. MURRY: Karen Murry, deputy director, Office of Nonprescription Drugs. I'm a little bit hesitant to begin discussions of a variety of supposedly minor suggested changes to the Drug Facts label as a way to get to a vote of either yes or no by the committee. So again, I would encourage the committee to consider the label only as it is currently written and as it has already been tested.

DR. COYLE: Thank you for that clarification.

Dr. Haun, did that answer your question?

DR. HAUN: Yes. Thank you.

DR. COYLE: I think to summarize our, at least, initial discussion here, there does seem to be support across the panel, of those who have spoken, that use of the norgestrel tablet in a safe and effective manner seems very reasonable in the OTC setting, particularly for the general population of females, given that there are challenges even to prescription adherence, and maybe in a general sense, that healthcare provider interactions substantially may affect that or may be available in such a way as to make it a necessary component of safe and effective use.

I would like to invite anyone who has a differing opinion to please raise their hands so that that can be heard, if necessary, and also to move the conversation specifically to the population of adolescents and those with limited literacies, and then we'll address the final subgroup maybe at the end here.

Dr. Berlan, go ahead.

DR. BERLAN: Alright. Thank you. This is

Dr. Elise Berlan from Ohio State University and Nationwide Children's Hospital. I want to thank the FDA and the sponsor for sharing this information and inviting me to participate. I'm an adolescent health expert, and this is work I do clinically day in and day out.

I have just some comments on the question around effectiveness, safety, and comprehension by adolescents. To frame this, access barriers impact adolescents more than anyone else. They are actually healthier than other pregnancy people or persons, and they're at the highest risk for unintended pregnancy.

I don't think I have any concerns about the effectiveness of this progestin-only contraceptive. The revised Pearl Index in the FDA analysis was 3.4, and that's highly acceptable to me, and it's more effective than any other over-the-counter contraceptive currently available. I understand the safety to be well established of this product.

In terms of the specific questions the FDA raised with the deselection, I found both measures

have some limitations, but overall, the absolute risk of harm to use of this product to adolescents is quite low. In terms of the abnormal vaginal bleeding deselection question, most adolescents with abnormal vaginal bleeding between periods do not have uterine cancer; they have anovulation, which is primarily due to pubertal immaturity and not a pathological cause. They may also have a sexually transmitted infection. There's a small risk of missing a pathological cause; however, bleeding related to an STI will not stop with the POP.

Other areas that the FDA raised concerns about adolescents include the risk of bone density, and in my professional opinion, risks related to bone density are low given the rebounds we see with use of injectable progestin contraceptives in adolescents. I'm not particularly concerned about them not understanding the mitigating behaviors because although that might compromise efficacy, it is not harmful.

With the risks related to them understanding

the label and taking emergency contraceptive in a timely way, the emergency contraceptive that would be interacting harmfully, potentially with this contraceptive, is the prescription emergency contraceptive. So again, it's probably unlikely that someone taking an over-the-counter oral contraceptive would be taking a prescriptive emergency contraceptive, which is the ulipristal acetate.

Regarding the off-label use that was disproportional in adolescents, off-label use happens frequently with prescription oral contraceptives. It is unlikely to be harmful, and I know that's not within the label indication, but it is unlikely to be harmful; and there, off-label use among adolescents may roll into contraceptive indication as the patients age.

With regard to the just previous question about the adding by mouth, if this delays the availability of this product, I do think the imperative for an oral contraceptive that's available is now, and I would encourage us to keep

that in mind.

With regards to adherence -- and I will wrap up very shortly -- the adherence in the prescription setting among women and adolescents already is highly imperfect. I do think what's been presented to us does show that adolescents can adhere to daily contraceptive use in the ACCESS trial, and non-adherent daily dosing is likely to compromise effectiveness, but it's unlikely to pose harm greater than non-use.

In sum, I believe that the potential incremental benefits to this product, with regards to safety, effectiveness, and the questions about reading the label, are really less than the potential incremental benefit of access to this product. Thank you.

DR. COYLE: Thank you.

Ms. Robotti, please go ahead.

MS. ROBOTTI: Hi. Thank you. Suzanne Robotti. I questioned yesterday about the limited literacy and low literacy group, and I do have to say I'm still not very happy with the low number of

participants; however, I don't think that's a reason to not move forward with this. In both groups, adolescents and limited literacy, the comprehension of use and deselection was pretty good, and there's no clarity that the direction that any woman gets -- old, young, low literacy -- that they get counseling in a warm and supportive environment that facilitates questions and interaction. That would be ideal for everyone, but that often doesn't happen. The pregnancy rate already of women using prescribed oral contraceptives, the higher rate than perfect adherence shows that compliance is not perfect already. I don't see any reason why OTC distribution would be worse with compliance.

Just a quick comment on D, concomitant products like anticonvulsant drugs, I would hope that those women are seeing a doctor and under some sort of care so that would help them, period -- period; I'm dictating -- but I do worry about herbs and St. John's wort, products like that. I think that people don't understand their

power. I don't know what to do about that for any drug interaction. Thanks.

DR. COYLE: Thank you.

We will move on to Dr. Walker-Harding.

DR. WALKER-HARDING: Thank you. Leslie Walker-Harding from the University of Washington. I wanted to underscore Dr. Berlan's very comprehensive list of reasons why adolescents really urgently need this. With 70 percent of adolescent reproductive age women either having no or lower efficacy birth control methods available to them, this would dramatically increase the ability of kids not having unintended pregnancies.

I agree that focusing on safety is real important. Whether somebody takes it exactly correctly or whether they miss some, that happens all the time. After over 20 years of doing this work, talking to an adolescent in an office for 20 minutes, and then giving them a one-year prescription is really probably about the same as somebody reading it on the label. There's not a lot of counseling or any particular thing that

happens with oral contraceptives, and the amount of kids that don't have access to a provider is tremendous.

Particularly around the emergency contraception, that theoretical risk is only valid in the sense that a kid could get emergency contraception. That's very hard to access. Even in states where it is over the counter, it's still difficult for adolescents to access and talk to the pharmacist to get that. So I wouldn't hold it up for that theoretical risk, given the lack of access, even to emergency contraception for adolescents.

Then in terms of adolescent decision making, there's no evidence that adolescents make poor decisions and, in fact, adolescent decision making when researched is equal to adults when given the same information, so I wouldn't want us to have any feeling as though we are protecting adolescents, and they might not understand. It would be at the same level as anyone else who is reading the information.

I would say it's also equally urgent for those with limited literacy to be able to have the opportunity to take this medication. The safety profile is so good that we would need to take every other medicine off the market, like Benadryl, ibuprofen, Tylenol, which causes deaths, and people can get any amount of that without any oversight, and this is extremely safe, much safer than all three of those medications, and incorrect use still doesn't appear to have problematic issues just like it doesn't with the prescription. So I'm very much in favor of both adolescents and those with limited literacy, and I would hate to see it delayed, and that's it.

DR. COYLE: Thank you.

I will now call on Dr. Berenson, again, trying to focus our conversation on effectiveness and safety in the adolescents and limited literacy population, and particularly adding points that have not been discussed thus far.

DR. BERENSON: Thank you. Abbey Berenson. I would like to point out that the only true

contraindication for this product is active breast cancer, and adolescents don't usually have active breast cancer. That would be extremely rare, so they may be the safest population to prescribe this for.

There was a point made about bone mineral density, and I did an NIH-funded study on this, and that is not related to whether it's given over the counter or by prescription. Adolescents are given birth control pills, and whether or not you think it affects their bone density, I don't think it matters how they access the birth control.

The last thing I would like to say is from the data presented, adolescents appear as well as those with limited literacy, the groups that are most at risk for an unintended pregnancy due to lack of access, so that would make them a priority group for over-the-counter medication. Thank you.

DR. COYLE: Thank you.

Dr. Roth?

DR. ROTH: I have a very quick comment. The pills are called OCs, oral contraceptives.

