FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT AND ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEES

Open Session

Thursday, May 5, 2016

9:15 a.m. to 4:20 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:15 a.m.)

Call to Order

Introduction of Committees

DR. BROWN: Good morning. I would like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would like to also identify our press contact, Sarah Peddicord.

Sarah? Hi, how are you doing? She's in the back.

My name is Ray Brown. I'm the acting chair of the Anesthetic and Analgesic Drug Products Advisory Committee. I'll be chairing this meeting. I'll now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order.

We'll start by going around the table and introduce ourselves. Let's start on the left with the FDA.

DR. HERTZ: Sharon Hertz, division director

for the Division of Anesthesia, Analgesia, and Addiction Products.

DR. FIELDS: I'm Ellen Fields, deputy director of the same division.

DR. STAFFA: Good morning. Judy Staffa, acting associate director for public health initiatives, Office of Surveillance and Epidemiology, CDER.

DR. KLEIN: Michael Klein, director of controlled substance staff.

DR. TYLER: Linda Tyler, chief pharmacy officer, University of Utah Hospitals and Clinics.

MS. SHAW PHILLIPS: Good morning. Marjorie Shaw Phillips, Augusta University Medical Center and University of Georgia College of Pharmacy.

DR. GUPTA: Dr. Anita Gupta, vice chair of anesthesiology at Drexel University College of Medicine. I'm an anesthesiologist and pharmacist.

DR. BATEMAN: Brian Bateman. I'm an anesthesiologist at Massachusetts General Hospital, Harvard Medical School.

DR. STERGACHIS: Andy Stergachis, professor

of pharmacy and global health and associate dean, University of Washington.

DR. MORRATO: Good morning. Elaine Morrato, an epidemiologist at the Colorado School of Public Health and associate dean for public health practice.

DR. SHOBEN: I'm Abi Shoben. I'm a biostatistician at the Ohio State University.

DR. CRAIG: David Craig, Moffitt Cancer Center, Tampa, Florida.

LCDR BEGANSKY: I'm Stephanie Begansky, the designated federal officer for today's meeting.

DR. BROWN: I'm Ray Brown. I'm a pediatric anesthesiologist at the University of Kentucky.

DR. PERRONE: Good morning. I'm Jeanmarie Perrone. I'm an emergency physician and the Director of medical toxicology at the University of Pennsylvania.

DR. EMALA: Charles Emala. I'm an anesthesiologist, vice chair for research, Columbia University in New York.

DR. KAYE: Good morning. Alan Kaye. I'm a

pharmacologist, anesthesiologist, and pain expert, and chairman of anesthesia at LSU School of Medicine in New Orleans.

DR. CAMPOPIANO: I'm Melinda Campopiano, medical officer and branch chief for regulatory programs at the Center for Substance Abuse Treatment at the Substance Abuse Mental Health Service Administration.

DR. HALL: I'm James Hall, epidemiologist, Nova Southeastern University in South Florida.

MR. O'BRIEN: Joe O'Brien, patient representative and president, CEO, and patient at the National Scoliosis Foundation.

DR. HIGGINS: Jennifer Higgins, consumer representative.

DR. GERHARD: Tobias Gerhard, pharmacoepidemiologist, associate professor of pharmacy at Rutgers University.

DR. MICHNA: Ed Michna, a pain physician at Brigham and Women's Hospital in Boston.

DR. DONOVAN: Maureen Donovan, associate dean and professor of pharmaceutics, College of

Pharmacy, University of Iowa.

DR. ISRAEL: Heidi Israel, associate professor at Saint Louis University School of Medicine.

MR. HERRING: Good morning. I'm William Herring, a neurologist employed by Merck, industry representative.

DR. BROWN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a 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 topic during breaks or lunch. Thank you.

Now, I'll pass it to Lieutenant Commander, Stephanie Begansky, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR BEGANSKY: Thank you. The Food and Drug Administration is convening today's joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

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 these committees' 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 the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's

meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 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 New Drug Application 208653, benzhydrocodone and acetaminophen oral tablets submitted by KemPharm with the proposed indication of short-term up-to-14 days management of acute pain.

The product has been formulated with the intent to provide abuse-deterrent properties. Benzhydrocodone is a hydrocodone prodrug, which, according to the applicant, is rapidly converted into hydrocodone by enzymes in the gastrointestinal tract. The active drugs in this fixed-dose combination are hydrocodone and acetaminophen.

The applicant has submitted data to support abuse-deterrent properties for this product. The committees will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling and whether the nasal route of abuse is relevant for combination products made up of hydrocodone and acetaminophen.

This is a particular matters meeting during which specific matters related to KemPharm's NDA 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. Joseph Herring and Dr. Linda Scarazzini are

participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Herring is employed by Merck and Dr. Scarazzini is employed by AbbVie.

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 they may have with the firm at issue. Thank you.

DR. BROWN: We will now proceed with the FDA's introductory remarks from Dr. Ellen Fields.

FDA Introductory Remarks - Ellen Fields

DR. FIELDS: Good morning, Dr. Brown,

members of the Anesthesia and Analgesia Drugs Advisory Committee, members of the Drug Safety and Risk Management Advisory Committee, and invited guests. Thank you for joining us today. Many of you have been here for the previous two days for the REMS AC, and some are here for the first time today. We sincerely thank all of you for spending your valuable time assisting us with these important issues.

Today, we will be discussing an application from KemPharm for a new immediate-release formulation of benzhydrocodone and acetaminophen with the proposed trade name, Apadaz, which is intended for the short-term management of acute pain.

Benzhydrocodone, known as KP201 during development, is a prodrug of hydrocodone and is intended to be converted into hydrocodone by enzymes in the gastrointestinal tract. The applicant maintains that this requirement for conversion in the GI tract can modify the pharmacokinetic profile and decrease the exposure

to the active drug, hydrocodone, when taken by the nasal or intravenous routes of administration for the purpose of abuse.

The reason for bringing this NDA to an advisory committee meeting today is to ascertain whether the applicant has demonstrated abuse-deterrent properties for their product, whether these properties are relevant to the public health, and whether the benefits of Apadaz outweigh its risks.

During this meeting, you will hear presentations from KemPharm and FDA on the studies conducted by the applicant to demonstrate abuse-deterrent properties of Apadaz. You will also hear presentations regarding the epidemiology of the routes of abuse for hydrocodone/acetaminophen combination products, specifically regarding the relevance of the intranasal route of abuse for these products.

We are aware of the immense public health problem that exists in the United States today from the abuse of prescription opioids. As part of a

larger effort across HHS, we at FDA have encouraged drug companies to develop novel interventions to reduce or, when possible, prevent this abuse. To this end, we have supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community.

In April 2015, we issued the guidance for industry abuse-deterrent opioids, which explains the agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how these studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

In response to the growing epidemic of opioid abuse, dependence and overdose in the United States, the commissioner announced an opioid action plan in February of this year to take steps toward reducing the impact of opioid abuse on the public health.

As part of this plan, the agency has committed to work more closely with its advisory committees before making critical product and labeling decisions. And as you may know, we are calling on all of you more often to fulfill this goal.

As we work to make opioid analgesics less desirable targets for abuse, we cannot forget that the underlying purpose of these opioid analgesics is the management of pain in patients for which other alternatives are inadequate and opioids remain an important component of pain management.

The greater amount of opioid available in many extended-release opioid analgesics relative to immediate-release products is associated with greater risk for overdose and death but also makes these a desirable target for those seeking to abuse opioids. However, immediate-release opioids are also abused, and the development of abuse-deterrent immediate-release formulations that can reduce abuse is also an important public health goal.

While the most common route of abuse for

opioids is oral, the risk for infection and overdose associated with intravenous and nasal routes make these routes of abuse important targets for abuse-deterrent properties.

With every new product, we weigh risks and benefits. With new abuse-deterrent formulations, we are also watchful for any evidence that the product results in a new or increased safety risk for patients who take the product as directed, as discussed at an advisory committee meeting last September, and for any evidence that by deterring abuse by one route of administration, the new product may shift abuse to a riskier route of administration; for example, deterring oral abuse but inadvertently making nasal or intravenous abuse more attractive.

There are currently six approved extended-release opioid products with abuse-deterrent properties, and we are watching the postmarketing data closely for any signs of unintended problems associated with these products. If it is approved with abuse-deterrent language in

the label, Apadaz would be the first immediate-release opioid analgesic with such labeling.

Today, you will be asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling.

In addition, you will be asked to discuss whether the nasal route of abuse is relevant for Apadaz and products that contain hydrocodone and acetaminophen as active ingredients, as this pertains to the applicant's claim for their product representing a benefit over hydrocodone/acetaminophen products. And finally, you will be asked whether the benefits of Apadaz outweigh its risks and whether it should be approved.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience, and your best insights in order to help us find a reasonable and responsible path forward.

Your advice and recommendations will be

essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us and look forward to this important discussion.

DR. BROWN: Thank you, Dr. Fields.

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, 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 presentation, it will not preclude you from speaking.

We will now proceed with KemPharm's presentations.

Applicant Presentation - Travis Mickle

DR. MICKLE: Good morning. I'm Travis Mickle, and I'm the co-Founder and chief executive officer of KemPharm. I'd like to thank the FDA and the members of the advisory committee for your time in reviewing the data on Apadaz, our abuse-deterrent hydrocodone immediate-release combination product.

Apadaz is composed of benzhydrocodone hydrochloride, which is also known as KP201, a prodrug of hydrocodone and benzoic acid with acetaminophen. Each tablet of Apadaz contains 6.67 milligrams of the prodrug, which is equivalent to 7.5 milligrams of hydrocodone bitartrate, as well as 325 milligrams of acetaminophen.

Similar to other approved immediate-release

hydrocodone combination products, Apadaz is meant to be taken every 4 to 6 hours for the treatment of acute pain.

Historically, the development of opioids with abuse-deterrent features have focused on agonist/antagonist combinations, aversive agents, and formulations with physical or chemical barriers, including hard-to-crush tablets or formulations with gelling agents.

These opioids impart their abuse-deterrents by adding ingredients to the formulation, unlike naltrexone, that are not necessary for analgesia and have potential to lead to adverse effects.

As a prodrug, Apadaz is different. The abuse-deterrent properties are conferred at the molecular level by adding a naturally occurring substance to hydrocodone. Crushing or grinding has no effect on the release profile of Apadaz. Unlike other abuse-deterrent approaches, our prodrug does not affect analgesia and comes at no additional risk to patients.

Let me describe how the prodrug approach to

abuse deterrence with Apadaz works in more detail. The prodrug is a new molecular entity formed by a covalent bond between hydrocodone, the active opioid, and benzoic acid, the ligand. The prodrug itself is inert and does not bind effectively to opioid receptors.

When taken orally, as intended, Apadaz is rapidly metabolized by esterases in the intestinal tract, which allows that active hydrocodone to bind to opioid receptors and deliver effective analgesia. And while abuse-deterrent properties are important in the context of public health, these features do not pose any additional risk to a patient being treated for pain.

Our clinical pharmacology program has shown that the abuse-deterrent features of Apadaz will be transparent to patients.

Apadaz was bioequivalent to the listed referenced drugs and met the requirements of the 505(b)(2) pathway. It was also bioequivalent to the clinically relevant comparator, Norco, an immediate-release hydrocodone/acetaminophen

combination product like Vicodin, Lorcet, and Lortab.

We found no clinically significant effect of food with Apadaz on bioavailability of hydrocodone or acetaminophen. Furthermore, there was no systemic exposure to the prodrug when taken orally because it's very rapidly converted to hydrocodone in the intestinal tract.

As expected for two products that are bioequivalent, there was a similar incidence of adverse events. The most commonly reported adverse events were consistent with what we expect to see in opioid studies, including nausea, drowsiness, and constipation.

Because Apadaz was designed to bioequivalent to currently available immediate-release hydrocodone combination products, it was not designed to provide barriers against oral abuse by overconsumption. So as expected, the oral drug-liking scores for Apadaz and Norco were similar.

Apadaz was designed to deter non-oral routes

of abuse of hydrocodone combination products. Snorting Apadaz led to lower hydrocodone exposures and lower drug liking at early time points compared to Norco. In fact, snorting Apadaz provides either similar or lower drug liking than simply taking Apadaz orally. This is important because abusers won't receive the reinforcement of faster or greater highs. Adverse nasal effects from snorting were also more common and more severe with Apadaz compared to Norco.

Apadaz will deter abuse by the IV route because it cannot be effectively extracted for IV injection and because the prodrug converts slowly to hydrocodone in blood. And finally, smoking or vaporizing Apadaz does not release any hydrocodone.

With this background in mind, I'll review the agenda for our presentation. Dr. Jeff Gudin, a pain and addiction expert, will share his clinical perspective on the topic of today's meeting. I will return to discuss the Apadaz development program and the results of our tampering studies.

Dr. Lynn Webster, vice president of

scientific affairs at PRA Health Sciences, will present the results of our clinical abuse-deterrent studies, then I will outline KemPharm's plans for postmarket surveillance and postmarket studies. And Dr. Gudin will conclude the presentation with a discussion on the benefit-risk of Apadaz.

Experts from Inflexxion are also available to answer any questions you may have on our epidemiology data. All of our external experts have been compensated for their time and travel expenses.

I'll now turn the presentation to Dr. Gudin.

Applicant Presentation - Jeffrey Gudin

DR. GUDIN: Good morning. My name is Jeff Gudin. I'm director of pain management and palliative care at the Englewood Hospital and Medical Center in New Jersey and clinical instructor of anesthesiology at the Icahn School of Medicine at Mount Sinai.

My board certifications include anesthesiology, pain medicine, addiction medicine, and hospice and palliative care medicine. My

clinical responsibilities include the treatment of patients with pain and addiction disorders. I've published on safe prescribing and appropriate risk management related to opioid analgesics, and I've devoted my career to educating clinicians on strategies to address opioid abuse.

The FDA and other federal agencies have led the effort to reduce opioid misuse and abuse. One central part of that effort, as highlighted in a recent FDA editorial published in the New England Journal of Medicine, has been encouraging the development of abuse-deterrent formulations.