Everybody knows that oral -- in fact, there are Oral-B toothbrushes -- means mouth. And I think it's actually insulting to add "take by mouth." When somebody seeks an oral contraceptive, they know it should be taken by mouth. I don't mind if you put it in. It's a little bit mansplaining and a little bit paternalistic, I think, but I think that anybody who would seek out this product would know that this is a pill that's meant to be taken by mouth, and I really think if that language change would hold up the release of the medication, that we should allow that, and I think adolescents would understand that oral means taken by mouth. Thank you very much.

DR. COYLE: Thank you.

Ms. Everhart, please go ahead.

MS. EVERHART: Thank you. Sabrina Everhart. I do have confidence in the general public's ability to understand the importance of dosage adherence. Birth control pills, in all forms, have been around for a very long time, and they do have enough popularity that I feel like their knowledge

is well known. However, in regards to adolescents and literacy, without significantly more data on the adolescent and the limited literacy populations presented in this meeting, I am not sure whether or not they could comply on their own or understand concomitant use without additional guidance.

Now, I'm referring specifically to the very young population here, those not old enough to have an ID, who may be of reproductive ability and not comprehend the literature, and that's what this question is about. And somebody who has a reproductive granddaughter, at 11, it brings me pause, as I wouldn't feel confident sending her into Walgreens to choose that for herself without having the bravery to ask a pharmacist or myself. I'm not sure she could even understand the literature and what's written.

I also have nieces and daughters of reproductive age, and I do feel that age is an important factor here in this particular question we're referring to. So I want to make that clear that when we're referring to adolescents and those

with limited literacy, that I do have concerns in that, but I don't want that to be the reason why this doesn't go over the counter. I would just like some considerations to be discussed in regards to that very young population. Thank you.

DR. COYLE: Thank you.

Dr. Haun, what would you like to add?

DR. HAUN: I would first like to say that I do agree with Katalin Roth; that though I made the suggestion around the language, that if it were going to prevent the availability of this medication over the counter, that would not have been my intention. So I would like to retract my comments earlier if that would delay the release.

I would also like to add -- I don't think anybody has mentioned this, so I would like it to be noted in the record -- that the major construct here in this question is around the construct of adherence. It is very clear in the literature that adherence and the ability to take medication such as this kind of pill is largely related to factors such as self-confidence and motivation.

Adherence is most certainly predicted by confidence and motivation, so if an individual, be them an adolescent, one with limited literacy, or the general population, had enough confidence to go and get this medication over the counter -- and self-efficacy -- that we can make a safe assumption that they have the motivation. And motivation is a highly recognized predictor of adherence, such that it would be more so than having an interaction with a healthcare professional who might do the prescription for them if it stayed prescribed.

So I think that when we think about adherence, we need to be very clear that there are other factors such as motivation and confidence that would support adherence to this medication, not to mention the fact that the data showed that thresholds were either met or exceeded when the trial was conducted. Thank you.

DR. COYLE: Thank you.

To summarize where we are to this point, I think in speaking to the effectiveness of the norgestrel tablet in the OTC setting, the panel

expresses, I think, great confidence in the effectiveness, not only in the general population of females, but also in adolescent populations and those with limited literacy for a variety of factors that we've discussed.

I think in terms of risk, risk from the medication itself, the panel seems very comfortable with the limited number of risks from the medication itself, so physical risks from taking a norgestrel product on a daily basis may be -- particularly in adolescent populations that are overall quite healthy and less prone to the kinds of conditions that would be a contraindication such as breast cancer. In fact, the benefit may far outweigh risk if that were the sum total of the equation. I think risk from unintended pregnancy, because of not understanding or not adhering to a daily regimen taken very close in time each day, may be the greater risk that we're discussing.

I have heard a little bit of mixed opinion, many people expressing that it is better than what

is currently available, and it would not necessarily be information or directions that would be beyond the capability of all of these populations that we've talked about thus far, maybe with the possible exception of very young adolescents; and in that case, maybe some further information or data would have been helpful to understand that aspect of risk for very young adolescents.

One other point that I wanted to make because I've heard it in all of our conversation or several of the comments made by panelists thus far, was that even looking at the more conservative analysis provided by the FDA, of the data from the ACCESS study, I think there's still quite a bit of confidence in this product in the OTC space. So I just wanted to make sure that that was reflected in our summary here.

I'd like to turn our attention finally to that last subgroup, those who are using concomitant products that may interact with or reduce the efficacy of this oral contraceptive. I heard a

little bit about the fact that these folks would likely be under physician care for that additional product or that interacting drug, maybe with the exception of some OTC supplements, which are not regulated in the same way as our traditional over-the-counter drugs.

So I'll just ask if there are any further comments around concomitant products, and I will begin -- Maria Coyle, Ohio State University -- just in saying that I know that in my practice, when I am working with patients who have conditions that require regular medications, I'm consistently screening for drug interactions, including interactions with over-the-counter products like this product would be, and making sure to ask about not only side effects, but also potential concerns around loss of effectiveness; so making sure that patients are educated and aware of maybe the interaction with that over-the-counter oral contraception, and that would not be any different than what I would normally do when talking with a patient with epilepsy, or a patient on a statin

medication for cholesterol, or a patient for high blood pressure medications, et cetera.

So I'll just add that, and then invite any other comments from the panel.

Yes, Dr. Shaw?

DR. SHAW: Yes. Thank you for bringing our attention to this item. Pamela Shaw. I think there was some discussion and concern yesterday about specifically the emergency use contraception and whether or not people will be taking that when taking this over-the-counter progestin-only pill. I personally did not have raised concern regarding that specific concomitant product, and that it would be unlikely if people already on, I think, oral contraceptives, that they would be also seeking that out, and just the overall safety profile of the medication. So for me, that did not raise additional concern, and I just wanted to add that comment.

DR. COYLE: Thank you.

Dr. Walker-Harding?

DR. WALKER-HARDING: Leslie Walker-Harding

from University of Washington. I also just wanted to say I think that I don't see any additional concern for that group. I also wanted it on record that I strongly believe that an adolescent of reproductive age, of any age, even early adolescence, this would be safe. I would be very concerned if there were any restrictions on younger adolescents who are at reproductive age and need the medication.

DR. COYLE: Thank you.

Dr. Berlan?

DR. BERLAN: Hi. Thank you. This is Elise Berlan, Ohio State University, Nationwide Children's Hospital. I just want to comment on this question. In the adolescent participants in the ACCESS study, there were a higher proportion that reported concomitant use of other contraceptives, and we discussed that yesterday.

My comments for the panel would be that it is common to prescribe two contraceptive hormonal products at the same time, and that is generally very unharmful and can have a therapeutic effect.

So with regards to the concomitant multiple contraceptive, I would not have any clinical concerns about that. And just to echo Dr. Walker-Harding, I would really not endorse any age restriction for this product because I do think this product can be used safely by even the youngest adolescents.

DR. COYLE: Thank you. Thank you for adding that perspective from your clinical experience to both you and Dr. Walker-Harding.

I'm scanning here our roster to see if there are any additional comments around this question before we move on.

Dr. Espey?

DR. ESPEY: Eve Espey, University of New Mexico. I'll just state the obvious, that even with a one-time provider visit, patients will often begin taking other medications that could potentially have interactions without going back to that provider for additional guidance. Also, there are very few actual medications that have been shown to reduce the effectiveness of contraceptives

to the point of recommending a different medication. Thank you.

DR. COYLE: Thank you.

Alright. I think we will be ready to move on to question 2, not seeing any further comments.

Once again, I'm going to read the question and ask for any clarifications or questions around the wording itself, and then we will open the discussion for comments, again, trying to go point by point so that we fully discuss.

We will begin this question, and maybe we'll go for another 10 or 15 minutes, and then we'll take a break for lunch. So just to begin, this is the discussion question.

The ACCESS study use phase had improbable dosing in approximately one-third of participants. If FDA were to recommend the applicant conduct another actual use study, what changes to the actual use study design would the committee recommend? Considering the following, and these subpoints: e-diary design; e-diary recall period; participant compensation structure; methods

ensuring data entry instructions that are adequately comprehended; incorporating a pathway allowing participants to ask a healthcare provider before deciding study drug purchase; or study questions to determine timing of when they spoke to a healthcare provider during the study.

Are there any questions on the question itself, on the wording?

Dr. Pisarik, did you have questions on the wording of the study?

DR. PISARIK: I do not.

DR. COYLE: Thank you.

Okay. Seeing none, I will then open the conversation for panelists discussion, and Dr. Pisarik, you may go ahead.

DR. PISARIK: I just had a question. Since there's a big deal made about when pills were taken and what time they were taken, isn't that a place for using an electronic pill dispenser where you would know exactly when the pill was taken?

DR. COYLE: Just to summarize, it sounds like you're recommending that if this study were to

be repeated, it would have some sort of a mechanism that was more objective in measuring pill dispensing or pill removal from the pill pack.

DR. PISARIK: Exactly.

DR. COYLE: Yes.

Ms. Everhart, go ahead.

MS. EVERHART: Thank you. Sabrina Everhart. Since we don't know the actual design information of that e-diary, as far as I'm aware, that was not made available. If it is available, I would like to see it, but I would recommend maybe revising that overreporting, and [indiscernible], given what little information we've been given on that, possibly further future studies as well, anything postmarketing.

Also, I would advise maybe to include in that e-diary, if this is possible, the ability to maybe virtually speak to a nurse, whether it's video or chat, if so desired by the participant, to be able to ask questions, specifically if they can't get back to the study site or can't contact their own doctor, and maybe that might help with a

little bit of data input. Those are really my only recommendations based on what I've seen so far. Thank you.

DR. COYLE: Ms. Everhart, are you saying that in terms of the e-diary design and use, having a resource to check in on use of the diary itself would be helpful, or are you --

MS. EVERHART: Absolutely.

DR. COYLE: -- speaking more to a later point?

MS. EVERHART: Yes, absolutely. If this study were to be re-done, the ability to in app, chat specifically, even with a medical personnel. I think would be helpful for them to be able to contact support on the app itself, as this generation is frequently well-versed in how to use that method of communication more so than others.

DR. COYLE: So it sounds like you're suggesting that both in terms of the use of the diary itself or how to track information in the e-diary, it might be useful to have a chat function or live support, but also maybe for one of the

later points there about accessing healthcare providers.

MS. EVERHART: Yes, ma'am. Thank you.

DR. COYLE: Excellent.

Dr. Catlin, please go ahead.

DR. CATLIN: Hi, everyone. Jesse Catlin, Cal State University, Sacramento. Just quickly related to the last comment by Ms. Everhart, I did find, I think, that the FDA presentation, slide 123, added some clarity for me on how the diary was actually designed.

I definitely understand the sponsor's perspective and the FDA's concerns about the study. As someone who does a lot of consumer behavior research, I think it's helpful maybe that we consider the extreme. If we did another study, we could design a trial with a daily reminder that makes them enter the data every day and doesn't allow any reporting when they don't have any pills, and this will obviously yield a study with no missing data and no overreporting. Of course, we could design this study, but would we believe the

data? Would it really represent actual use?

So I would ask us to consider that. We probably could request a study that goes the other way, but would it yield -- we'd be having a different conversation now of whether it represents actual use. Now we're having a conversation that maybe the study wasn't necessarily restrictive enough, which led to some messy data and some problems, but I think if we have things like a chat feature, if we did other stuff like that, does it actually represent how the consumers are going to use the product when they're left to their own vices? Thank you.

DR. COYLE: Thank you, Dr. Catlin. That's very helpful.

Dr. Horn, would you like to say something? Would you like to add to the conversation?

DR. HORN: Thank you.

Yes, Dr. Coyle. I just wanted to respond to the comment about where the study design information is located, so thank you, Dr. Catlin, for pointing out where it is in the slides. In the

background document, FDA background document, the study design description starts on page 44, and goes on from there, and includes some information about the e-diary design.

DR. COYLE: Thank you.

Dr. Walker-Harding, anything that you would like to add about the e-diary in particular?

DR. WALKER-HARDING: Hi. Leslie Walker-Harding, University of Washington. No. I was going more generally to the question at hand.

The question itself, to me, is concerning. If there was a recommendation to do another study, I very much agree with Dr. Catlin who just spoke. I'm not sure. What would that do? We already know the safety profile. What would we be doing, trying to have a better actual study with, again, information that might not even approximate the real world.

Any of these studies are going to be imperfect; we're trying to look at real use, and any amount of delay, during the time when people have less access to primary care providers

post-pandemic than they ever have, is really, in a way, causing further harm to adolescents and others who don't have access to these medications, which could help them prevent an unwanted pregnancy. So I would say that I would really be not interested in seeing another actual use study on something like this, where we know the safety profile is so great to begin with.

DR. COYLE: Thank you.

Dr. Curtis?

I apologize. Let me back up. I've misread my roster. It's Dr. Armstrong next, and then Dr. Curtis.

DR. ARMSTRONG: Yes. Deb Armstrong from Johns Hopkins. Two issues. The first is, I know you're not asking us this in this question, but I think you've been hearing that most of us, if there was another actual use study, would not want that to be a barrier to having the drug available; that that shouldn't delay access to the drug if that's the ultimate decision; that there shouldn't be a delay based on this.

That said, another actual use study, I really champion what Ms. Everhart, which is that if there could be included a contact for questions. I would also strongly encourage, whether another actual use study is done or not, a video that basically says everything that's in the written comments that individuals can access at any time, a YouTube type of video. It could address the literacy issue. It could address the adolescent compliance issue. It could be done in different languages.

I think for modern-day young individuals in particular, seeing a video is worth 10 small print written directions. So again, I would be opposed to an actual use study that delayed availability of this, but if it were done, I think that those two things, a contact information line or person and a video to address the recommendations in the small print, would be very helpful.

DR. COYLE: Thank you.

I'm going to allow Dr. Curtis to speak next, but just with the caveat we're going to do one more

question, and then we'll take a break for lunch. And we'll reconvene after lunch with Dr. Horn, and then we will wrap up the conversation around question number 2.

Sorry. I'm trying to manage a few moving parts here but, Dr. Curtis, we'll let you speak, and then we'll break for lunch.

DR. CURTIS: Great. I'll be quick. Thank you. Kate Curtis, CDC. I just wanted to say that the improbable dosing issue is important, and I don't think it's been adequately addressed and certainly leads to some uncertainty in the findings. But despite this, I would not recommend another actual use study at this time, and I think we can make a decision on the totality of the evidence. Thank you.

DR. COYLE: So to summarize where we are at this point in discussion question number 2, it sounds like there is a strong recommendation from the panelists who have spoken thus far to not necessarily investigate or to go down the path of an additional actual use study, which I realize is

outside the scope of what we've been asked to specifically address but is something that has come through. There may be some recommendations for improvement, and we will focus on that aspect of this discussion question when we reconvene after lunch.

We will take a break for 30 minutes, so we will plan to start again at 12:30, which I acknowledge is a short break, but in the interest of ending as close to on-time as possible, I'm going to suggest that we break for 30 minutes with panelists re-logging in again at about 12:20-12:25 to be sure that we can start promptly at 12:30.

Just as a final reminder, there should be no chatting or discussion of these meeting topics or questions with other panel members during the lunch break, and I will see you all at 12:30. Thank you so much.

(Whereupon, at 11:58 a.m., a lunch recess was taken, and meeting resumed at 12:29 p.m.)

A F T E R N O O N S E S S I O N

(12:29 p.m.)

DR. COYLE: Thank you, all. I hope you had a nice break, and we will now reconvene our meeting.

I would like to return our attention to discussion question number 2, and I will first call on Dr. Horn to address the panel.

DR. HORN: This is Pamela Horn, DNPD II. I'm going to pass it over to Dr. Murry.

DR. MURRY: Hi. Karen Murry, deputy director, Office of Nonprescription Drugs, and I'd like to thank the panel for their very thoughtful discussion so far.

I wanted to mention a couple of things that were relevant to some comments that were made. First of all, there was one suggestion that a nurse could be involved somehow, either in a redesigned actual use trial or in the eventual use of the product. And I just want to remind the panel that the legal definition of a nonprescription drug in the United States is that there is no healthcare

professional involved, and nurses are definitely highly trained healthcare professionals. So a drug that needed the involvement of a nurse would not be a nonprescription drug.