The Center for Drug Evaluation and Research has said that bringing abuse-deterrent opioids to the market is a priority for the FDA and that the agency looks forward to a time when the majority of opioids on the market have abuse-deterrent properties.

We've made some progress in abuse-deterrent technology. As you heard this morning, there are currently six FDA-approved abuse-deterrent extended-release opioids.

Abuse deterrence suggests that a medication has been developed in line with FDA guidelines to exhibit properties that could lower, but not totally eliminate, the ability to abuse the formulation. These properties make some routes of abuse like crushing, snorting or injecting either more difficult or less rewarding.

None of these abuse-deterrent products can eliminate the most common route of abuse, oral abuse by overconsumption. Although doctors understand that these formulations are not abuse-proof, we know that they play an important role in combating the epidemic. Unfortunately, as of yet, there are currently no approved immediate-release products that are labeled with abuse-deterrent properties.

In 2015, there were over 90 million dispensed prescriptions of hydrocodone combination products, which are the most commonly prescribed opioids in the United States. It's, therefore, not surprising that hydrocodone is often the first opioid an individual abuses. An abuse-deterrent

formulation of hydrocodone may play a role in preventing the escalation and progression of opioid abuse, especially at early stages.

We know from epidemiologic research, as well as clinical experience, that opioid abusers usually start by abusing opioids orally with products like hydrocodone combinations. As tolerance develops and their addiction progresses, it becomes more and more expensive to maintain their abuse habits.

Now, what happens next is critical. They start to experiment with more potent opioids or move to more dangerous routes of administration such as snorting, smoking, and injecting in order to maintain their high or to get high faster with less opioid, altering the route offers both euphoric and financial incentives to the abuser.

The majority of information we have on abuse of hydrocodone combinations comes from surveillance data collected from drug treatment centers. We all recognize that the data generated from these surveillance systems are not generalizable to the entire population of abusers.

For example, most recreational abusers have never been admitted for drug treatment or presented to an emergency room, so these individuals would not be captured by those databases. However, drug surveillance does offer us a window into the extent of abuse and the routes of abuse of opioid products.

We know from surveillance data that hydrocodone combination products are widely abused. This figure shows the rate of abuse over the last 30 days among adults being evaluated for drug treatment. The blue bar represents hydrocodone immediate-release combination products, orange bars represent immediate-release oxycodone products, and the green bars represent extended-release or long-acting opioids.

Drug abuse surveillance data can also give us a picture of how these products are being abused and who is abusing them. This slide shows the rates and routes of hydrocodone abuse in the last 30 days among people being evaluated for drug treatment. Adults are shown in yellow and

adolescents in red.

As with most opioid products, oral abuse was the most common. The second most common route was by snorting, which was reported by about 1 in 4 adult hydrocodone abusers and nearly 1 in 2 adolescent hydrocodone abusers. This surveillance data didn't come as a surprise to me. They simply illustrate what everyone involved in treating opioid addiction has known for years; many recreational abusers and addicts snort hydrocodone.

One of the questions that the FDA has posed to you today is whether snorting is a relevant route of abuse of hydrocodone immediate-release products. As someone who has treated pain and addiction for over 20 years, the answer to this question is clearly, yes.

Another important perspective comes from a survey of opioid abusers who actively participate on internet drug abuse forums. This 2015 survey was conducted in order to understand how and when abusers began abusing opioids.

The survey found that 3 out of every 4

abusers said that hydrocodone combination products were the first opioid they ever abused, and 2 out of every 3 reported their first abuse of hydrocodone combination products was before the age of 18. These are important findings because early experimentation can have an enormous impact on later risk for drug abuse, as well as related psychiatric conditions.

While abuse-deterrent formulations are one important component of the response to the opioid abuse crisis, it's important to recognize abuse-deterrent formulations are just that, one component.

An effective strategy at reducing abuse needs to be comprehensive. It's also critical to understand that no abuse-deterrent formulation can be abuse-proof, and that's because these products especially must deliver rapid and effective pain relief to the patients who need them like those with acute pain.

Although non-opioid strategies may help, opioids are one of the few, if not the only class

of drug, effective for severe pain. Considering that there are 90 million prescriptions for hydrocodone combinations annually, and the fact that so many people start abusing these products as children and teenagers, highlights the need for a hydrocodone product with features to interrupt and deter the progression of abuse at its early as possible stage.

Thank you for your time. I'll now turn the presentation back to Dr. Mickle.

Applicant Presentation - Travis Mickle

DR. MICKLE: Thank you, Dr. Gudin.

In order to characterize the abuse-deterrent properties of Apadaz, KemPharm followed the FDA guidance on the development and evaluation of abuse-deterrent opioids. Our abuse-deterrent studies correspond to the three categories outlined in the FDA guidance.

Category 1 refers to laboratory-based in vitro manipulation and extraction studies. Because Apadaz is a prodrug, grinding and crushing the tablet has no impact on its release profile, so

there was no need to conduct a thorough evaluation of physical barriers. However, as a prodrug, we went above and beyond what is required by the guidance because we wanted to evaluate the potential of advanced methods to break the covalent bond through hydrolysis to extract hydrocodone.

Category 2 studies assess the pharmacokinetics of oral overconsumption and intranasal abuse, and Category 3 studies evaluate pharmacodynamics and human abuse potential among recreational opioid abusers.

In each of these studies, we compared Apadaz to a relevant comparator, which was either Norco or a generic equivalent. For the purposes of this presentation, we'll refer to all the comparators as Norco. We'll start with our Category 1 studies.

The rationale for the Category 1 tampering studies of an immediate-release hydrocodone combination product like Apadaz is to understand how abusers might manipulate the product to maximize its abusability. Abusers would want to remove the acetaminophen and isolate the

hydrocodone for several reasons depending on the route of abuse. These include trying to avoid the risk of liver toxicity, reducing the volume of powder to snort, preparing the drug for injection, or getting the drug ready to freebase or smoke.

The goal of an abuse-deterrent formulation is to make manipulation of the product for abuse more difficult and thus less attractive to abusers. Because all abuse-deterrent products need to bioavailable to treat pain, no product can be abuse-proof. However, the willingness of an abuser to manipulate a product is a matter of how much time and effort it takes to get the opioid in an abusable form.

In our extraction studies, we used a variety of ingestible solvents and also non-ingestible solvents that an abuser might use. Five of these we considered common ingestible solvents, and we tested both Apadaz and Norco for up to 24 hours.

The Y-axis on this slide shows the maximum percentage of hydrocodone extracted in up to 24 hours from Apadaz and Norco. As you can see,

hydrocodone was almost completely extracted from Norco for these ingestible solvents often reaching peak extraction in a matter of just a few minutes while none were able to extract hydrocodone from Apadaz through 24 hours.

The next step might be to try advanced solvents that are not ingestible. Most of the advanced solvents were able to extract an appreciable amount of hydrocodone from Norco, though this is probably irrelevant because full extraction can be achieved with ingestible solvents. The important point here is that none of the advanced solvents were able to extract hydrocodone from Apadaz.

Another way that abusers might try to extract would be with advanced buffers of varying pHs. In these experiments, one buffer was able to extract 37 percent of hydrocodone from Apadaz, but this product had an extreme pH that could not be ingested, and it took 6 hours to achieve this limited extraction.

We also examined many of the same solvents I

just reviewed with heating and continuous agitation to see whether it would increase the amount of hydrocodone extracted from Apadaz or accelerate the release. Sixteen solvents were not effective at extracting any hydrocodone. Approximately 50 to 60 percent of hydrocodone could be extracted with 4 of the solvents, but it took 4 to 24 hours. Time and complexity serves as an abuse-deterrent feature here.

As a prodrug, the covalent bond between benzoic acid and hydrocodone has to be broken to release hydrocodone. Hydrolysis experiments focused on evaluation of strong acids and weak to strong bases at various temperatures.

For the sake of time, I won't be covering the results of our hydrolysis experiments in great detail. The results were submitted to the FDA and included in the briefing materials for this meeting.

While these studies were necessary to test Apadaz to the limit, these experiments frequently used dangerous chemicals with extreme modifications

to temperatures over several hours.

Even though the experimental conditions were very extreme, fewer than 20 percent of all samples tested released more than half of hydrocodone from Apadaz. Hydrolysis occurred only under specific conditions related to pH with temperature modifications over an extended period of time.

If an abuser were to conduct an effective hydrolysis, considerable additional work would still lie ahead for them in order to obtain abusable hydrocodone since all of these mixtures were not ingestible.

Next, I'll turn to the route-specific manipulations where we evaluated how an abuser might prepare Apadaz or Norco for injection or smoking. I'll start with injection where we assess the feasibility of using several of the most common ways that abusers extract hydrocodone and prepare aqueous solutions for injection.

We evaluated 164 conditions that an abuser might use to prepare Norco and Apadaz for injection. Thirty-nine of the conditions yielded

more than 70 percent of hydrocodone from Norco while only one condition yielded more than 70 percent of benzhydrocodone from Apadaz.

Apadaz was not designed to resist syringeability. Therefore, the ability to get solutions derived from Apadaz or Norco into a syringe were similar. One of the abuse-deterrent properties of Apadaz against IV injection came from the fact that the inactive prodrug can only be inefficiently extracted and filtered, and no active hydrocodone can be extracted.

As I mentioned earlier, the common extraction technique reported on drug abuse forums for small volume extraction to prepare for injection was much less effective for Apadaz. The technique was effective at removing over 80 percent of the acetaminophen from both products. If an abuser attempted this technique with Apadaz, only 36 percent of the inactive prodrug would have been extracted. If an abuser attempted the same technique with Norco, nearly 70 percent of the hydrocodone would be extracted.

The resulting IV solutions after filtering were still hazy to cloudy. The cloudiness was likely due to the presence of undissolved excipients and acetaminophen because we know that both hydrocodone and benzhydrocodone are soluble at these concentrations.

The reason an abuser injects drugs such as cocaine and heroin is to bypass first-pass metabolism so that the opioid will reach the brain more quickly. While injected hydrocodone can bind immediately to opioid receptors in the brain, we wanted to determine how quickly benzhydrocodone breaks down into hydrocodone in blood.

In vitro experiments evaluating the stability of the Apadaz prodrug when injected in human blood have shown that the prodrug has a slower rate of conversion to active hydrocodone than simply taking the product orally. These data illustrate that benzhydrocodone converts to hydrocodone much more rapidly in intestinal fluid than in whole blood.

So overall, Apadaz can be expected to deter

abuse by the intravenous route due to the slow conversion to active hydrocodone in blood and the inefficiencies of preparing it for injection.

We also conducted a series of experiments looking at smoking. These experiments show that freebasing Apadaz was not possible. Vaporizing or smoking Apadaz or benzhydrocodone at any temperature did not produce any hydrocodone.

To summarize, our Category 1 studies have demonstrated that Apadaz provides substantial barriers against manipulations for the purpose of abuse. Most of the commonly ingestible solvents extracted nearly all of the hydrocodone from Norco in just a few minutes.

On the other hand, no active hydrocodone could be extracted from Apadaz from the common ingestible solvents at all time points up to 24 hours. Only advanced solvents and buffers could extract considerable hydrocodone but typically required applying heat over several hours.

For the route-specific manipulations, we found that preparing Apadaz for IV injection was

less efficient than Norco and that prodrug converts only slowly to hydrocodone in blood. Finally, we found that smoking or vaporizing Apadaz was not effective.

Now, I'd like to turn the presentation to Dr. Lynn Webster to review our Category 2 and Category 3 studies.

Dr. Webster?

Applicant Presentation - Lynn Webster

DR. WEBSTER: Good morning. I'm Lynn Webster, vice president of scientific affairs at PRA Health Sciences. I am board certified in anesthesiology, pain medicine, and addiction medicine, and I am former president of the American Academy of Pain Medicine.

The main focus of my research over the last 20 years has been the development of safer and more effective products and programs for pain management. I'm pleased to present the clinical abuse deterrence studies for Apadaz.

The goal of Category 2 is to evaluate the pharmacokinetic profile of a new formulation versus

a comparator for various routes of abuse, and Category 3 assesses the pharmacodynamics.

Three studies in the Apadaz development program assessed both Category 2 and Category 3 claims. Study A01 evaluated oral abuse. As Apadaz was not expected to deter oral abuse, I won't be covering the results from that study, but the results can be found in the KemPharm's briefing book. I will focus my comments this morning on the two intranasal studies.

Study A02 evaluated the intranasal abuse of the tablet formulation and study A03 evaluated intranasal abuse of the acting pharmaceutical ingredients to simulate, the common scenario where an abuser tries to isolate the opioid by removing the acetaminophen.

Before I start with the results, I want to provide some background on how and why abusers snort opioid products and how evaluating drug liking for an immediate-release product is different from an extended-release product. First, I'll start with a review of the health consequences

of snorting hydrocodone.

We know from clinical practice, as well as peer-reviewed literature, that chronic snorting of hydrocodone can lead to severe nasal and facial pain, nasal obstruction, necrosis of the nasal passages, fungal, rhinosinusitis, and septal and palatal perforation.

Because taking pills orally is easier than snorting powder, it's important to remember why abusers snort opioids in the first place. Snorting an opioid gets the drug into the system circulation faster than oral abuse by circumventing the GI tract. As a result, an abuser can achieve greater opioid exposure much faster, which in turn produces a faster high.

For combination products like Apadaz that contain acetaminophen, it was important to evaluate both of the ways an abuser might snort the product. The first way is simply crushing the tablets and snorting them as is, which was evaluated in the study A02. The second way is snorting after attempting to remove acetaminophen, which is

accomplished by using a common tampering method found on drug abuse websites.

The procedure reduces the volume the abuser would need to snort and also reduces the potential for liver toxicity. This scenario was evaluated in study A03.

Per FDA guidance, the primary endpoint in human abuse potential studies is the maximum drug liking or Emax, which is assessed on a bipolar Visual Analogue Scale. A score of 50 indicates neutral liking and scores above 50 indicate positive liking. The average score in a study is calculated as the average of every subject's maximum drug liking regardless of the time it occurred, so Emax is calculated without regard to time.

We're used to seeing these types of endpoints in Category 3 studies of abuse-deterrent extended-release opioids, such as Xtampza, which this committee reviewed late last year. In those studies, the drug liking of a manipulated, abuse-deterrent, extended-release product like crushed

Xtampza was compared against a high dose of a non-abuse-deterrent immediate-release comparator like Roxicodone.

If dose dumping doesn't occur with the extended-release product, we will see a significantly lower peak opioid exposure compared to the immediate-release product. It's only with these large differences in peak exposure that we would expect to see significant differences in peak drug liking or Emax. This proved to be the case with Xtampza, which resisted dose dumping when it was manipulated.

With an abuse-deterrent immediate-release opioid like Apadaz, Emax is a harder concept to apply because both the quantity of the opioid being evaluated, as well as the speed that the opioid is supposed to be delivered.

Extended-release products are designed to release large amounts of opioid slowly. However, immediate-release products are designed to release smaller amounts of opioid quickly in order to provide immediate relief for acute pain.

Given the fundamental differences between extended-release and immediate-release opioids, the time course of drug liking, particularly at early time points, may be more relevant than Emax, which isn't sensitive to time. Today, I'll be presenting both Emax and the time course of drug liking.

Another way to evaluate the abuse potential of an opioid is to evaluate the rate of rise in drug levels using PK data. This is achieved quantitatively using the abuse quotient. There are two factors in calculating the abuse quotient: Cmax or the maximum concentration and the speed in which Cmax is achieved, or Tmax.

Displayed here is an example of abuse quotient where there is a rapid rise to Cmax. This would be typical of an immediate-release opioid formulation. Here, the abuse quotient has a value of 100.

The black line represents a second example illustrating a typical extended-release formulation that has not been manipulated. It takes longer to reach Cmax, and therefore, the abuse quotient is

lower with a score of 15. Manipulating an extended-release product without abuse-deterrent properties would typically convert the black line to the red line.

In this third example, if we assume the product in green is another immediate-release product with the same Cmax of 50 but delays Tmax to 2 hours, the abuse quotient is 25 compared to 100 for the product in red. Therefore, when evaluating two immediate-release formulations, the abuse quotient is an appropriate quantitative comparison of the two drugs. With this background in mind, I'll start by reviewing the results.

Study A02 evaluated the intranasal abuse potential of the crushed tablet formulations without removing acetaminophen. This study consisted of two parts. In part A, subjects participated in a dose-selection test that evaluated intranasal administration of doses ranging from 1 to 4 crushed tablets of Apadaz or Norco.

It was determined that two tablets was the

maximum tolerated dose that could be consistently insufflated and produce reliable drug-liking scores. Therefore, the two-tablet dose was used in part B. Part B evaluated the intranasal bioavailability and drug liking of Apadaz and Norco and included oral dosing for both products for comparison.

This chart shows the oral and intranasal hydrocodone PK curves for Norco. You can see that snorting Norco produced its desired effects by considerably increasing the onset of hydrocodone levels compared to oral dosing. For Apadaz, abusers did not achieve faster hydrocodone concentrations by snorting. The Apadaz PK curves for the oral and intranasal routes essentially overlap.

In terms of the abuse quotient, when the two products were snorted, the more rapid increase in hydrocodone levels at early time points with Norco translated into nearly double the abuse quotient compared to Apadaz.

Drug-liking Emax for not significantly

different for snorted Apadaz and Norco. However, as I mentioned earlier, we need to evaluate a drug liking over time for immediate-release products because Emax does not take into account when abusers liked the product.

The trends in drug liking over the first 2 hours essentially mirrored the pharmacokinetic results. For Norco, the faster onset of hydrocodone concentrations translated into significantly greater drug liking at early time points. On the other hand, drug liking over time was essentially identical for Apadaz via the oral and intranasal routes. Therefore, snorting Apadaz does not give abusers the more rapid high that they would want and expect.

In addition, each of the pharmacodynamic measures that evaluated adverse nasal effects found that Apadaz was harder to insufflate than Norco. An ease of insufflation score was administered in subjects in study A02 where zero was scored as very easy to snort, and 100 indicated that the product was very difficult to snort. The ease of

insufflation scores were higher for Apadaz compared to Norco.

In study A02, we also asked subjects to complete nasal effect assessment score, which was a 0 to 33 scale with zero being no effect and 3 being severe. On each of the individual nasal effect subscales, you can see that subjects reported significantly higher burning, pain, the need to blow their nose, nasal irritation, congestion, and discharge.

In addition to subjective ratings, we also observed a higher rate of nasal and respiratory-related adverse events when subjects snorted Apadaz compared to Norco. The study documented higher rates of nasal discomfort, nasal congestion, rhinorrhea, and throat irritation.

Next, I'll turn to study A03, a comparative intranasal bioavailability study of the APIs for Apadaz and Norco, benzhydrocodone, and hydrocodone bitartrate.

Subjects were administered the equivalent amount of the API that would be found in 2 tablets.

This reflects a best-case scenario where abusers were able to extract all of the hydrocodone for benzhydrocodone from the tablet formulations by tampering. The population included in this analysis was not enriched using a drug discrimination test to confirm that subjects could discern between active drug and placebo.

The fact that the population wasn't enriched with highly discriminant subjects actually made it less likely that the study would find differences in drug liking. Even though current FDA guidance recommends a discrimination phase, these data are informative.

Dr. Mickle mentioned that the most common extraction method earlier in the context of IV abuse. However, abusers often use the same tampering method to facilitate snorting as well. Recall that while this tampering method effectively removes over 80 percent of the acetaminophen from both Norco and Apadaz tablets, only 36 percent of the inactive prodrug could be extracted from Apadaz, while 68 percent of the hydrocodone could

be extracted from Norco.

This means that for an abuser to get equivalent amounts of inactive benzhydrocodone and active hydrocodone, an abuser would need to extract twice as many Apadaz tablets compared to Norco tablets.

Despite this practical disadvantage from tampering with Apadaz, the study design for A03 assumed a best-case scenario where an abuser was able to remove all of the acetaminophen and extract all drug out of both products.

As you can see, the hydrocodone concentrations in the first 4 hours after intranasal administration were considerably lower at early time points for benzhydrocodone compared to hydrocodone bitartrate. Therefore, tampering with Apadaz to try to optimize it for snorting by removing the acetaminophen actually improves its abuse deterrence.

Abusers would end up with significantly lower hydrocodone exposure from snorting the tampered product than they would have by just

taking the tablets orally.

The considerable differences in PK profiles resulted in an abuse quotient that was 5 times lower for snorted benzhydrocodone than snorted hydrocodone bitartrate.

In this study, snorted benzhydrocodone had a significantly lower drug-liking Emax compared to hydrocodone bitartrate. The drug-liking results over the first several hours mirrored the study's pharmacokinetics where lower early exposures with Apadaz led to lower drug liking early in the time course of abuse compared to Norco.

Study A03 also measured the ease of insufflation. Scores were significantly worse for Apadaz prodrug compared to hydrocodone bitartrate demonstrating that Apadaz is not as easy for an abuser to snort.

In summary, the two intranasal clinical studies demonstrate that intranasal abusers would not achieve the rapid highs that they seek from snorting an opioid product.

In study A02, we observed essentially the

same pharmacokinetics and drug liking via the oral and nasal routes when the tablets were crushed and snorted as is. This was not the case for Norco, where more rapid onset of hydrocodone from snorting led to greater drug liking than the oral route right after administration. Study A03 simulated the case where an abuser successfully removed the acetaminophen using the most common tampering method.

The first way that Apadaz will deter intranasal abuse in this scenario is a practical one. The most common method to extract acetaminophen is half as efficient in extracting the prodrug from Apadaz as it is extracting hydrocodone from Norco.

However, even when abusers snorted equivalent doses of benzhydrocodone and hydrocodone bitartrate, we observed significantly lower hydrocodone exposures and drug liking with the isolated Apadaz prodrug, and we also found that Apadaz was harder to snort than Norco regardless of whether it was snorted with or without

acetaminophen.

Taken together, the results of the intranasal studies support that Apadaz has a lower intranasal abuse potential than existing hydrocodone immediate-release combination products. The totality of the data suggests that there is no incentive over the oral route to abuse Apadaz intranasally, by smoking, or IV injection.

I'll now turn the presentation back to Dr. Mickle.

Applicant Presentation - Travis Mickle

DR. MICKLE: Thank you, Dr. Webster.

The continued study of opioid misuse, abuse, and diversion and the responsible prescribing and postmarket surveillance of Apadaz is a high priority for KemPharm.

We understand the dynamic nature of abuse, as well as the discussions over the last two days regarding the monitoring of opioid pain products. We also understand that given the size of the IR opioid space, a different approach to monitoring abuse of a new product, like Apadaz, may be

necessary. We will work closely with the FDA and industry experts to design an appropriate program to address these very issues.

Initially, we are proposing an epidemiologic approach to postmarket surveillance. We'll design formal epidemiologic studies to evaluate abuse and route of administration patterns for Apadaz in populations considered at high risk for abuse of opioid analgesics.

In addition, we'll design market surveillance programs to measure the potential impact that Apadaz has in reducing abuse in the IR market. Additionally, KemPharm will continue to monitor current abuse patterns and trends for other opioids.

We'll also continue the market surveillance work that was started during the development of Apadaz with all the opioids, with special emphasis on hydrocodone combination products. We'll add survey data to better understand how and when abuse starts and progresses with IR opioids and abuse-deterrent IR products as they become available.

With Inflexxion, we'll conduct a series of examinations using data from the NAVIPPRO system. This will include data from adults assessed for substance abuse treatment in the ASI-MV network, the CHAT database of adolescents, as well as data collected from individuals who frequent and participate in online drug-related discussion forums with the WIS Internet Monitoring tool. As needed, we will collect data from other sources to measure factors beyond the scope of these databases.

When we first launched Apadaz, we expected abuse may be low and sporadic as availability and use increases over time. Therefore, regular surveillance monitoring and review of observations of abuse will be necessary. We will conduct two epidemiology research studies to assess the abuse deterrence of Apadaz after approval.

The primary study will collect data on the rates and routes of abuse of Apadaz compared to other relevant products among individuals entering or being assessed for substance abuse treatment.

In addition, we will conduct a supportive study to monitor and assess what recreational drug abusers are saying about Apadaz on drug abuse forums.

I now turn the presentation back to Dr. Gudin.

Applicant Presentation - Jeffrey Gudin

DR. GUDIN: Thanks, Dr. Mickle.

I'll be closing the presentation with my appraisal of the benefit-risk profile of Apadaz.

As we reviewed earlier, based on these data and other sources, we know that hydrocodone immediate-release combination products are one of the most abused opioids in the United States. Drug surveillance tells us that snorting is the second most common route of abuse of the most commonly abused opioid in the country, hydrocodone.

The FDA has asked whether the nasal route of abuse of hydrocodone products is relevant. Both clinical experience and surveillance data show that it is. Snorting is a common route of abuse and may be more common among adolescents.

This is a critical point because the

majority of lifetime abusers of opioids reported that they began to abuse between the ages of 10 and 18 and that hydrocodone combination products were the first opioid they ever abused.

Therefore, the introduction of abuse-deterrent properties to hydrocodone combination products may play an important role in deterring the progression of abuse to more dangerous opioids and more dangerous routes of abuse.

The data presented this morning indicates that Apadaz has properties that will deter abuse by all of the non-oral routes. The first step to abusing an opioid by any of these routes starts with tampering, physical or chemical manipulations that make the product easier to abuse.

One of the unique aspects of a prodrug is that physical manipulations have no impact on the release profile. As you've seen, it's also very difficult to chemically manipulate the product. There are three non-oral routes for which Apadaz can deter abuse. Multiple experiments show that

Apadaz cannot be smoked, freebased, or vaporized to release hydrocodone.

Apadaz can also be expected to deter abuse by IV injection. Extraction for injection is inefficient and expensive. Also, as you've seen, the prodrug converts much slower to active hydrocodone in blood than in intestinal fluid.

The most common route of non-oral abuse of hydrocodone combinations by far is snorting. Snorting crushed Apadaz tablets did not lead to greater hydrocodone levels or earlier drug liking than with oral administration.

Apadaz was also found to be harder to snort than Norco as shown by a higher rate of nasal adverse events and subjective ratings of snorting difficulty.

KemPharm also studied the situation where an abuser would try to remove the acetaminophen first. The most common procedure for extracting acetaminophen was half as efficient for Apadaz compared to Norco. Even when abusers snorted equivalent amounts of the active ingredients, they

got considerably lower exposures and lower drug liking with the Apadaz prodrug than they did with hydrocodone bitartrate.

So overall, no secondary route of administration would be more effective than just taking the drug orally. The importance of this abuse deterrence is amplified when we considered that of the 90 million hydrocodone prescriptions written in 2015, none contained any abuse-deterrent properties whatsoever.

When considering risks, the clinical data suggest that Apadaz poses no additional safety concerns beyond currently available hydrocodone combinations. It is bioequivalent to currently marketed products so patients can expect the same effective analgesia. There's also no clinically significant effect of food, and there was no systemic exposure to the prodrug after oral administration. Finally, the ligand in the prodrug, benzoic acid, is safe and occurs naturally in berries.

We're meeting today in the setting of a

prescription opioid crisis, one in which immediate-release opioids are the most commonly prescribed and the most commonly abused. While there are several approved abuse-deterrent extended-release opioid products, there has yet to be approval of any abuse-deterrent immediate-release products.

I think we all recognize that solutions to the prescription drug crisis have to be multifaceted. Any approach should include all stakeholders, patients, families, clinicians, pharmaceutical companies, and regulatory agencies.

Abuse-deterrent formulations are just one component of the strategy to reduce abuse of opioid products but they're an important component. Like the FDA, clinicians in the pain community are hopeful that all opioids, at some point, will be abuse-deterrent. Right now, for immediate-release hydrocodone combination products, abuse deterrence is a piece that's missing.

In light of the fact that Apadaz poses no additional risks beyond existing products and

offers several abuse-deterrent features in a class where there are currently none, it is my opinion that Apadaz has a positive benefit to risk profile and ought to be approved with a label that reflects its abuse-deterrent properties.

Thank you for your attention. I'll now turn the podium back to Dr. Mickle.