Then there was another suggestion that perhaps a video could be used. If the panelists suggest seeing a video or some type of technology element would be something that would be needed in order to get past some of the difficulties that the application is facing, then that would probably fall under our paradigm of an additional condition for nonprescription use, for which the agency recently put out a proposed rule, and the applicant would need to propose that additional condition for nonprescription use and do consumer behavior testing to show that, again, consumers would use the drug correctly, safely, and effectively in the nonprescription environment.

So while those are creative and innovative potential approaches to overcoming the problem, one of them is not consistent with nonprescription law in the United States, and the other one would

require that the applicant go back to the drawing board on their development program and submit another application.

DR. COYLE: Thank you, and we always appreciate those helpful guidances from the FDA just to remind us of the lane that we are in when we're considering over-the-counter medications, so I appreciate that.

I will go back to the hands that were raised in the order that they were available to us before our break, but before doing so, I just want to acknowledge that we've heard from several panelists that they are not proposing -- they are not in favor of redoing or asking the FDA to redo an actual use study with the applicant.

So I think that message has been captured and has been delivered to the FDA, so I would like the panel to truly consider what the question itself is asking, and that would be what improvements could be made to an actual use study method that might actually address some of the concerns that were raised with the data that was

presented; so not to minimize the importance of the other message, but also just to use our time wisely and make sure that the FDA does end up with the information that they are needing from our expertise here as we are assembled today.

So I will ask Dr. Haun to begin.

DR. HAUN: Hi. My name is Dr. Jolie Haun, and I am representing James A. Haley Veterans' Hospital and the University of Utah, with the acknowledgement that I do not support the recommendation of another trial.

I do think that there's something that has actually not been discussed, nor is it listed on this design option inquiries A through F, which is the addition of qualitative inquiry with potential patient and/or user consumer participants to not only engage some of the questions that have come up around the overreporting, but also preferences for use, as well as needs along the different topics that are addressed here, such as the pathway, as well as the idea around timing which participants would like to be able to engage in the process.

There has been little to no mention of qualitative inquiry, so I do believe that mixed methodologies are always a superior design, and I have heard of no qualitative inquiry, and I do think it would also speak to consumer demand for an OTC application of this medication. Thank you.

DR. COYLE: Thank you, Dr. Haun.

Dr. Shaw, what would you like to share?

DR. SHAW: Hi. Thank you. Pamela Shaw. I'd just like to respond to the question about if this were of interest to the FDA, what kind of design recommendations would there be. And I'd like to emphasize what Dr. Catlin said, which is we don't want to put in aspects of this study that artificially increase adherence. I have concerns about that reminder that happened every 4 days, as this is supposed to be measuring actual use.

So to the best that it's possible, looking at other studies that have used e-diary to encourage the participants fill out a study instrument; that participants need to remember the protocol for the study they're in. Those sorts of

reminders can be helpful, but this is not a study about increasing adherence, so I had some concerns about the reminders were messing up the message.

I also had concerns that the device, the e-diary technology, perhaps was not properly tested. It's a little, I think, of the wild west sometimes in the app world. So I would like to see, if this were of interest to the FDA, that there would be a proper pilot that would test the diary in the matter it would be intended to be used to catch any weird flaws that seem to compromise the interpretation of previous studies, and even completely invalidate; I think it was the OPTION study where the e-diary had a total failure.

So I feel like a pilot is a very important aspect, and even perhaps the credentials of the vendor and past use of an instrument. All instruments in a study, before they're launched on hundreds or thousands of people, hopefully are being properly tested. Those are my main comments. Thank you.

I'm sorry. One last thing was the last

question F. If actual use interest is in whether or not a participant contacted a healthcare provider before or after starting, if that is of interest in an actual use study, then that question should be asked. That's my final comment. Thank you.

DR. COYLE: Thank you, Dr. Shaw.

Dr. Baur?

In particular, I would also invite others who have not yet spoken to get in line so that we could wrap this question up, particularly around items maybe C, D, and E, which we have not really discussed in great detail yet -- or I'm sorry, B, C, and D, which we have not discussed in great detail.

Dr. Baur, you can go ahead.

DR. BAUR: Yes. Cynthia Baur, University of Maryland. I would just add to the list the actual stimulus itself, which as the FDA keeps reminding us, is the label and any other consumer information, because that is part of what goes into the decision making and the consumer behavior. So

I would just make sure that any consumer information that was included in any trial was on this list as part of any consideration for changes. Thank you.

DR. COYLE: Thank you.

Dr. Baron?

DR. BARON: Just to contribute a little bit specifically to letter D, methods ensuring e-diary data entry instructions are adequately comprehended, one of the things that we have always done is a teach-back mechanism. And I'm not sure if that was done, and if it was, I'm sorry; I'm Monday morning quarterbacking here. But teach-back is one of the ways, during the screening, or that point in time in which instructions are given, we always make sure that teach-back is performed to ensure that they understand. Thank you.

DR. COYLE: Thank you.

Dr. Shaw, did you have another comment?

DR. SHAW: No. Pamela Shaw, failure to lower hand. Thank you.

DR. COYLE: You're acknowledged and

forgiven.

Maria Coyle from Ohio State University. I will add one comment about the participant compensation structure. I understand that there is some concern that in the ACCESS study, payment was linked to frequency of reporting or frequency of adherence entries into the diary, and it does seem like perhaps there might be some alternative ways to reward or incentivize attention to the diary that are not connected directly to number of entries. So perhaps there are other ways to look at milestones and, again, looking at other studies that maybe have done this successfully to just consider alternatives, would be worthwhile.

Are there any final comments from any of our panelists regarding this study question?

While I wait to do that scan of our members, I will just attempt to summarize that, again, the panelists have a strong preference not to endorse a repeat actual use study or ask the FDA to do that, which was beyond really the scope of this question but was expressed sincerely and frequently, so I

feel like it's important to reiterate that.

I think there are some elements of the study design around the e-diary, particularly maybe piloting a tool that would address some of the uncertainties that we're seeing in the existing study, maybe re-evaluating how best to compensate participants that's not required on a number of entries directly, and other ways to both inform use of the platform but also to help participants in asking for help when needed around use of the product or use of the e-diary itself.

I also want to acknowledge the comment that Dr. Catlin had made, and that was also supported by many of our panelists that it is a very delicate balance in having sufficient control to fully understand the results, but also not so much that you really interfere with the simulation of a real-world environment. I think the panel acknowledges those challenges and would, again, not necessarily favor being too restrictive or too controlling in the study design itself.

Not seeing other comments or others wishing

to speak, I'm going to move on to our discussion question number 3.

This question asks the panel to discuss whether there's sufficient information to conclude consumers in the following scenarios will appropriately deselect from norgestrel use; so consumers with a history or current diagnosis of breast cancer; consumers with abnormal vaginal bleeding of undiagnosed etiology; and consumers who are using other hormonal contraceptives.

I will begin by just asking the panel to first identify if there are any questions around the wording or language that needs to be clarified, and we'll pause for just a moment.

(No response.)

DR. COYLE: Seeing none, I will now open the floor for discussion.

Dr. Baron, please go ahead.

DR. BARON: Elma Baron. I think for letter A, for consumers with a history of or current diagnosis of breast cancer, we've heard that this is really the one contraindication. I

think I was reassured yesterday when Dr. Goodwin stated that the attitude of breast cancer patients -- and, of course, I'm not an oncologist -- is such that they are so preoccupied with not getting breast cancer again, so they will not be careless about taking anything that will cause a recurrence of the breast cancer. So I just wanted to make that moment. Thank you.

DR. COYLE: Thank you.

Dr. Armstrong, please share your comments, a particularly if they're focused on that sub-bullet A around the history of or diagnosis of breast cancer.

DR. ARMSTRONG: Yes. Thank you. This is Deb Armstrong. I just would echo what I think it was Dr. Baron just said, which is that women with breast cancer should or almost always are under the care of an oncologist and avoiding hormonal factors. Even in women with hormone receptor negative breast cancer, it's something that we really target, and I would think that any woman who had breast cancer diagnosis in the past or who has

currently active breast cancer would be highly aware of that. So I don't think that's going to be a concern.

Since I'm on, I would just ask with the bullet point B, if any of the gynecologists can talk about what's abnormal vaginal bleeding, particularly in an adolescent girl. Sometimes what we call abnormal might actually not be all that abnormal during adolescence.

DR. COYLE: Dr. Espey, do you have a response for Dr. Armstrong's question.

DR. ESPEY: Yes, I do. Eve Espey, University of New Mexico. That's a really good question. I think the major concern about abnormal vaginal bleeding of undiagnosed etiology is the concern about cancer, either cervical cancer or uterine cancer, both of which are extraordinarily rare, certainly in young people. But even in older women, it is unusual to have bleeding that would be made worse by by taking the medication.

The concern is, do you delay diagnosis of somebody who's got unscheduled bleeding, irregular

bleeding between periods, who might have endometrial hyperplasia, thickening of the lining of the uterus, or uterine cancer, because the patient is taking this birth control pill? That would be an unusual scenario, and the medication that we typically use to treat hyperplasia is progestin.

I'm not saying that it's an appropriate use of the medication to utilize it in the absence of an actual diagnosis of endometrial hyperplasia, but I think the safety concern about missing patients with this unexplained vaginal bleeding that actually have an endometrial cancer is very, very low. Abnormal vaginal bleeding, as was mentioned by I think both the sponsor and the FDA, is one of the most frequent reasons for visits by patients to women's healthcare providers, and typically, particularly in young people, is normal or at least not dangerous.

DR. COYLE: Thank you, Dr. Espey.

I think thus far we've heard from several of our panelists regarding the information provided

from clinical experience and their own training. I think the specific discussion question probably is intended to capture that, but also information from the applicant's packet, the data from the actual use study and the ACCESS study, and the additional analysis completed by the FDA.

So if there are any individuals on our panel who would like to speak to their interpretation of that data and whether the information contained therein is enough, either by itself or with clinical expertise added in, to further bring us to closure on this question, I would invite those now, especially anyone who maybe has not spoken or has thoughts that have not been shared.

(No response.)

DR. COYLE: So specifically, this really goes back to that self-selection question that was being addressed in the application, so we would invite your thoughts on that.

(No response.)

DR. COYLE: I can begin. Maria Coyle. I spent a few minutes this morning looking at this

side by side, between the FDA interpretation of the ACCESS data and then the sponsor's interpretation, and I think, for me, it was reassuring to have that reanalysis and to look at some of those sensitivity analyses. I felt that that information, although viewed through a slightly different lens, was overall quite confirmatory that patients who do not really meet criteria for OTC use of the norgestrel were largely not using it, to quite a large extent, maybe with the possible exception of limited literacy, where we don't necessarily know enough to draw conclusions.

Some by my read, I was fairly comfortable, especially given that there were multiple viewpoints represented.

Dr. Haun?

DR. HAUN: Thank you. I would like to echo your sentiments. I do think that the deselection data that was presented by the ACCESS trial team was compelling and supports that consumers with contraindications would not use the over-the-counter pill.

I could be mistaken on my recall, so I invite others to correct me, but I believe what I -- and if somebody has the ability to put up the slide, that would be very helpful. But as I recall, there were figures and I think maybe a table that presented that data that indicated that those thresholds for deselection were met. I don't know if we can show those to the committee again.

I was trying to find it in the slide deck while you were speaking, Dr. Coyle, and I was unable to find it myself, but if anyone else could present that slide, I think it might be helpful to the committee. I believe there was actually one based on limited literacy. I believe there may have been one for adolescents, and possibly even though it was the smaller -- the adolescents, I believe, had the smaller sample, but I do believe that was made available to us for viewing.

DR. COYLE: Yes. Dr. Horn, go ahead.

DR. HORN: We're going to try to pull up the slides. This is Pamela Horn, DNPD II. We're just looking for the --

DR. HAUN: Thank you.

DR. HORN: -- correct slide number.

Can you bring us to slide 105 of the FDA presentation?

(Pause.)

DR. HORN: We'll turn it back to the committee to continue discussing if this is the slide that Dr. Haun wanted.

(Pause.)

DR. COYLE: Dr. Horn, I think we're having a little bit of trouble hearing you here. I don't know if you could repeat that.

DR. HORN: Sorry. This is the slide that we think Dr. Haun was referring to. Can you just confirm? And please continue your discussion if this is what you were looking for.

DR. HAUN: This is Dr. Jolie Haun with James A. Haley Veterans' Hospital, University of Utah. I recall that the slide that you showed before this one showed that the thresholds were exceeded for those with limited literacy, and I don't know if the other committee members saw that,

but it was presented, though briefly, before this slide. Then, as I recall, this was a very small sample size, but it did give an indication of the data available.

I think, based on what I'm seeing here, this sample size is challenging for us to make any conclusive statements, but as one of our oncologists and colleagues mentioned previously, this is going to be a very rare event that women with breast cancer history would allow themselves to be without clinical advice, based on their current cancer diagnosis, opposed to needing a physician to promote or contraindicate the use of the birth control pill.

I believe that this data that's now represented on the slide provides conclusive and ample evidence that give us the ability to indicate that individuals that are adolescents and/or have low health literacy would deselect from the use. Thank you.

DR. COYLE: Sponsor, would you like to respond to that at all? I believe I saw your hand

up.

DR. LAURORA: Yes. We just wanted to show the slide that we believe was being requested.

DR. COYLE: So you're comfortable with this slide now that's been shared.

DR. LAURORA: Yes. Thank you.

DR. COYLE: Thank you.

And FDA, can I clarify, the slide that was up previously -- so this question is for FDA -- that was information that was really relevant to a previous version of the Drug Facts Label; so some adjustment has already been made in response to that?

DR. HORN: This is Pamela Horn, DNPD II.

DR. COYLE: I'm sorry. We can't hear you, Dr. Horn.

DR. HORN: Sorry. This is Pamela Horn, DNPD II. I'm going to let Barbara Cohen respond to that clarifying question.

MS. COHEN: This is Barbara Cohen, FDA. Correct. The label version that was used in the ACCESS study said "Do not use if you have any

cancer," and the current label says, "Do not use if you have or ever had breast cancer, and then ask a doctor before use if you had any cancer."

DR. COYLE: Thank you. I appreciate that clarification.

Dr. Berlan?

DR. BERLAN: Hi. Elise Berlan, Ohio State University, Nationwide Children's Hospital. Just to comment on your request for thoughts on the question in B, which is I'm looking at the FDA slide 175 around self-selection for abnormal vaginal bleeding and, to me, they found 34 participants reported unexplained vaginal bleeding before use. And this is the FDA slide. Twenty-seven percent did not report speaking to a healthcare provider, but the flip of that, to me, is 72 percent did report speaking to a healthcare provider and, to me, I am reassured about this, and I don't have additional concerns. And I've already spoken around concomitant use of hormonal contraceptives I think being clinically acceptable. Thank you.

DR. COYLE: Thank you.

Are there other comments from the panel regarding this discussion question? I'm doing a scan of our virtual room here to be sure I have not failed to recognize anyone.

Dr. Shaw?

DR. SHAW: This is just a quick clarification -- Pamela Shaw -- with regards to the label around vaginal bleeding. It's version H that's being proposed in the submission, but I just wanted clarity that those changes that included changes around vaginal bleeding, was that tested in any of those changes in H versus G, which was done in the targeted selection study? Were those changes evaluated or they're just newly submitted?

DR. COYLE: Dr. Horn, could you address that?

DR. HORN: This is Pamela Horn, DNPD II. I'm going to ask Barbara Cohen to respond.

MS. COHEN: This is Barbara Cohen. Yes, the change was evaluated.

DR. SHAW: Alright. Thank you very much for

clarifying my question. Thanks.

DR. COYLE: I don't see any further panelists who are requesting input, so I will do a brief summary, and then we'll let Dr. Horn speak and perhaps close us out here.