DR. MICKLE: That concludes our presentation. We now would be happy to take any questions from the committee.

Clarifying Questions

DR. BROWN: Are there any clarifying questions for KemPharm? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Higgins?

DR. HIGGINS: I believe this will be best answered by Dr. Mickle. My question, it relates to the validity of the study methods that are used.

When you rely solely on internet data for the study methods, how are we to know that this is actually the ways in which drugs are really being

abused?

DR. MICKLE: So we don't rely solely on the internet data. That's a source that we use to make sure that we're using methods and methodologies that are grounded in what current practices are.

But we use the wealth of information on how these products could be tampered with, as well as just simple organic chemistry, knowing what pHs may break down the bond between hydrocodone and benzoic acid, as well as knowing what the properties are to really push the product to the very limit to make sure it will hold up once it's distributed widely, if approved.

DR. BROWN: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien, patient representative. My question is for Dr. Gudin, specifically with referring to slide 15 and 18.

In looking at the transition from oral to snorting, clearly, oral is one of the largest intended or unintended abuse that we see among the patient community.

In your practice, what do you see

within -- and try to categorize the oral? In the briefing documents, it indicated it was just increased volume of pill taking. Is that primarily what you see within that category?

DR. MICKLE: I think, Jeff, you can -- Dr. Gudin, you can answer that best.

DR. GUDIN: I'll certainly [inaudible - off mic] --

DR. BROWN: Could you turn on your microphone, please?

DR. GUDIN: Thank you. I'll certainly agree with the surveillance data that oral overconsumption is by far what we've seen in clinical practice as the most common route of abuse.

When it comes to the extended-release opioids, we extend that oral overconsumption to include chewing, whereby the misuser will try to tamper with that current delivery system. But with immediate-release products, they're meant to do just that, and that's release immediately.

So the purpose of the presentation was not

to suggest that intranasal or other routes of abuse are more common. We recognize that oral abuse is the most common, but the fact is that these other routes are common secondary means of abuse.

MR. O'BRIEN: I asked the question because as a patient, and as a patient representative and my own anecdotal experience, with it, the real concern is, as you know, there's quite a difference between oral versus the snorting, smoking, injection.

The snorting, smoking, injection are intended abusers, whereas the largest population are unintended or uninformed abusers. And I'm curious as to how many they end up in our crisis in terms of adverse outcomes.

For example, in my own experience, at the age of 16, after two spine surgeries, which required me to be in bed for nine months in a body cast from my neck to my hips, and then coming out of that -- I was in a state hospital that was a population of several different syndromic, cerebral palsy and others that were there.

The practice at that time with adolescents was that the oral abuse was that they would save up -- as a club almost, they would save up their pills during the week that they got, and then they would all gather together in the weekend, and someone who was ambulatory, who had weekend privileges, would go out and get a bottle of vodka or some marijuana. And then the method of choice there to get high was to take those pills, and then you just smoke or to drink the vodka.

In a similar environment, as an adult in dealing with a large patient community and in my own experience, those that are using -- whether it'd be extended or IR -- opioids, then the first natural gravitation is not so much for euphoric or for a rapid high, but it is to either extend the pain relief that you're looking for.

Because of the stigma of not being considered to be someone who's abusing -- so you don't want to have to go back for additional prescriptions because that's a very negative and difficult process, so that now, you all of a sudden

have a glass of wine, or a glass of whiskey, or a glass of whatever, or smoking marijuana again.

So while it's different from the adolescent experiences, it's the same thing. And that seems to be the most prevalent form of abuse that we see beyond that. And I was just curious as to how much of that population that's in adverse outcomes are actually those what I would call "unintended" or "uninformed" abusers, not trying to get a rapid high or euphoria, not snorting, smoking, injection -- which are very complicated processes. You want to do that as opposed to the other one, which is very simple.

So in your experience, how much of the problem that we have is really those that I categorize as quote "unintended" or "uninformed" abusers?

DR. GUDIN: Yes --

DR. MICKLE: Sorry. Didn't mean to interrupt. Dr. Gudin, you can certainly chime in here.

I think we don't know exactly what those

numbers are. That's a difficult number to capture. We certainly do know those that have entered into substance abuse treatment that have claimed within the last 30 days, they have this issue here.

So if we can bring up the slide again with the abuse --

MR. O'BRIEN: Yes. If you look at slide 18 --

DR. MICKLE: Slide 18, that's right.

MR. O'BRIEN: Right. Slide 18. Of those that, say, in the 90 percent or the 81 percent -- depending on their age -- high amounts of them are doing oral abuse, then how many of those are actually -- their next level -- rather than before they get to snorting, their really next level of abuse is either adding alcohol, or marijuana, or some other combination of things to enhance their --

DR. GUDIN: I think it's a valid question, and one of the points during our presentation that we brought up is that these surveillance data are not necessarily generalizable, not only to the

recreational, or the abuser, or addiction population, but certainly not to a patient population.

So I could tell you from a clinical standpoint, being in the anesthesia/pain management practice for 20 years or so, oral overconsumption and compliance -- I think we're kind of talking about compliance -- is a big and complex issue.

Are they seeking additional pain relief or are they indeed seeking some more euphoric issues? And that's something we ferret out, and it's very difficult on a clinical nature on a day-to-day basis.

From looking at product-specific differences, I think we recognize that oral overconsumption is an issue. But with the product at hand, there's no additional benefit to using the drug any way other than orally. And I think that's one of the things we were asked to look at.

DR. BROWN: Dr. Emala?

DR. EMALA: Actually, I have three questions. The first two are for Dr. Mickle in

slide 32. I'm very curious about the extraction with Solvent X. At 4 hours, it achieved 60 percent isolation. I think this matches the FDA briefing document of Stress Condition 1.

My first comment is that Solvent X is labeled as an advanced buffer, and it's my understanding that it may not be an advanced buffer. It may be a buffer that's easily achievable by people in diverting interest. And the second comment is, was this same solvent tried under stressing conditions 2 as the FDA had asked for some of the additional studies?

DR. MICKLE: To the first part of your question, the buffer used in Solvent Z as listed here, we don't agree. We think, in fact, that this is a complex buffer to prepare. We've seen the conditions in which we've prepared this. It uses a very high pH as well.

DR. EMALA: I was asking about X, not Z.

DR. MICKLE: Oh, X.

Could we bring up the buffers and the pHs for the codes, not to show the codes but just to

recall my memory?

DR. HERTZ: Please don't show those. If you need to jog your memory, maybe you can just look.

DR. MICKLE: Yes. Thank you. Take that down and actually get the codes, please.

We can get you that information in more detail after the break. I just can't recall exactly what those coded numbers exactly refer to, to answer your question the best.

DR. EMALA: And do we know if Solvent X was tried under Stress Conditions 2?

DR. MICKLE: I can check that as well.

DR. EMALA: Okay. My second question for Dr. Mickle is slide 40, and it also refers to data within the FDA briefing document referring to an experiment that was done with pancreatin, which is an enzymatic attempt to release the active ingredient from the prodrug.

It's my understanding from the briefing document of the FDA -- I'm not sure who did this experiment. But 99.9 percent of the active drug appears to be available after a 15-minute

pretreatment with pancreatin, which is an enzymatic mixture widely available as a food supplement, widely available and cheap over the internet. And I'm curious whether a consideration of a diversion practice using this formulation of the prodrug was considered.

DR. MICKLE: It was. We know that when -- that is actually one of the enzymes responsible for breaking down the prodrug in our own GI tract. So we know that the esterases in the intestinal fluid break this product down completely and within a few minutes. But again, there's no benefit to pre-releasing the product if the intent is just to swallow it.

So really, here, you're thinking about, well, what would an abuser do with this particular product? Using the enzymes outside of the body, they would probably snort the product, inject the product, or try to smoke the product. In these particular instances, you still have the enzyme present. You either snort it or inject it with an enzyme present with an unknown effect, or you

perhaps try to remove that, just lowering the yield perhaps of what you would get.

So there's no tamper-proof method. We think this is a great approach to limiting all of the routes that you've probably seen with other products where they can release very quickly in just a small amount of water or other substances.

Here, we're really focused on covering the vast majority of those methods for tampering.

DR. EMALA: Thank you.

My final question is for Dr. Webster in slide 68. And in slide 68, the mean drug-liking scores are displayed comparing the oral and snorted route for Norco versus Apadaz.

It seems to me, with the discussion of both of these A02 and A03 studies, that the critical question was -- at an early time point, was the drug liking more desirable, snorting one versus the other?

So I think an interesting comparison would be Norco snorted versus Apadaz snorted at an early time points, say, 30 minutes. And as I look

at -- I'm sorry, my mistake. It's slide 58. I'm sorry.

So looking at the snorted Norco versus snorted Apadaz, for example, at 30 minutes, I think we're looking at a difference in drug-liking scores of about roughly 72 for Norco and 63 for Apadaz at 30 minutes.

So I'm curious if a statistical analysis was done since this seems to be the take-home message of whether Apadaz offers an advantage, at an early time point, of snorting over the non -- the different formulation.

DR. MICKLE: So let me just make sure I understand your question so I can answer it best. You want to know if there are statistically significant differences between Norco intranasal and Norco -- or Apadaz intranasally administered for the drug liking at early time points?

DR. EMALA: Correct.

DR. MICKLE: So this study, study A02, as you can see here, there was statistically significant differences of intranasal Apadaz versus

Norco up through what appears to be 2 hours, the mean differences here -- and this is looking at area under the effect curve differences.

DR. EMALA: But area under the curve kind of gets away from the point that's being made about a rapid high. So if we look at area under the curve for several hours, that gives a very different message than the rapid high of the intranasal route. So I think it's important to look at early time points and not just area under the curve.

DR. MICKLE: Sure.

Do we have that data? We can get that for you as well after the break.

DR. EMALA: Thank you.

DR. BROWN: Dr. Michna?

DR. MICHNA: Ed Michna, Brigham and Women's Hospital. I have a few questions, one for Dr. Gudin.

On slide 14 and 15, the assumption is that this technology will somehow prevent that progression. My question is, is there any evidence in the literature to suggest, by manipulating a

drug in this manner, that you actually have any effect on this progression, or people just go to other drugs like heroin, or oxycodone, or whatever to inject?

DR. MICKLE: I think that's part of the intent by what we meant by progression, is progression not just with the particular drug to the other routes of administration, but those early exposures and perhaps experimentation with some of these more dangerous routes might inform them of how to abuse other products.

So we did some early work. And there's not a lot of literature on this, so we actually had to work with Inflexxion on how to generate data here. We conducted a survey of hydrocodone abusers.

These are individuals who felt that hydrocodone abuse had an impact on their life; it somehow influenced how they abused other products. And when they were asked, you know, between the products, would you swallow it whole or snort it, depending on the age of when they started, they answered with, "Well, I snort more products --" and

this may not be currently just hydrocodone products that they snort but, I snort more products; I smoke more products; or, I inject more products.

So we don't know the answer. I think by looking at survey data, we're able to get out at least some hints that's possible. But there's certainly no definitive data, yet, that progression of abuse can be stopped like this.

DR. MICHNA: Right. But that was a major point that you were trying to make there.

My other question is on slide 40, on the blood study, what temperature was that conducted? Was it at body temperature or --

DR. MICKLE: It was. It was actually whole blood -- fresh whole blood, was held at 37 degrees Celsius and put on a rocker so it was maintained; it wouldn't coagulate.

DR. MICHNA: Was there any studies done where people would extract their own blood, expose it to this drug in whatever form, and then reinject it?

DR. MICKLE: We did not do studies in humans

with this product.

DR. MICHNA: My other question is, are there esterases in human saliva?

DR. MICKLE: There are esterases, and they're throughout your body. I mean almost every cellular system has them.

What we've seen is that esterases that are most effective -- actually, the only ones we've been able to find that break it down are the intestinal esterases and the family and host of esterases related to that.

So the other enzymes throughout the body, the other esterases, actually don't break down the prodrug to hydrocodone.

DR. MICHNA: So do you have data on human saliva and its exposure in terms of extraction?

DR. MICKLE: Sorry? What was the question again?

DR. MICHNA: Do you have data on the exposure of this drug to human saliva in terms of extraction?

DR. MICKLE: No. We just looked at singular

enzymes, enzymes that are typically found in those systems.

DR. MICHNA: And my final question is on slide 58. It looks like your intact oral product, when compared to Norco is actually more likeable. I don't know if that's a statistical significant difference in the half-hour time frame.

It looks like people liked it a lot better early than Norco when it's taken orally.

DR. MICKLE: Can we bring up the other slide that shows the oral-oral and intranasal-intranasal?

DR. MICHNA: So if you look at the half-hour, it looks that the likeability is much higher in the oral Apadaz versus the Norco. I'm not sure if that's statistically significant, but it looks like it.

DR. MICKLE: Yes, so we looked at this both way. And it could be just, again, the trick of the eye and, trying to look across two different graphs. In this particular case, there was no statistical difference between liking, really, at any time point of oral-oral Apadaz and Norco.

DR. MICHNA: Okay. Thank you.

DR. BROWN: We're going to take a break for 15 minutes. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any other member of the audience. We'll resume at 11 o'clock. And those folks that are on the list to ask questions, we will get back to those questions at a later time.

(Whereupon, at 10:46 a.m., a recess was taken.)

DR. BROWN: If we could get started. We're now going to proceed with the FDA presentations. We will move to the remainder of the clarifying questions from the sponsor's presentation after FDA presentations.

FDA Presentation - Benjamin Stevens

DR. STEVENS: My name is Ben Stevens. I'm a chemistry reviewer in the Office of New Drug Products at the FDA. And today, I'll be speaking about the FDA's interpretation of the in vitro abuse-deterrent studies carried out by the

applicant for NDA 208653, KP201 acetaminophen tablets.

Just a brief overview of this presentation, the presentation will focus on interpretation of key data from a subset of the in vitro studies carried out to evaluate the abuse deterrence of this product. The goal of this presentation is to give the advisory committee an understanding of any open questions or potential liabilities associated with the proposed abuse-deterrent features of this product.