What I have heard is that in addition to just clinical experience, providing reassurance that the data as presented by either the sponsor and the FDA -- I guess presented from both perspectives -- seemed overall to be quite reassuring to panelists in that consumers with a history or diagnosis of breast cancer were not likely to be inadvertently or incorrectly selecting to take the norgestrel, and more likely was a scenario where a consumer might have abnormal vaginal bleeding, and in that case, there was less concern, given the data that was presented.

Dr. Horn, what would you like to add to this before we wrap up these discussion questions?

DR. HORN: Thank you, Dr. Coyle. I'm going to pass it to Dr. Murry.

DR. MURRY: Thank you. Karen Murry, deputy

director, Office of Nonprescription Drugs.

I just want to, first of all, thank the panel for all of their extremely useful input, and I just want to emphasize from the FDA that we really realize how important it is that U.S. women have increased access to effective contraception, and I don't want any of our discussion or our pointing out the deficiencies of the development program to take away from that message. We realize that it is extremely important, and we thank the panel for their many comments that had to do with their experience apart from their interpretation of what the study showed.

We do want to point out, though, that when a development program is proposed for a nonprescription drug, we can't just approve it based on the experience in the prescription setting without the applicant doing adequate studies to look at what's likely to happen in the nonprescription setting. And it would have been a much easier time for the agency if the applicant had submitted a development program and an actual

use study that were very easy to interpret and did not have so many challenges, but that was not what happened for us.

So the FDA has been put in a very difficult position of trying to determine whether it is likely that women will use this product safely and effectively in the nonprescription setting, but I wanted to, again, emphasize that FDA does realize how very important women's health is, and how important it is to try to increase access to effective contraception for U.S. women, and I'll close with that.

DR. COYLE: Thank you.

Ms. Rosetti [Robotti], would you like to make a comment?

(No response.)

DR. COYLE: I apologize. Ms. Robotti, would you like to make a comment?

MS. ROBOTTI: [Indiscernible - audio garbled].

DR. COYLE: Ms. Robotti, I'm sorry to interrupt, but I'm afraid we can't hear you. We

see to have some connection difficulties your audio.

MS. ROBOTTI: [Indiscernible].

(Pause.)

DR. COYLE: Ms. Robotti, would you like to try again?

MS. ROBOTTI: [Indiscernible].

DR. COYLE: I'm sorry. It's still not coming through. I apologize, but we aren't able to hear your comment.

MS. ROBOTTI: [Indiscernible].

DR. COYLE: Ms. Robotti, I'm afraid we can't understand that's coming through your audio, so we'll have to move on. I'm afraid you're having connection issues. I'm so sorry.

MS. ROBOTTI: Yes. Can you hear me?

DR. COYLE: We are not able to hear you. I'm sorry.

MS. ROBOTTI: Can you not hear me? [Indiscernible].

DR. COYLE: So unfortunately, we're going to have to move on with the agenda due to that

connection, and we're not able to recognize or understand what Ms. Robotti is sharing.

So at this point, I would like to summarize and take a look back at these three discussion questions. I think, overall, the panel is in favor of the norgestrel tablet being used in a safe and effective manner in both the general population and some subpopulations, based on the information presented by FDA and the sponsor, as well as a more broad clinical experience.

The panel was not in favor, particularly, of conducting another actual use study, but did have some recommendations around perhaps improving the methodology, particularly piloting use of an e-diary platform or an app that might be more sufficient to the needs of answering the study questions, and possibly providing some support to users of that platform during the study period, and then feeling comfortable with the information presented around deselection for those who may be inappropriate users of the norgestrel, particularly around the diagnosis or history of breast cancer or

vaginal bleeding, although that perhaps is more skewed by clinical experience rather than the data itself, but we did talk about both.

Can I ask, Dr. Horn, did did we address these questions sufficiently for FDA, or are there additional conversations or questions that you would like to pose for our consideration before we move on to the vote?

DR. HORN: This is Pamela Horn, DNPD II. Yes, the discussion was adequate, and thank you all for your contributions.

DR. COYLE: Thank you as well.

And just in summary, I guess I would also like to say I appreciate the challenge presented by this application, both the urgent need for access to oral contraceptives, not limited only to prescription access but also being true to the process that has served us well in the United States with OTC medications for these many, many years.

I just appreciate that position and the due diligence that everyone has shown in answering our

questions here on the panel and also the efforts of the public speakers yesterday, truly a remarkable discussion in my experience.

At this point, we're going to move on to the next question, which is a voting question, and Dr. Moon Hee Choi will provide the instructions for voting.

DR. CHOI: Question 4 is a voting question. If you are not a voting participant, you will be moved to a breakout room. Voting members will use the Zoom platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussions regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

A voting display will appear where you can submit your vote. There will be no discussion during the voting session. You will select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the

submit button, you will not be able to change our vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to; however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. CHOI: Thank you.

DR. COYLE: Dr. Choi, are we ready to proceed? Is everyone in the breakout?

MR. SWETT: I will now begin opening the

breakout rooms.

(Voting.)

DR. CHOI: Voting has closed and is now complete. After I read the results into the record, the chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to; however, you should also address any subparts of the voting question, if any.

For the record, we have 17 yes, zero no, and zero abstentions.

DR. COYLE: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to. And in fact, in this case, I would recommend that we do ask each individual to provide their own reasoning for the vote, and not just simply default to other reasons that have been given previously. For example, please do make sure each individual state why you

voted as you did, and give the specific reasoning so that we may fully understand the rationale behind this vote.

We'll start with Dr. Armstrong.

Dr. Armstrong?

DR. ARMSTRONG: Thank you. I voted yes. I feel that the risks of unintended pregnancy is lower with this approach than any of the other available contraceptive approaches that women have access to without seeing a healthcare provider. I believe that the contraindication to use issues I think will be well understood; thus, I voted yes.

I would also like to say that listening to the eloquent and intelligent informed and passionate individuals, who are mostly young and mostly women, who presented at the open public hearing restores my faith in the future.

DR. COYLE: Thank you.

Dr. Curtis?

DR. CURTIS: Kate Curtis, CDC. I voted yes, and I voted yes because the evidence demonstrates that the benefits clearly exceed the risks. The

benefits of moving Opill over the counter include increased access to contraception, especially those who face multiple barriers that we heard about yesterday; reduction in unintended pregnancy and associated risks and improved reproductive autonomy; and improved equitable access to contraception, which we've also heard about so passionately yesterday. So for all of these reasons, I think Opill has the potential to have a huge positive public health impact.

With respect to risks, for safety, safety was established 50 years ago when the original approval was made, and the accumulating body of evidence since then has shown that these pills are safe with very few contraindications and long-term safety concerns.

With effectiveness, effectiveness was also established a few years ago, and while the methods for assessing effectiveness and the population characteristics have changed over the years, all of the estimates that we heard about over the last two days fall somewhere between 2 and 4 per hundred,

which is much lower than any of the other over-the-counter products, and lower than the generally accepted typical use failure rate of 7 for oral contraceptives received in a prescription setting.

The large body of evidence on the safety and effectiveness is very reassuring. The data presented over the last two days from the applicant on comprehension of the label and actual use were also generally reassuring, even with the problems with the data. And even for the subgroups of younger adolescents and those with lower literacy, those were the two groups that did sometimes have some of the lower scores. Even for these groups, the risk of harm is low and the potential for benefit is high. So that's why I believe that the evidence demonstrates that the benefits exceed the risks. Thank you.

DR. COYLE: Thank you.

Dr. Baron?

DR. BARON: Elma Baron. I voted yes. I believe, first, when we were asked to serve in this

panel, we were asked to scrutinize the evidence, the data that was presented in this study, in this trial, and to take into consideration the risks and benefits of having this medication available as an over-the-counter pill, so I'd like to speak to the study first.

My concerns, number one, regarding the breast cancer patient who failed to deselect was what was most bothersome to me initially. As I've mentioned earlier, I think I have been reassured that this is not normal behavior of the breast cancer population. The number two concern that I had was the low representation of the low literacy population.