Throughout this presentation, we'll be using several abbreviations. The definitions are provided here. HB stands for hydrocodone bitartrate. HC stands for hydrocodone. KP201 is benzhydrocodone hydrochloride. LV stands for large volume, which is greater than or equal to 50 milliliters. SV stands for small volume, which is greater than or equal to 3 milliliters. And these two bottom abbreviations will be used in the context of some of the extraction size I will discuss.

This is an overview of the studies, which we'll address in this presentation. The first set of studies that we'll discuss are large volume extraction studies, a limited number of large volume extraction studies. And what you'll see from these studies is that, in certain cases, acetaminophen can be more effectively separated from KP201 than from the comparator product hydrocodone bitartrate acetaminophen under certain conditions.

We'll then move to a discussion of the hydrolysis of the KP201 prodrug and show that under certain simple and nontoxic conditions, KP201 can be, in fact, hydrolyzed quite effectively.

We'll then discuss the solubility of KP201 versus hydrocodone bitartrate and discuss the solubility in the context of its proposed abuse-deterrent features.

We'll move then to the discussion of some small volume extraction studies, which were designed to simulate the preparation of injectable solutions, and show that the results in these

solution preparations indicate that the extraction efficiency of KP201 and hydrocodone bitartrate are similar, and that overall, the concentrations of either of these two active agents in these simulated solutions are very low.

Finally, we'll move to a discussion of the results from simulated smoking studies, which show that both KP201 and hydrocodone have similar volatility and also that, overall, there's very low levels of hydrocodone that are obtained in vapors from smoking studies of the reference product, hydrocodone bitartrate acetaminophen tablets.

So this was discussed previously in the applicant's slides. We'll just, again, summarize the proposed mechanism of abuse deterrence here. So again, KP201 is a prodrug of hydrocodone. The intact prodrug itself is a weak opioid receptor agonist, and therefore in order for it to act in vivo, it must be cleaved to the active agent, which is hydrocodone.

The applicant also indicates in numerous locations in the NDA that the solubility of the

KP201 prodrug is very low when compared to hydrocodone, and that this offers an advantage in the sense that it can be more difficult to manipulate this product or administer it by non-oral routes of administration.

So as was also noted previously, physical manipulation studies were not carried for this particular product, and that's because of the fact that unlike many of the other abuse-deterrent products that we're all used to looking at, there is no formulation-based deterrent features in this product, so there was no need to carry out these extensive of crushing or grinding studies.

One thing that was examined was the particle size for the crushed tablets for either KP201 acetaminophen tablets or the comparator in order to show that those two profiles were similar when used in the extraction studies, and in fact, they were.

So at this point, we'll switch to a discussion of the first large volume extraction study. And what you'll see in this study is that acetaminophen can actually be selectively extracted

away from KP201 prodrug under certain conditions, whereas for hydrocodone bitartrate, in fact, it's more challenging under certain conditions to separate this from acetaminophen.

So what you're looking at in this chart is a time course extraction study using the large volume extractions that were discussed previously in the closed session. We're describing this extraction for Common Solvent X using non-stressing conditions. And in this chart, you're seeing the percent label claim of hydrocodone that's being extracted from either the KP201 acetaminophen or hydrocodone bitartrate acetaminophen tablets, which were either crushed or intact.

You can see under these conditions that hydrocodone is rapidly and effectively extracted using Common Solvent X, but for KP201, the prodrug does remain intact under these conditions, hence very low levels of hydrocodone are observed in solution. It is important to note -- and there was a question about this solvent earlier, Solvent X -- that Solvent X is safe and potentially

injectable and ingestible and potentially relevant for IV use.

This second slide is still the same study. We're looking again at Common Solvent X, non-stressing conditions. But now, we're looking at the percent label claim of KP201 that's being extracted into solution. And again, because of the fact that we're looking at KP201 levels, you don't see the comparator being examined under these conditions.

Under these conditions, what you can see is that no KP201 is going into solution. So KP201 remains behind with whatever solid components from the drug product excipients that are also not extracted into solution. So it remains behind as a solid.

Finally, in this last slide, again, the same study, now we're looking at extraction of acetaminophen into solution with Common Solvent X. We now see that for either drug product, acetaminophen is quite effectively extracted and rapidly extracted into solution.

So if you take these three slides together and what the data implies, what it's implying is that under these conditions, which are potentially quite relevant, we can selectively partition away KP201 under these conditions and leave it behind as a solid, whereas hydrocodone bitartrate and acetaminophen tend to go into solution together. And I think that's an important factor to note.

What you'll see now, we're moving to large volume extractions, study 2, is that under certain other conditions, the exact opposite trend can be observed.

This is Solvent O, again, under non-stressing conditions. We're starting again with the percent label claim of hydrocodone that's extracted. You could see that under these conditions, only very small levels of hydrocodone are extracted from the reference product, only a maximum of about 30 percent. And meanwhile, as in the first case, the prodrug is intact under these conditions, so we see no hydrocodone being obtained from KP201 tablets.

It's important to note that Solvent O is, in fact, a toxic solvent although it is quite volatile. So it would have to be evaporated prior to use of anything that was extracted out of it for further manipulation or administration.

Again, continuing on with the same study, we're now looking again at Common Solvent O, now, the KP201 extraction levels. And you can see, essentially in complete opposite form of the first study, that now we're getting very rapid and very efficient extraction of KP201 into solution, nearly 100 percent of the label claim essentially at the first time point, which again is completely the opposite of what we saw in the first case.

Then finally, when we look at the acetaminophen levels extracted by Common Solvent O for either drug product, you can see now that acetaminophen isn't extracted for either drug product and remains as a solid behind.

So what you're seeing here is essentially the opposite. Now, with these solvents, we can obtain KP201 essentially in pure form and leave

behind acetaminophen, whereas for the other set of conditions, we could obtain very rich KP201 in the solids that were left behind from the extraction.

At this point, we'll now move on to discussion of the hydrolysis of KP201. And again, this is under large volume extraction conditions. I do want to point that there was an error in the coding here, so this refers to Common Solvent G, which in the applicant's closed session materials is actually different from the way that FDA is referring to Common Solvent G. So please look at the FDA background to know what Common Solvent G is because it's very important to the interpretation of this data.

So again, Common Solvent G, we're now looking at another one of these extraction studies, Stressing Conditions 2. Common Solvent G and Stressing Conditions 2 were both requested by the FDA after initial review of the application material and the data were subsequently provided in the response and information request. In Solvent G in Stressing Conditions 2 -- Solvent G is safe, is

readily injectable and ingestible, and is potentially highly relevant for IV use.

What you can see here is that under these conditions, we're now seeing almost 80 percent of the prodrug being processed in the hydrocodone, although it is noted that it takes some time, about 3 hours to reach optimal yield. But the key thing to take away from this slide is that, again, these are not optimized conditions but that there are safe and relevant conditions that can be used to process this prodrug into hydrocodone prior to administration.

The next two slides will address another factor, which is I think of importance when looking at these studies, which is the fact that the hydrolytic behavior of this prodrug is actually very sensitive to the conditions, which have been examined during the study.

So what you're seeing in this first slide again is another one of these hydrolysis/large volume extractions studies, which was in the original application using Common Solvent A under

Stressing Conditions 1, which were, again, in the original application. And we're looking at the hydrocodone levels for either drug product under these conditions.

As you can see, under these conditions, hydrocodone is rapidly extracted from the reference product, but the prodrug is not cleaved to any appreciable degree. So KP201 is remaining intact.

So after review of this data, the FDA, again, requested some additional studies to be carried out, now using Common Solvent F. And again, like in the previous situation, there was a coding error here, so Common Solvent F is different in the applicant's material from the FDA's material, so please look at the FDA material to understand what Common Solvent F is.

Now, using Stressing Conditions 2, Common Solvent F and Common Solvent A, which were in the last slide, there's a very, very small difference between these two solvents. And in Stressing Conditions 2, which were requested by FDA, are only very slightly different than the

Stressing Conditions 1 that were used in the original study.

What you can see here is now we're starting to see some level of hydrolysis of KP201 to hydrocodone, although it is noted that this does take an extended amount of time. But they key message here is that, again, the results from these studies can -- very small changes in parameters can result in very different outcomes and the ability to hydrolyze this prodrug. And the reason why we address this particular study is because of the very significant importance of these two solvents when interpreting the overall stability of the prodrug. So I definitely encourage you to look at the conditions that are being used for these studies.

We'll now move into a short discussion regarding the solubility of KP201, which in the previous slide, I indicated that the applicant has made it clear that one of the things that they look at as being advantage of this product is that it has a substantially lower solubility than

hydrocodone bitartrate.

Although the data that was obtained for solubility was quite variable for these two drug substances, it is conclusively -- it is able to be concluded that, in fact, KP201 is significantly less soluble than hydrocodone bitartrate. Depending on the conditions, you can see a difference between about 10-fold or up to about a thousand-fold difference in solubility, so it's quite variable.

Probably more important than the intrinsic solubility of these two drug substances, however, is the fact that the KP201 solubility profile is far more variable than that for hydrocodone bitartrate. So hydrocodone bitartrate tends to stay quite consistent across various conditions, whereas KP201, its solubility behavior changes quite a lot depending on the conditions that you're looking at.

We've already seen in some of the previous slides how in certain instances, that can be used to an advantage of an abuser to selectively

partition this away from acetaminophen. But what you'll see in the next slide is that in certain cases, you can actually circumvent this solubility effect on the hydrolysis rate.

So again, another large volume extraction/hydrolysis study looking at now hydrolyzing Solvent 18 under Non-Stressing conditions, we're looking at the hydrocodone being extracted just from KP201 tablets in this instance. And in this situation, you see very low levels of hydrocodone being processed from the prodrug. So under these conditions, hydrolyzing Solvent 18 is only modestly affected for this transformation.

However, we now see in this next slide the addition of Solvent C. We're still using hydrolyzing Solvent 18, so the same hydrolyzing agent, but we've added an additional solvent in. And Solvent C is not a hydrolyzing agent. It's just simply a solvent. And what you see now is under these conditions, a lot more hydrolysis of the prodrug. Although again, to get the optimal yields, it is noted that it does take an extended

period of time.

What I think is key to address here is the fact that this solubility effect is very likely what was causing the slow rate of hydrolysis in that previous study, and that there are ways to get around this sort of issue; and that, furthermore, Solvent C and hydrolyzing Solvent 18 are both widely available, safe for oral or injectable use, and overall are commonly available to abusers. So this is quite relevant to potential manipulations that would be carried out.

So we'll now move into discussion of some of the small volumes extractions carried out by the applicant to investigate the feasibility of preparing injectable solutions of either KP201 or hydrocodone bitartrate from their respective drug products. And as was discussed previously, the applicant looked at a wide variety of conditions for this.

But in order to facilitate our analysis for this slide, what we've done is essentially grouped all these conditions into two sets of -- two

classes of conditions. And the only difference between these classes -- there's a lot of differences, but there's one main difference between these two classes, which pertains to a single parameter, which differentiates them.

What you see, there are two take-away messages here. First of all, these are optimized conditions. And you can see that using the optimized conditions, ultimately, there isn't a very significant difference between the percent extraction of either the KP201 acetaminophen or the hydrocodone bitartrate acetaminophen tablets.

So for example, at the highest levels, you can see for KP201, we're at 72-percent extraction, whereas for the hydrocodone comparator, we're seeing about 79 percent. So overall, once these procedures have been optimized, there's not a very big difference in extraction efficiency.

One thing that's more important to note probably is the fact that there are some conditions under which KP201 is significantly less efficiently extracted than hydrocodone bitartrate. And as you

can see here, this tends to trend with the fact that the extraction conditions are being carried out under Conditions 2.

So this is really not a representative behavior. It's more of a solvent class effect or conditions class effect, and that overall, the extraction efficiencies of these two drug substances are probably quite comparable.

So following on the results of these small volume extractions studies, as was also previously mentioned, the syringeability of the solutions made for either of these two drug products were essentially comparable, which is not unexpected given the nature of the formulation.

A very important aspect to note here is the fact that using these optimized small volume extraction conditions, it ultimately required multiple steps and still resulted in solutions that had very low levels of KP201 and hydrocodone overall.

So for KP201, the range using the optimized procedures was anywhere between 0.22 to 2.6 mg per

mL, and for hydrocodone, it was about 2.9 to 3.6 mg per mL.

So the key question that emerges from this is really whether or not -- using solutions like this, you might be expected to have to deliver larger volumes of solution in order to get the desired effect.

So really, the extent to which drug abusers might use such procedures or inject multiple milliliters of this solution -- even for the reference product, not just for the KP201 acetaminophen tablets, but also for the reference product -- are unknown at this point in time, and that I think is an important factor to address.

So moving on to our final study slide, we're now looking at data from the smoking studies of KP201 acetaminophen or hydrocodone bitartrate acetaminophen tablets and also their freebase forms.

Several important things to note. As was pointed out earlier, smoking studies, the simulated smoking studies of the KP201/APAP tablets lead to

no measureable levels of hydrocodone. However, when you look at the data that was obtained from the reference product, you see that we're only seeing 4.7 percent of hydrocodone collected from the vapors using the reference product.

So the question really then becomes, even for the reference product, does smoking directly using this particular combination product or a fixed-dose combo, even a feasible or reasonable route of abuse?

Again, another thing to point out is that once we compare the freebase forms of these two drug substances, KP201 freebase or hydrocodone freebase, the volatilities do compare to be comparable. So while hydrocodone isn't being formed during the smoking, they are being volatilized at similar levels when you look at the freebase forms.

So at this point, I'll turn over to the conclusions. KP201 may be more efficiently separated from acetaminophen using common conditions that in some cases are safe when

compared to hydrocodone bitartrate acetaminophen. There are mild, safe, and relevant conditions that exist for hydrolysis of the KP201 prodrug to hydrocodone, although it is noted that optimization of the conditions may require extensive abuse, or experimentation, or longer processing times to get the optimal yields.

The low solubility of KP201, which is proposed as an abuse-deterrent feature, may in fact help to reduce the rate of hydrolysis of the prodrug under certain conditions, but, in fact, this advantage can be limited based on the use of certain safe and relevant co-solvents.

In general, the prepared small volume extraction IV injectable solutions of KP201 and hydrocodone have comparable concentrations. And although it is noted that extraction efficiency for KP201 may be reduced using certain classes of solvents or conditions, very importantly, the KP201 or hydrocodone levels obtained in the extractions of these two products under these small volume extraction conditions are very low.

Therefore, there's question as to the extent of which these procedures or whether these solutions at these low concentrations would be used by abusers.

Finally, hydrocodone was not recovered from smoking experiments of KP201 acetaminophen. However, the two drug substances, when they're in their freebase form, do appear to have similar volatility. And probably more importantly is this aspect that even when the reference product is looked at, we're still only seeing 4.7 percent of hydrocodone emerging from these simulated smoking studies of the reference product. So the question as to whether or not smoking of the reference product is a feasible route of administration or abuse is really, I think, an open question.

So at this point in time, I'll turn it over to my colleague, Jim Tolliver in CSS, to present the FDA's interpretation of the clinical studies that were carried out for KP201 acetaminophen.

FDA Presentation - James Tolliver

DR. TOLLIVER: Good morning. My name is

James Tolliver. I'm a pharmacologist for the controlled substance staff within the Office of the Center Director, Center for Drug Evaluation and Research at the FDA.

I will briefly discuss two human abuse potential studies, KP201.A01 and KP201.A02, as well as clinical study, KP201.A03, all submitted as part of the abuse-deterrent assessment for KP201/APAP tablets under NDA 208653.

For the purpose of this presentation, I will use the term "KP201" to refer to benzhydrocodone hydrochloride, "APAP" to refer to acetaminophen, and "KP201/APAP," and not Apadaz, to refer to the product under development.

The pharmacodynamic measures I will discuss include the Visual Analogue Scales, abbreviated VAS, or drug liking, high, and take drug again. The drug-liking VAS, the primary measure is used to assess at-the-moment drug liking. Subjects were asked, "Do you like the effect you are feeling now?" The response is documented on the 0 to 100-millimeter bipolar scale anchored on the left

by zero, strong disliking; at the center by 50, neither like or dislike; and on the right by 100, strong liking.

High VAS, the assessment of euphoria, uses a 0 to 100-millimeter unipolar VAS scale with anchors on the left of zero equals to none, and on the right by 100, extremely. Subjects are asked to respond to the question, "How high are you now?"

Take drug again VAS is an overall global assessment taken at 12 and 24 hours post-dosing. The specific question asked is, "Would you want to take the drug you just received again if given the opportunity?" It is rated over bipolar VAS scale anchored on the left by zero, definitely would not; in the center by 50, do not care; and on the right by 100, definitely would.

Pharmacodynamic parameters will include the maximum effect, designated Emax; the time to achieve maximum effect, designated TEmax; and the area under the effect curve for selected intervals post-dosing.

The primary endpoint for both abuse

potential studies is Emax of drug liking, statistical analyses of pharmacodynamic measures were conducted by the FDA CDER Office of Biostatistics utilizing the mixed effects model with treatment period in sequence as fixed effects and with subjects as a random effect. Tests were one-sided with an alpha of 0.025.

To test treatment differences, the null hypothesis consisted of the mean of Norco, the positive comparator, minus mean of KP201/APAP by less than or equal to zero.

For studies KP201.A01 and KP201.A02, the validity of each of these measures was established using the null hypothesis of the mean Emax of Norco minus that of placebo is less than or equal to 15 for drug liking and take drug again, and less than or equal to 30 for high.

For purposes of examining pharmacokinetic/ pharmacodynamic relationships, I will limit my discussion to the pharmacokinetics of plasma hydrocodone following active treatments and rely on statistical analysis conducted by the sponsor using

least square geometric mean ratios with corresponding 90 percent confidence intervals.

Pharmacokinetic parameters will include maximum plasma hydrocodone concentrations, Cmax, time to Cmax, namely Tmax, and the area under the plasma hydrocodone concentration curve -- concentration versus time curve, abbreviated AUC, as selected intervals post-dosing and representing cumulative drug exposure.

Study KP201.A01 is a randomized, double-blind, placebo-controlled single-dose 7-way crossover study having the primary objective to determine the abuse potential KP201/APAP tablets relative to Norco tablets when administered orally to non-dependent recreational opioid users.

Each KP201/APAP tablet contains 6.67 milligrams of KP201 and 325 milligrams of APAP. Each Norco tablet contains 7.5 milligrams of hydrocodone bitartrate and 325 milligrams of APAP. Sixty-two subjects comprised completer population.

In this study, 3 doses of each product were evaluated, comprised at a low dose of 4 tablets,

medium dose of 8 tablets, and high dose of 12 tablets. The low, medium and high doses of KP201/APAP roughly correspond to 26, 56, and 80 milligrams of KP201, respectively. Low, medium, and high doses of Norco corresponded to 30, 60, and 90 milligrams of hydrocodone bitartrate, respectively.

Provided here is the mean plasma hydrocodone concentration as a function of time following low, medium, and high doses of KP201/APAP and Norco. Note that dose-dependent increase in hydrocodone plasma levels with much of a rise occurring over the first 30 minutes post-dosing. Medium Tmax is about 1 hour for all treatments.

For the medium and high treatments, but not the low treatment, total systemic hydrocodone exposure over the first hour, as reflected by Cmax and area under the curve from 0 to 1 hour, was statistically significantly lower for KP201/APAP compared to Norco.

This slide provides the mean time course profile for drug liking following oral treatments

with the low, medium, and high doses of Norco and KP201/APAP. At similar dosage levels, there was a general overlap between Norco and KP201/APAP.

For all active treatments, most of the rise in mean drug-liking response occurs within the first hour at each dosage level as reflected in the area under the effect curve versus time curve. Cumulative mean drug liking was not statistically significantly lower following KP201 compared to following Norco.

So the lower initial plasma hydrocodone exposure following medium and high oral doses of KP201/APAP compared to oral Norco did not translate to a lower level of drug liking over the first hour.

This slide provides the mean time course profile for high VAS following oral treatments with a low, medium, and high doses of Norco and KP201/APAP. At similar dosage levels, there was a general overlap between the Norco and KP201/APAP. For all active treatments, most of the rise and mean high occurs within the first hour.

Within each dosage level, there are no statistically significant reductions in the cumulative high experience over the first hour following KP201/APAP compared to following Norco.

So again, we see a similar situation observed for drug liking, namely that the early reduction in hydrocodone exposure following medium and high doses of KP201/APAP were not accompanied by, were not associated with, a reduction in high as compared to that evoked by medium and high Norco.

This slide provides the mean standard error Emax of drug liking, high, and take drug again for all treatments. Note that for drug-liking VAS and high VAS, there are dose-dependent increases in Emax following KP201/APAP and Norco treatments. For drug liking, high, and take drug again, when comparisons are made within each dosage level, the mean scores are numerically very similar and not statistically significantly different between KP201/APAP and Norco.

With the comparable levels of drug liking

and high at each dosage level, it is not surprising that subjects expressed a very similar willingness to take KP201/APAP or Norco again if given the opportunity to do so.

Study KP201.A02 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, five-way crossover study. There were two parts to this study. Part A was the dose-selection phase intended to determine an intranasal dose to be used in the main part of the study, designated Part B. The objective of Part B was to assess the abuse potential of crushed KP201/APAP and Norco when administered intranasally to non-dependent recreational opioid users.

Based on the results of Part A, 2 tablets each of KP201/APAP constituted 13.34 milligrams of KP201 and 650 milligrams of APAP; and of Norco, containing 15 milligrams hydrocodone bitartrate and 650 milligrams APAP were selected for the main study.

Forty-two subjects constituted the completer population and were administered double-dummy

during the treatments phase oral and intranasal Norco, KP201/APAP, and placebo. The weight of powder to be snorted varied from 850 milligrams for Norco to a maximum of 1,100 milligrams for KP201/APAP. All subjects were able to insufflate virtually all of the active intranasal treatments and most of the intranasal placebo treatments.

The mean hydrocodone plasma concentration as a function of time post-dosing is shown in the graph on this slide for both intranasal and oral administration of KP201/APAP and Norco. For all treatments, most of the rise in plasma hydrocodone concentration occurred within the first 30 minutes, although in the case of intranasal Norco, the absorption was faster with most of the rise occurring within the first 15 minutes.

Norco produced a Cmax for hydrocodone in plasma that was not statistically significantly different from that produced by intranasal KP201/APAP based on the sponsor statistics. What you have seen the slide here is an error, and so it's corrected by as not being a difference between

the Cmax.

Hydrocodone exposure over the first half hour, 1 hour, and 2 hours, following intranasal KP201/APAP, was significantly less than that from intranasal Norco but similar to that following oral KP201.

The mean time course profiles for drug liking following intranasal treatments of Norco -- the blue line, and KP201/APAP, the red line -- are shown on this slide for both treatments. Most of the rise in drug liking occurred within the first 30 minutes. The cumulative drug-liking experiences following intranasal KP201/APAP over the first half hour and 1-hour post-dosing were statistically significantly lower than those following intranasal Norco. The clinical significance of these differences from a possible abuse-deterrent perspective is not clear. Median TEmax for drug liking was 0.6 hours for intranasal Norco and 1.4 hours for intranasal KP201/APAP.

The mean time course profile for high

following intranasal treatments of Norco and KP201/APAP are shown in this slide. For both treatments, most of the rise in high occurred within the first 30 minutes following dosing.

In contrast to what was found for drug liking, there were no statistically significant reductions in mean differences in cumulative high experienced over the first half hour and 1 hour following intranasal KP201/APAP compared to Norco. Median TEmax was 1.2 hours for intranasal Norco and 1.4 hours following KP201/APAP.

This slide provides the mean Emax values for drug-liking VAS, high VAS, and take drug again VAS. For each of the three measures, the mean Emax for both intranasal and oral after treatments have a very narrow range. Statistical analyses of the drug liking, high, and take drug again failed to demonstrate that the mean Emax values produced by intranasal KP201/APAP were smaller than that of intranasal Norco. It was a failure of the primary endpoint of Emax of drug liking.

Intranasal administration of Norco and KP201

produced similar maximum levels of drug liking and high. In addition, there was a similar willingness of subjects to, again, insufflate either of these treatments if again given the opportunity to do so.

I would also point your attention to the take-drug-again column just to be aware that although between Norco oral and Norco intranasal, there were differences from the pharmacokinetic standpoint in hydrocodone exposure and differences with respect to drug liking, the cumulative drug liking.

When it came to asking subjects would you be willing to take these two treatments again if given the opportunity, the scores are almost identical: 74.5 versus 75.6, almost identical, similar willingness to take oral or intranasal Norco.

I want to briefly discuss study KP201.A03. However, I want to note at the outset that this study has some issues with study design that make it difficult to use in assessing the abuse-deterrent effects of KP201/APAP to intranasal abuse.

Study KP201.A03 is a pharmacokinetic study to which was added the pharmacodynamic measure of drug-liking VAS. The study is a randomized, double-blind, single-dose, crossover study having the primary objective of comparing the rate and extent of absorption of hydrocodone and hydromorphone from hydrocodone bitartrate API in KP201, administered to non-dependent recreational opioid users.

The treatments consisted of the active pharmaceutical ingredients, 13.34 milligrams KP201 and 15 milligrams hydrocodone bitartrate. There were only two treatments. There was no placebo group.

Two cohorts were used in this study. Due to blood sampling errors, no pharmacokinetic data for hydrocodone in plasma was obtained from cohort 1, although drug-liking data was obtained. With the recruitment of cohort 2, both hydrocodone pharmacokinetic data and drug-liking VAS --

DR. BROWN: Excuse me.

DR. TOLLIVER: -- were obtained from the

same individuals.

This slide provides the hydrocodone plasma time course on your left and the drug-liking time course on your right using only cohort 2, for which both hydrocodone PK data and drug-liking data were available, were obtained.

The Cmax for plasma hydrocodone following intranasal KP201 API was approximately 36 percent lower compared to that found following intranasal hydrocodone bitartrate API. The time to achieve Cmax was also significantly delayed following intranasal KP201 API, 1 hour and 75 minutes, compared to following intranasal hydrocodone bitartrate API, median of 0.5 hours. However, do note that most of the rise in the mean plasma hydrocodone is achieved within 1 hour. Area under the hydrocodone plasma concentration versus time curves, AU, at all intervals were significantly lower following KP201 API versus hydrocodone bitartrate API.

No statistically significant reduction in mean maximum drug liking was found following

intranasal KP201 API compared to following intranasal hydrocodone API. Median time to maximum drug liking was 0.5 hours and 1.1 hours for hydrocodone API and KP201 API, respectively. One thing to keep in mind is that these data come from just one cohort, that is cohort 2, so you will see some differences between what I'm showing here versus what you saw earlier in the sponsors presentation, where it appears that both cohorts were used for purposes of drug-liking VAS.

The purpose of choosing just the cohort 2 alone for this presentation is because you have drug-liking and pharmacokinetic data from the same individual.

There are some deficiencies with this study, and they're included below. The study involved insufflation of KP201 API and hydrocodone bitartrate API and not the products KP201/APAP and Norco. As such, the study does not take into account possible effects of either mass of powder to be insufflated, that is 13 to 15 milligrams versus 850 to 1,100 milligrams, or the effects of

APAP on the insufflation experience as would occur following insufflation of the products.

There was no drug discrimination, also known as qualification phase. There was no placebo treatment for the treatment phase. And I think an important point is there were no additional subjective reinforcing measures, such as high and take drug again conducted, which could have been used to support observed effects of the drug-liking VAS.

In conclusion, an oral human abuse potential study KP201.A01 at similar dosage levels of low, medium, and high, oral KP201/APAP and Norco produced similar levels of drug liking, high, and take drug again. So this study failed the primary endpoint of Emax for drug liking.

The greater early exposure to plasma hydrocodone following median and high oral doses of Norco compared to that following similar doses of KP201/APAP did not translate to higher levels of drug liking, high, or take drug again.

In study KP201.A02, insufflation of Norco

and KP201/APAP produced similar maximum drug liking, high, and take drug again. There was a failure of the primary endpoint of the Emax of drug liking. Results of the take drug again VAS demonstrate that subjects have a similar willingness if given the opportunity to again insufflate either Norco or KP201/APAP.