I think the explanation that the REALM method, the REALM assessment method, could under-detect the low literacy population, so there might actually be more than 14 percent, that's represented in this study, so that is reassuring to me. I still have questions, like most people, about the improbable dosing but, again, as a healthcare provider who lives weighing risks versus

benefits on a daily basis, I do think that in this situation, the benefits outweigh the risks. Thank you.

DR. COYLE: Thank you.

Ms. Everhart?

MS. EVERHART: Sabrina Everhart, patient representative. Thank you to the FDA for the opportunity to be part of this historical review. I did vote yes with adolescent recommendations. I agree that the efficacy and the safety profile has definitely withstood the test of time and that the DFL is appropriate for over the counter. I understand the need for more options and access to reproductive health. I believe the population would benefit from this product over the counter and could safely self-select.

However, I would like to say that I am reserved about the data in adolescent and limited literacy population and their ability to properly make medical choices for this product for themselves without guidance outside of the DFL leaflet. If FDA does not approve this over the

counter for these reasons, it could be a reason to consider behind-the-counter availability.

Also, with respect to public speaker number 35 -- and I'm sorry, I missed her name; she was a pharmacist -- I appreciated her input on the pharmacy role here, as I had a lot of questions regarding that particular topic that were answered, so I thank you for that.

My recommendation could be maybe a public awareness campaign by the sponsor designed specifically for the adolescent population. That falls within the over-the-counter regulations, so thank you to the FDA for clarifying those regulations.

Finally, I'd like to thank the public for their comments, as it's an important part of my decision process here as a patient representative. I feel like the lack of adolescent and limited literacy studies was my struggle here today, but you also urged us to follow the science. Thus, based on that data presented yesterday and today, my recommendation stands with over-the-counter

approval, with considerations for young adolescents or possible third-class considerations if denied by the FDA. Thank you again.

DR. COYLE: Thank you.

Dr. Roth?

DR. ROTH: Thank you for the opportunity to be on this panel. I agree with almost everything that everyone else has said, so I'm going to try not to repeat it too much. But I think the safety profile of oral contraceptives, since their inception and of the progesterone-only pills, were very well established, so I think that the public will be well served from a safety perspective.

The risks to women of an unintended pregnancy are much greater than any of the things we were discussing as risks of putting this pill out over the counter. The history of women's contraception is a struggle for women's control over their reproduction, and we need to trust women.

I think that the speakers yesterday, especially the younger speakers, really brought

home to all of us how much more we have to do to repair our broken health system and how poorly we have made access to healthcare available for so many young women, adolescents, and older women. To the extent that approving this pill to be available over the counter will go toward rectifying that, I think it's a very important move. So thank you very much, and I urge the FDA to approve the over-the-counter availability of Opill. Thank you.

DR. COYLE: Thank you, Dr. Roth. And can you just restate your vote for the record as well?

DR. ROTH: Sorry. I voted yes --

DR. COYLE: Thank you.

DR. ROTH: -- in favor of Opill's application to have over-the-counter permission to sell their drug. Thank you.

DR. COYLE: Thank you.

Dr. Espey?

DR. ESPEY: Thank you. I also really appreciate the opportunity to be on the panel. Eve Espey, University of New Mexico. I voted yes. I do believe there's adequate information, both

from the sponsor and from prior evidence, that consumers can use norgestrel safely and effectively. Understanding the methodological concerns, I do believe the sponsor has shown that the single absolute contraindication was well understood, and the track record of safety of POPs for the 30 years that it was on the market is well established. It would, therefore, I think take a very high bar of concern to justify non-approval of over-the-counter status, given what we know about this medication.

I also was very moved by the testimony of the public and agree with the strong endorsements of our major professional organizations. My personal experience practicing in a large rural state, New Mexico, over the last 30 years, I see it firsthand, people who face all of these barriers, and who also experience the maternal morbidity and mortality that goes along with unintended pregnancy that I think was really eloquently expressed by Dr. Glasier, and which is highly relevant to this conversation.

So from my perspective, despite the FDA concerns about the study design and differing interpretations of the studies, the overall very rare and unlikely harms are outweighed by the tremendous benefits of improved access without any restrictions. Thank you.

DR. COYLE: Thank you.

Dr. Berenson?

DR. BERENSON: I voted yes. I felt that both sides did an excellent job of presenting the data and the studies, and certainly gave us many issues to think about, especially with regard to the subpopulations. But overall, the data showed that Opill is safe and effective to offer women as an over-the-counter option, and the public comments were very strong in showing the support and the need for this change.

Access is an incredibly important issue to women, especially now, and making this change to over-the-counter hormonal contraception will improve access and allow women to use more effective methods. Thank you.

DR. COYLE: Thank you.

Dr. Pisarik?

DR. PISARIK: Paul Pisarik, and I voted yes also. I'm not as eloquent as the other speakers on this panel, but I feel the benefits of having a more reliable oral contraceptive outweigh any risks that might be involved in it. I am concerned a little bit about the subpopulations, those with limited literacy and adolescents. I'm sure it won't be as effective for them, but it will still be more effective than what's out there and available right now.

DR. COYLE: Thank you.

Maria Coyle. I also voted yes in support of the Rx-to-OTC switch for Opill, primarily because I think in the balance between benefit and risk, we have a hard time justifying not taking this action. The benefits are large. The drug is incredibly effective. I think it will be effective in the over-the-counter realm just as it is in the prescription realm, particularly given that there may be minimal education occurring currently, even

for prescription users of some of these medications, and that those populations of greatest concern -- those with a history of breast cancer or active breast cancer -- are already highly engaged in the healthcare system. I think the risk of the medication itself is incredibly low for the vast majority of users, and the risk of unintended pregnancy, while real, is less than that of existing over-the-counter methods of birth control.

Like many of the other panelists here today, I was incredibly moved by the public hearing comments, and I'm also particularly sensitive to the plight of the FDA having to follow a very stringent process to ensure high quality of our medication products, but also in the greater context of where is the greatest good. So on balance, I felt that the OTC switch served both the public, as well as my patients in my own practice settings the best; so I voted yes.

Dr. Berlan?

DR. BERLAN: Hi. Thank you. Elise Berlan, Ohio State University, Nationwide Children's

Hospital. I vote yes on making Opill available over the counter. From my perspective as an adolescent medicine pediatrician, I understand that barriers and access to contraceptives are real and very harmful, and amplified in adolescence. These inequities in access perpetuate inequities in communities for neonatal and obstetric morbidity and mortality, and also unfairly and unjustly distribute the benefits of contraceptive use.

We should also keep in mind that the health risk of pregnancy, which is the condition that these products seem to prevent, is much greater than the use of any contraceptive product, and this is among the safest of the contraceptive products. So given the evidence presented by the FDA and HRA Pharma, the sponsor, I believe that women and pregnancy capable people of all reproductive ages will safely and effectively use the Opill, and the potential benefits outweigh the risks of this product.

I also wanted to emphatically state that I do believe that adolescents will make good

decisions about their reproductive health, and we can trust teens to make these decisions. So I do recommend that the FDA make Opill available to reproductive age women of all ages without delay. Thank you.

DR. COYLE: Thank you.

Dr. Gass?

DR. GASS: My name is Margery Gass, and I can echo the comments of all the other speakers so far. I would just like to thank the FDA for considering this product for over-the-counter use. I think this represents a landmark in our history of women's health. Unwanted pregnancies can really derail a woman's life, and especially an adolescent's life, so I'm very pleased that the FDA is seriously considering this, and I look forward to it being on the market.

DR. COYLE: Dr. Catlin?

DR. CATLIN: Yes. Jesse Catlin, Cal State, Sacramento. I voted yes. The comments from the various clinical experts I think clearly indicate that the drug has a favorable safety profile and

strong public health benefits. Given my background as a marketing professor and consumer behavior researcher, I focused a lot of my attention on the consumer studies, and certainly while there was some very valid concerns, I believe the limitations of the studies were acknowledged and subject to a very thoughtful analysis by both the sponsor and the FDA.