The extent of drug liking but not of high, experienced over the first hour, as demonstrated by the areas under the effect curves, was higher following insufflation of Norco compared to insufflation of KP201/APAP. However, the clinical relevance of this higher drug-liking experience is not known, particularly in light of the fact that there was an absence of differences with respect to high, or the amount of euphoria that was experienced and recorded, and also in the take-drug-again measures.

For a variety of reasons noted in this presentation, study KP201.A03 cannot be used to assess either the abuse potential or abuse-deterrent effects of KP201/APAP tablets

against Norco via the intranasal route of administration. Thank you.

FDA Presentation - Rajdeep Gill

DR. GILL: Good morning. My name is Rajdeep Gill, and I'm a drug utilization data analysis team leader in the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will be presenting drug utilization patterns for combination hydrocodone/acetaminophen and other opioid analgesics from 2011 through 2015 to provide context for the discussion today.

The outline of my presentation will be as follows. First, I will discuss national sales distribution of hydrocodone/acetaminophen, followed by patient and prescription utilization of hydrocodone/acetaminophen and other opioid analgesics, with the focus on the outpatient retail settings. I will then present findings on top prescriber specialties, as well as diagnoses associated with the use of hydrocodone/acetaminophen and will end my talk with

limitations and conclusion.

Several databases were used to conduct these analyses. I will describe each database briefly before presenting the results of each analysis.

Our analyses are focused on hydrocodone/acetaminophen because the drug in discussion today, as you have heard, the benzhydro acetaminophen is a prodrug and gets metabolized to hydrocodone. We also looked at the opioid products market into which this product, if approved, will be introduced to, such as combination oxycodone/acetaminophen, immediate-release single entity oxycodone, oxymorphone, morphine, hydromorphone, tapentadol, and extended-release single-entity hydrocodone.

To determine the primary settings of care, we used the IMS National Sales Perspectives Database to provide the sales distribution data of hydrocodone/acetaminophen products sold from the manufacturers and wholesalers into the back door of various settings of care. These sales data are nationally projected to all settings of care.

As displayed in this chart, 72 percent of combination hydrocodone/acetaminophen products were distributed from manufacturers to retail settings, 25 percent to non-retail pharmacies, and 3 percent to mail order pharmacies. Therefore, the drug utilization analyses for the rest of my presentation will be focused on U.S. outpatient retail pharmacy settings.

For unique patient analysis, we used the IMS Health Total Patient Tracker Database. These data are based on a robust sample and are nationally projected. For prescription analysis, we used the IMS Health National Prescription Audit Database, which measures the dispensing of prescriptions from retail pharmacies into the hands of the patients via formal prescriptions in the U.S. The prescription data can be stratified by prescriber specialty as well.

This figure shows the nationally estimated number of patients who received a dispensed prescription for hydrocodone/acetaminophen and other opioid analgesics from U.S. outpatient retail

pharmacies from 2011 through 2015.

As shown in the top red line, the total number of patients who received a dispensed prescription for hydrocodone/acetaminophen decreased from 46.5 million patients in 2011 to 40 million patients in 2015. Although there is a decline in utilization, patients who received a prescription for hydrocodone/acetaminophen still accounted for the majority of patients compared to the rest of opioid analgesics in our analysis.

As shown in this figure, the total number of prescriptions, as shown by the top red line, dispense for hydrocodone/acetaminophen decreased from approximately 125 million prescriptions in 2011 to 90 million prescriptions in 2015. Similar to the patient data, hydrocodone/acetaminophen accounted for the majority of prescriptions compared to the rest of the opioid analgesics in our analysis.

This figures shows the top prescribing specialties for hydrocodone/acetaminophen in 2015. Approximately 28 percent of

hydrocodone/acetaminophen prescriptions were written by general practice, family practice and osteopathy, followed by internal medicine and dentistry at 12 percent each.

Now, we will transition to our analysis of diagnoses associated with the use of hydrocodone/acetaminophen. To determine this, we used a database that contains data from monthly surveys of 3200 office-based physicians representing 30 different specialties across the U.S. who report on all patient activity during one typical work day per month. These data are nationally projected by physician specialty and region and are helpful in characterizing the use of drug products in clinical practice.

The top diagnosis associated with the use of hydrocodone/acetaminophen for year 2014 reported as acute or chronic conditions by the prescribing physicians are shown here. Diagnoses coded to ICD-9 were linked to drug product mentioned during a patient encounter and then grouped into diagnostic categories that were collapsed to

3-digit ICD-9 codes.

Conditions reported by the physicians as acute accounted for approximately 51 percent of hydrocodone/acetaminophen drug use mentions while chronic conditions accounted for approximately 44 percent of the total drug use mentions.

Among the acute conditions, 42 percent of hydrocodone/acetaminophen use mentions were associated with diagnoses for injury and poisoning, which include injuries related to sprains, fractures, dislocation of joint, wounds and contusions, and 17 percent were associated with disease of the musculoskeletal system and connective tissue.

Among the chronic conditions, 54 percent of the hydrocodone/acetaminophen use mentions were associated with diagnoses for diseases of the musculoskeletal system and connective tissue, which include arthritic conditions and back pain, and 14 percent were associated with follow-up visits.

For limitations, only outpatient retail pharmacy-use was assessed. In-patient and mail

order pharmacy data were not included. The diagnoses data are based on physician survey data of an office visit. It is unknown if the patient ultimately received a dispensed prescription from the pharmacy.

Moreover, the diagnosis data obtained represent approximately 30 prescriber specialties but do not include prescribers such as dentists, which represents one of the top specialties that prescribed hydrocodone/acetaminophen as reported by the prescription data.

So in conclusion, there was a decrease in utilization of hydrocodone/acetaminophen from 2011 through 2015 with 90 million prescriptions dispensed and 40 million patients in 2015. The top prescriber specialties were general practice, family practice, osteopathy, followed by internal medicine and dentists. Hydrocodone/acetaminophen appear to be used widely for acute and chronic conditions that were often associated with musculoskeletal pain and pain related to injuries. Thank you.

FDA Presentation - Jana McAninch

DR. McANINCH: Good morning. It's barely still morning. I'm Jana McAninch. I'm from the Division of Epidemiology, and I'll be speaking about the relevance of snorting as a route of abuse for hydrocodone combination products.

First, I'll present some background information on hydrocodone combination products and on their misuse and abuse. I will also propose a framework for considering the relevance of specific routes of abuse for opioid products. Then I will discuss some key findings and limitations of the study reports submitted by the sponsor, as well as related studies in the published literature, closing with our overall interpretation of the available data on nasal abuse of these products.

Hydrocodone combination products, or HCPs, refer to the class of medications that contain immediate-release hydrocodone in doses up to 10 milligrams in fixed combination with a non-opioid active pharmaceutical ingredient, mostly commonly acetaminophen. Immediate-release

hydrocodone is currently available only as a combination product, and these products comprise the vast majority of the hydrocodone market.

As Dr. Gill just described, hydrocodone/acetaminophen products are the most widely prescribed opioid analgesics and remain so even after declines in prescription numbers following rescheduling in October of 2014.

Hydrocodone misuse and abuse are also widespread as you heard earlier. In 2011, there were an estimated 82,480 emergency department visits related to nonmedical use of hydrocodone. And according to the 2014 National Survey on Drug Use and Health, an estimated 24.3 million people in the United States have used hydrocodone for nonmedical purposes during their lifetime.

Some early data suggest that misuse and abuse of hydrocodone products may have declined after rescheduling. A recent publication reported a decrease in exposure calls to Texas Poison Centers involving hydrocodone misuse and abuse during the first six months after rescheduling with

a corresponding increase in coding related calls.

According to final FDA guidance issued last year, abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. Relevance is not explicitly defined in the guidance document, and this statement raises the question of how we might determine whether a route of abuse is relevant for a particular opioid product.

We can perhaps think about relevance in terms of the clinical and public health burden associated with a particular route of abuse. We can then consider two overarching questions that might informed by epidemiologic data.

The first is the question of scope, how widespread is abuse of an opioid via a particular route? In considering nasal hydrocodone combination product abuse, we can ask what proportion of abusers do so via the nasal route? How does this vary in different abuser subgroups? How often is snorting a preferred router an exclusive route? Do those who try snorting

hydrocodone combination products continue to abuse it via this route? And then, how might all these data translate to absolute numbers of individuals who snort hydrocodone combination products?

A second overarching question relates to adverse outcomes, what is the risk of harm associated with nasal abuse, and perhaps more specifically, what is the excess risk beyond that associated with oral ingestion?

To attempt to answer these questions, we reviewed reports from four NAVIPPRO studies submitted by the sponsor. These studies included two that describe information on recent drug abuse collected from adults and adolescents being assessed for substance abuse disorders in treatment centers and other settings participating in the NAVIPPRO surveillance network.

Also submitted were the results of two internet surveys conducted through the peer-to-peer online drug discussion forum, bluelight.org. These two surveys focused on different aspects of nonmedical use of hydrocodone combination products.

We also reviewed the published literature relevant to the question of both scope and adverse outcomes associated with nasal abuse of these products.

Next, I will discuss some key findings of these studies, first as they relate to scope and then to adverse outcomes.

As shown in this table, reported nasal hydrocodone combination product abuse is not uncommon in individuals entering or being assessed for substance abuse treatment, particularly among adolescents where approximately 43 percent of past 30-day hydrocodone combination product abusers reported snorting the drug as compared to 23 percent of hydrocodone combination product abusers in the ASI-MV sample of adults.

A third study published in 2013 examined drug abuse patterns in a sample of individuals entering non-methadone treatment for a prescription opioid addiction and found that 26.6 percent of participants whose primary drug of abuse was hydrocodone reported snorting the drug.

This table shows some additional analyses

based on the ASI-MV data, suggesting that nasal abuse is almost 3 times more common in those entering residential substance abuse treatment than in people assessed in correction settings. Those abusing multiple opioids are also roughly 3 times as likely to snort hydrocodone products as those reporting hydrocodone as the only opioid they abuse.

In this sample, a large majority of nasal hydrocodone abusers were found to have a considerable or an extreme drug problem based on addiction severity index scores, and nasal abusers were more likely than oral hydrocodone abusers to also abuse additional opioids.

This published study from 2010 further illustrates the variation in route of abuse patterns for hydrocodone products in different study populations.

This study examined opioid use in two convenient samples of nonmedical prescription drug users in Kentucky, one recruited from a rural Appalachian county and the other from a major

metropolitan county. Here, the rural abusers were substantially more likely than their urban counterparts to have used each of the opioids non-medically and to have done so via non-oral routes. For example, 64 percent of the rural participants had reported snorting methadone and 45 percent injecting OxyContin. Addiction severity index scores also indicated that rural participants had more severe drug problems.

In both groups, more than 90 percent reported using hydrocodone for nonmedical purposes at some point during their lifetime, but only 6.3 percent of the urban users reported snorting the drug, while 74 percent of rural users reported snorting it. No one in either group reported injecting hydrocodone.

As shown in this table, snorting is infrequently reported as the preferred or exclusive route by those using hydrocodone combination products non-medically. In the 2014 internet survey, more than one-third of nonmedical users of hydrocodone combination products reported snorting

these drugs at some point in their lifetime. However, only 6.7 percent reported that snorting was their preferred route for these products. And in the 2015 survey, 6.3 percent reported snorting as the route used at their most recent nonmedical use of hydrocodone combination products.

In additional data provided to FDA by authors of a published study using NAVIPPRO ASM-IV data, 5.5 to 7.5 percent of recent hydrocodone combination product abusers indicated only snorting as the route by which they abuse these products.

Data reported in the 2015 internet survey suggests that regular ongoing abuse of hydrocodone combination products via the nasal route may be relatively uncommon. Of the 394 respondents reporting continued use of hydrocodone combination products following their initial use, about three-quarters reported never snorting it.

Of the 26 percent who reported snorting it at some point during continued use, 3.3 percent reported daily snorting and 5.6 percent reported snorting a few times a week, while most reported

snorting these products a few times a month or less. The duration of continued use was not specified in this study.

Another important consideration is that because hydrocodone is the most commonly abused opioid, even a relatively small proportion of abusers snorting translates to absolute numbers that may be comparable to other classes of opioids. For example, this figure from the NAVIPPRO ASI-MV study shows the total number of individuals in the sample population who reported abusing selected groups of opioids by route of abuse.

In this sample, the number of individuals who reported snorting hydrocodone combination products is comparable to the number who reported snorting IR oxycodone products or opioids. This is in contrast to other non-oral routes where the number of individuals who reported injecting or smoking hydrocodone combination products was very low.

The study submitted by the sponsor, as well as those in the published literature, had

considerable limitations. Some important ones were that in general, the measures used for assessing route of abuse were not well-defined or validated. The referent time frame and intent of the questions was often not entirely clear.

For example, for each drug a respondent indicates they have used in the past 30 days, the ASI-MV and CHAT assessments asked, "How have usually used the drug? Please select all that apply," followed by a list of possible routes.

It's unclear whether the respondent is to select all routes that they have used or the one they used most frequently for this drug. And the referent time period is also somewhat unclear.

Second, the studies used convenient samples that may not reflect abuse patterns outside the sample population. First, the study samples are not geographically representative of the United States. For example, more than 70 percent of participating chat sites are located in the State of Missouri, and we know that drug abuse patterns vary widely across geographic regions.

Second, non-oral abusers may be overrepresented in the study samples. Both the ASM-IV and CHAT oversample individuals with more advanced substance use disorders and therefore non-oral abuse is likely to be more common in these samples than in a broader population of hydrocodone combination product abusers.

Recruiting survey participants from online drug discussion forums may also select for non-oral abusers as tampering methods and alternate routes are frequent topics of discussion on these websites, and it's possible that those interested in abusing via these routes may be more likely to visit these sites, and therefore be invited to participate in the survey.

So to summarize the available data on the scope of hydrocodone combination product nasal abuse, the estimated prevalence of nasal abuse among hydrocodone combination product abusers varies widely depending on the setting and characteristics of the study population and how the questions about route of abuse are asked.

The available data suggests that snorting is not an uncommon route in certain populations of hydrocodone combination product abusers, particularly adolescents being assessed for substance abuse treatment, those with more advanced addiction, and those abusing multiple opioids.