So taken together with the methodological trade-offs that we know exist in these studies, I think that the results are sufficient to convince me that the benefits of the switch outweigh the risks. I'd also like to say that I'm hopeful that if the FDA approves the switch, that the presence of an OTC oral contraceptive will lead to improved public knowledge about these products, and that this should have a compounding positive impact on consumers' ability to use these products safely and effectively, that goes well beyond what we even see here today.

DR. COYLE: Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. Can you hear me?

DR. COYLE: Yes.

MS. ROBOTTI: Great.

I voted in favor of moving the product from Rx to OTC. I support having sponsoring companies meet or exceed the standards set by the FDA; however, that often doesn't happen in these advisory committees because of mitigating circumstances.

The comprehension for primary selection, deselection, and purchase decisions came out pretty well. The areas in which the research seems short have to do with actual use after purchase. I say it seems short because we have no research to which we can compare the data. We have no proof that women received complete counseling when prescribed, or that they are in a situation where they feel comfortable asking questions. We have no way of knowing that they are better or worse in actual use.

I believe it was Dr. Glasier who offered two

studies that support imperfect compliance, pharmaceutically, in prescribed oral pills compliance, even with reminders. We also know there are a lot more unintended pregnancies than expected if oral contraceptives were consistently used appropriately.

The comment I could not make earlier due to a tech problem was, in response to the FDA comment that the sponsor's ACCESS data was not of a quality that they wanted, even if we had perfect data, without context, is it really useful? How to interpret the data with appropriate targets supported by research was not there. Is anyone here really comfortable with research that has no control group or comparison study? So that was a little bit doomed, I feel, from the start. I believe that is a mitigating factor, and the reason that the uncertain results of the ACCESS study should not impede approval.

In terms of safety, the standards for approving the Opill would be different today, yes, but that is true for many drugs, including other

oral contraceptives. I'm not sure why the FDA brought that issue up in their presentation when it's not a topic for conversation in this group, in this meeting. I found the selecting and deselecting results to be acceptable.

Access is the most important issue. I was struck by the sponsor's chart on OTC birth control methods versus prescription options. The methods available OTC are less effective. They need participation by both partners and, frankly, they also need explanation, and even practice, to use appropriately. The Opill use instructions are no more difficult to understand and apply than the products available by OTC, and the Opill is much more effective.

Pregnancy is a dangerous, physical risk in America and should be a choice, not a trap. POPs are more effective than other products offered OTC. More women are likely to be harmed by an unplanned pregnancy and unwanted pregnancy than by the side effects of POP. So once again, I support the transfer to OTC. Thank you.

DR. COYLE: Thank you.

Dr. Baur?

DR. BAUR: Cynthia Baur. I voted yes. We heard a lot about the drug itself over the last day and a half. The FDA team asked us to think about this, really, as a risk communication challenge, though, and as a director of a center focused on health literacy, of course I was very interested in the comprehension data and the extent to which comprehension transferred into actions.

So do I think that we got perfect data? No. Do I think it was a perfect study? No. Do I think it was adequate to feel reassured that a large number of people can use this drug as intended? Yes. I would encourage, however, the FDA to continue to raise the bar and continue to ask sponsors to bring in better data about comprehension.

I do want to note that while it is admirable that FDA is focused on limited literacy as one of the special populations, limited literacy and limited health literacy are not the same, and it

would be really important in future studies to make sure that sponsors are very clear on which populations they're including, and which measures they're using, and what kind of data they're providing.

So overall, I do think as a risk communication situation, the benefits outweigh the risks, and that's why I voted yes. Thank you.

DR. COYLE: Thank you.

Dr. Shaw?

DR. SHAW: Hello. Pamela Shaw, and I also voted yes. I think that the benefits outweigh the risks, given the overall safety profiles of the drug, and good levels of self-selection and deselection, particularly for the breast cancer survivors. I acknowledge there were some concerns due to some vulnerable subgroups -- the low literacy, the very young adolescents -- regarding comprehension and whether or not they understood how to use the drug effectively, but I feel like the concerns related to lack of access and the consequences there outweighed the concerns pointed

out by some of the low literacy challenges on certain questions.

I would like to acknowledge that the difficult position the FDA was put in by the compromised actual use study, and I think if the interest of women could be served by getting more data, or the FDA feels like they need more data, I hope it could be done in a way that was concurrent with approval and did not slow access to this drug, because I think, overall -- and the public statements, really, I think helped put this in perspective. In terms of the risks we're weighing here, I think the benefits do largely outweigh any risks. Thank you.

DR. COYLE: Thank you.

Dr. Haun?

DR. HAUN: Thank you. I, Jolie Haun, vote yes in support of the approval for the over-the-counter use for the Opill medication, birth control. I believe that the efficacy and safety of this birth control form was established over half a century ago, and we now have been

presented with ample data presenting and demonstrating the effective safe use and benefits of this medication for the people who want to have access to reproductive autonomy.

I do appreciate the scrutiny of the FDA board, and I understand that all studies can be improved upon, and knowledge base can always be advanced through further investigation. However, based on what we have available to us at this time, the benefit of Opill being available to diverse populations, including adolescents and those with limited literacy, is in demand, and we do have the data that reflects the ability to make this medication and birth control pill available over the counter. We can take this opportunity to increase access, reduce disparities, and most importantly, increase the reproductive autonomy of the women of our nation. I vote yes. Thank you for your time.

DR. COYLE: Thank you.

And Dr. Walker-Harding?

DR. WALKER-HARDING: Hi. Thank you. I

voted yes, and some of the reasoning is I do think even though this study had limitations, I'd be hard-pressed to find a study that won't have limitations, considering how it needs to be conducted to get some resemblance of real-world use.

I found that what we did find, even with the limitations, was very reassuring; that this safe and effective medication can be used by all ages, in particular adolescents and those with limited literacy. And with the knowledge that adolescents, even young adolescents, make the same decisions that adults make with medical information given to them, I see no reason to single them out to not have it available, even for the youngest adolescents, especially given adolescents have the lowest risk profile, again, given breast cancer is the only contraindication to taking this medication, and that is exceptionally rare in the adolescent age group.

Also, there's no evidence that the risk of using the medication properly is better managed

with having a medical professional there. There's no evidence of that. And what we do see really affirms that the use is very similar to what we know has happened in the past with prescription medication real use -- with oral contraceptive prescription use. So I see no reason to withhold this for even the youngest adolescents who can assess when they need that and use it appropriately. And if they don't use it appropriately, the safety profile is such that there is very little to no risk with that.

I also think it's very telling that public speaking providers and those here on the voting panel who care for adolescents and other women who have this need for contraceptives do not want to be a barrier to this, and do not want to have to be the ones that are withholding a needed medication for women and there's low access. And knowing that you are the barrier to a young person being able to make a decision about their body is very upsetting.

I really hope that we can get this approved and over the counter as soon as possible so that

more people aren't harmed by the lack of ability to make a decision on what they want to do with their body. Thank you.

DR. COYLE: Thank you.

Thank you to all the panelists, and just to summarize, we have a unanimous vote of our 17 voting members today to recommend the applicant's proposal to switch Opill from Rx to OTC status.

Before we adjourn, are there any last comments from FDA?

DR. HORN: Pamela Horn, DNPD II director. I just want to thank the panel so much for all of your careful consideration of the data, and for taking the time to explain your vote carefully to us. We paid very careful attention, and we appreciate the time you spent reviewing this application and giving us the expert advice that we wanted from the meeting, so thank you all.

Adjournment

DR. COYLE: Thank you, Dr. Horn, and I would would just echo the time and attention each of the

panelists has given over the last few days, even tolerating some of our overruns on the agenda to make sure that everyone was heard, including all of the members of the public who were advocating so strongly on their own behalf and others' behalf yesterday. I also want to thank the sponsor and the FDA for putting such preparation and thoughtful care into preparing the materials for us to consider, as it certainly is a lot of data, and those multiple viewpoints were much appreciated as we considered both the FDA's questions, but also the overall context of this switch to OTC that we were weighing in on.

So given that, I will thank you all one final time and now adjourn the meeting. Take care.

(Whereupon, at 1:48 p.m., the meeting was adjourned.)