Snorting is infrequently identified as the preferred or the exclusive route for abusing hydrocodone combination products and ongoing regular nasal abuse may be fairly uncommon among nonmedical users of these products.

Moreover, none of the studies provide information on nasal abuse of hydrocodone combination products in the general population, which likely includes more experimental or recreational users without advanced substance use disorders.

However, as I discussed earlier, misuse and abuse of hydrocodone combination products is widespread in the United States. Therefore, even a relatively small proportion of hydrocodone combination product abusers snorting may translate

to a large absolute number of people potentially exposed to harms from nasal abuse.

So this leads to the second question related to relevance of snorting as a route of abuse: What are the potential adverse effects of snorting hydrocodone combination products and what are the risks of these adverse outcomes?

As you've heard earlier, a number of case reports and case series have described damage to nasal passages, including tissue necrosis, perforated septum and palate, and fungal infections in patients with a history of nasal drug abuse, particularly combination opioid acetaminophen products.

In some cases, nasal hydrocodone combination product abuse was confirmed. However, drug abuse histories were typically incomplete, and some patients reported nasal abuse of other opioids, including oxycodone, as well as non-opioid drugs such as cocaine. Although these case reports are concerning, the actual incidents of nasal tissue damage associated with nasal abuse of hydrocodone

combination products is unknown.

Arguably, the outcomes of greatest concern with prescription opioid abuse are addiction and overdose. Nasal abuse is associated with more advanced drug use disorders. This has been described previously for prescription opioids in general and appears to apply to hydrocodone combination products specifically as well, as I have just discussed.

The existing data shed little light on whether this practice is more a cause or a consequence of worsening substance use disorder however, or on whether an opioid formulation that reduce nasal abuse would decrease the likelihood of an individual becoming addicted, or whether as tolerance develops, he or she would simply take more tablets orally or turn to other more potent opioids.

Unfortunately, the epidemiologic data are extremely limited with regard to the role of nasal hydrocodone product abuse in overdoses related to these drugs. Neither national overdose death data,

nor coded administrative overdose claims indicate specific prescription opioids or route, and data sources relying on medical record review, for example emergency department visit cases, also do not capture route of abuse consistently.

One published study analyzing West Virginia medical examiner records looked at 295 unintentional overdose deaths involving prescription opioids. Of these, 22.4 percent were known to have involved a nonmedical route of administration. However, it was not specified whether any of these involved nasal administration of hydrocodone products.

A separate published analysis of call data from U.S. poison centers suggests that nasal and parenteral opioid exposures may be associated with more severe outcomes. But again, the data do not indicate to what degree this finding applied to hydrocodone products specifically.

This figure is from a published analysis of 2006 U.S. poison center call data showing the number of exposure calls for selected opioids with

an outcome of death stratified by route of administration. The analysis found that in this single year of data, unlike for the other opioids, none of the fatal poisonings attributed to intentional misuse or abuse of hydrocodone involved inhalation or parenteral routes.

Several limitations of the poison center data must be considered, however. First, a caller may not always recognize or report non-oral routes of exposure even when they had, in fact, occurred. Second, unattended fatal overdoses will generally not result in a call to a poison control center, and therefore would not be captured in these data. In that more severe overdoses may be more likely to involved non-oral routes, these cases may be underrepresented in this database.

Finally, it must be kept in mind that the number of fatal opioid poisoning cases captured in poison control data represent a very small fraction of fatal opioid overdoses that occur nationally each year.

In addition to these very limited

epidemiologic data, we can consider the role of clinical and pharmacologic factors in assessing the risk of harm associated with nasal hydrocodone combination product abuse.

First is the relatively low dose of opioid that these products contain compared to the higher potency dosage forms available for single-ingredient opioid analgesics, particularly the extended-release long-acting opioids where nasal administration of crushed tablets has the potential to result in rapid absorption and bioavailability of a very high dose of opioid.

Second is the limited amount of material that can be administered nasally and absorbed at any one time. Third, although cases of fungal rhinosinusitis have been reported with opioid acetaminophen snorting, this route does not have the same level of infectious risk associated with injection.

Finally, in thinking about the excess risks associated with snorting hydrocodone combination products beyond those associated with the intended

route of ingestion, one must consider the substantial potential for harm associated with ingestion of supratherapeutic oral doses of acetaminophen-containing combination opioid products.

So in summary, the true incidence of adverse outcomes associated with nasal abuse of hydrocodone combination products is not known. There have been case reports of nasal tissue damage and infection associated with opioid acetaminophen combination products, but other opioid products and illicit drugs may have played a role in these cases as well.

Clinical and pharmacologic factors suggest that snorting hydrocodone combination products likely confers a lower risk of overdose than snorting single-ingredient higher dose opioid products. And finally, very limited data suggests that hydrocodone-related overdose deaths primarily involve oral ingestion.

In conclusion, the epidemiologic data interpreted within the context of what we know

about the clinical and pharmacologic characteristics of hydrocodone combination products suggest that the absolute numbers of individuals that have snorted hydrocodone combination products may be quite large. However, nasal abuse may make a relatively small contribution to the overall harms associated with misuse and abuse of these products. Thank you.

Clarifying Questions

DR. BROWN: We're now going to move on to clarifying questions for the FDA. We'll move back to clarifying questions for the presenters after lunch.

Are there any clarifying questions for the FDA at this point? Please remember, if you are asking questions, please state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. First of all, I want to really congratulate FDA for the really very informative presentation,

particularly on the epidemiologic data, which is obviously extremely limited. So putting together such a multifaceted view of all the data that is out there together, really identifying all the areas where we have lack of information and what we know from different sources is, I found, very impressive and want to thank you.

So the question is for slide 5, very simple, for Dr. McAninch, just because we've, I think, addressed this or talked about this a little bit before. In terms of terminology, can you give us the definitions for the terms "misuse," "abuse," and the specific definitions that were used in the two different references, 1 and 2, for nonmedical use? Or were these narrow definitions where it was specifically a question of, was the use to get high or was it --

DR. McANINCH: Yes.

DR. HIGGINS: -- any use that was not according to the package insert?

DR. McANINCH: Right. The definitions vary across every data source. But in general,

"nonmedical use" is a broader definition that includes both abuse, which we typically consider use to get high for some psychologically rewarding effect, as well as "misuse" which is use not according to the recommended prescription. And that would include taking someone else's medication but not specifically for the purpose of getting high.

So we think of abuse and misuse as being mutually exclusive, and then nonmedical use incorporates both of those. That's I think a rough breakdown of how those are used in the different databases.

Is that helpful?

DR. BROWN: Dr. Emala?

DR. EMALA: My question's for Dr. Stevens, slide 12. I think this gets very close to a question I asked this morning. I just want to ask your opinion on the solvent.

This basically shows under stress conditions, 2 and 3 hours, 80 percent extraction in Solvent G. Would you agree that Solvent G is very,

very close to Solvent X that we looked at earlier?

DR. STEVENS: Yes, I would. I think they're pretty much, almost identical in their properties.

DR. EMALA: And Solvent X under Stress Conditions 1 at 4 hours was about 60 percent, so this makes sense that with better stressing and shorter time, 80 percent extraction?

DR. STEVENS: Yes, and I'll even add to that a little bit. One of the reasons, as I pointed before, that we requested this follow-up study, based on an information request, was because, to some extent, the definition that was being used previously as an advanced buffer somewhat takes the results out of context. And I think when you look at this very specific solvent, it makes it a lot more apparent that this data is very relevant to what's commercially available and what's potentially useable by an abuser.

DR. EMALA: Thank you.

DR. STEVENS: Yes.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is for

Dr. Tolliver, and it relates to slide 14.

So one of the advantages of the product suggested by the sponsor was that abusers will not obtain a rapid high if they snort the medication compared with Norco.

I was interested in the fact that the high VAS was first measured at 30 minutes, and is there a potential we would be missing some of the benefit associated with the drug by having the measurements so far out from the time of snorting? Is this a standard approach to this kind of study?

DR. TOLLIVER: I'm having trouble hearing so -- are you able to --

DR. BATEMAN: So why was high VAS first measured at 30 minutes? Why not at earlier time points that might be more relevant if there is fact some advantage with this product in delaying the onset of high?

DR. TOLLIVER: Yes. We may be missing some time points in there. I can't deny that. I mean, that's -- how that curve goes between 0 and 0.5, I don't know. We don't have it in our slide.

DR. BATEMAN: Are high VAS not typically measured at earlier time points or is this just the way the graph was created, or were the data not generated? And maybe the sponsor can respond to it.

DR. MICKLE: Sorry. What was the question?

DR. BATEMAN: The first time point at which high VAS was measured as shown in this graph is at 30 minutes.

DR. MICKLE: Right.

DR. BATEMAN: And in your presentations, you talked about the advantage of the product being a delay in the onset of high and abusers not getting the immediate high they expect when snorting the medication.

So I would think it would relevant to measure the high VAS at very early time points after nasal ingestion.

DR. MICKLE: I think the reasoning behind the clinical design here was merely a clinical practice. And maybe, Dr. Webster, you'd be helpful here as well having actually conducted these

studies.

It's very difficult for subjects to do so many scores and to take blood and take vital signs. Again, there was a 15-minute time point, as well as a 5-minute time point, so 5, 15. It just felt that capturing drug liking, as it's typically measured using the bipolar scale, made more sense here than trying to capture all secondary measures.

Dr. Webster?

DR. WEBSTER: Yes, that's correct. Actually, since liking or Emax is really the primary endpoint and high is not, so you have to push something around. You're going to have to push the assessment of a high off so that you can just practically get everything in.

DR. BROWN: Dr. Stergachis?

DR. STERGACHIS: Thank you. Andy Stergachis. This question is also for Dr. Tolliver, slide 15, the next slide. Noted is that the similarities in each of the three endpoints between the comparator and KP201, I'm trying to understand that better.

Does that imply that the prodrug is somehow cleaved to hydrocodone through esterases in the blood? I'm just trying to understand why we're seeing the similarity between the two products.

DR. TOLLIVER: One of the things that I mentioned is the large amounts of powder that are being insufflated. So for example, with KP201, the subject is requested to insufflate 1.1 grams of powder.

One of the possibilities is that they're insufflating it, and some of it is going down into the throat and into the stomach where it's being converted, and that's a possibility. And part of it may be absorbed through the intranasal route as well. So I think those two were possibilities.

DR. BROWN: Dr. Hertz?

DR. HERTZ: You might want to put up slide 55, which shows the PK of exposure to hydrocodone. And again, it doesn't say where the conversion is taking place, but it does show the plasma concentrations with study A02.

DR. BROWN: Dr. Hertz, which presentation is

that from?

DR. HERTZ: Oh, I'm sorry. That's actually the sponsor's that I'm looking at.

(Laughter).

DR. HERTZ: Slide 12 of FDA.

DR. MICKLE: Actually, we would agree with Dr. Tolliver. It appears that the majority of the material actually goes down in the back of the throat when you have so much of it there. And certainly, you can see that Norco, even though you have more material, a lot of it does get absorbed very rapidly when insufflated.

DR. BROWN: Dr. Craig?

DR. CRAIG: Thank you. Maybe this is for Dr. Tolliver. The FDA is using the outcome measure of Emax as the differences in comparing the two groups here and specifically in study A02.

The sponsor discusses Emax and found no differences. The sponsor then again uses a different abuse coefficient calculation, and then their slide set shows a significant difference between the two groups. I know the FDA is using

Emax as the comparator as the sponsor found no difference, as the FDA found no difference in Emax.

Can you comment on the importance of the abuse coefficient here and if it's useful?

DR. TOLLIVER: Are you talking about the quotients that he mentioned? Okay. Well, that's in regard to pharmacokinetics. So the quotient that they were talking about was Cmax over Tmax.

One of the things to keep in mind is that both of these primary studies that were done, they were actually small -- there were some differences observed between the pharmacokinetics versus the pharmacodynamics. All right? You got certain pharmacokinetic effects such as maybe a change of the early total exposure, drug exposure, reflected in the area under the curve. And you saw that for example in the oral study and it was a significant difference.

However, when you went to any of the pharmacodynamic measures, drug liking, high, there was no effect. There was no difference. This is one of the things that I was stressing.

Likewise, when you go into the intranasal study, again, we saw there's this difference in the pharmacokinetic -- between the pharmacokinetics versus the pharmacodynamics, as far as I'm concerned, in two respects, at least two out of three.

One is that, again, we saw the increase in early drug exposure as reflected by the pharmacokinetics. Now, that was reflected with respect to drug liking, in the early drug-liking experience. So maybe there's something there. But when you go into high, at least from the data that we have and things like that, it was not there.

So I'm not sure how relevant, really, is this difference in quotient thing, this abuse-deterrent quotient paradigm -- parameter is.

I'd also say that, think of the difference, the large difference that was found in the third study in the pharmacokinetics, this really large rise with early rise with Norco versus the API for KP201.

To me, that was not reflected, really, in

the drug liking. Now, that's the only measure that was done. It really would have been nice to see more measures to see how it would have reflected. But, you do see a limited change in the area under the curve for the first hour in that third study, too, but you didn't see the change in Cmax. And if you look at the median TEmax, it was a lot earlier than what you might expect with the Tmax with the pharmacodynamics.

So I'm not sure there's a total connect between the pharmacokinetics and the pharmacodynamics.

DR. HERTZ: I just want to add the other point being I think that drug liking is an important outcome -- this is Sharon Hertz -- but it's not often that the single endpoint is going to describe an effect fully, which is why we thought it important to provide the three that we think are very relevant in this setting.

Human abuse potential studies are used for different purposes in different settings. The original purpose was to assess the abuse liability,

the abuse potential. We're using them in this not perhaps initially intended role of evaluating the abuse-deterrent properties.

So within that context, we think that if you want to show whether there is a deterrent effect, one should look at whether there's a difference in willingness to take the drug again for the purposes of getting high.

So that's why we present -- even though it's a secondary, we think it's critically important to provide context for the differences in drug liking or drug high because we know -- as committee members, you all know that often statistical significance in a difference versus clinical meaningfulness in a difference in outcomes are not always the same. So we look at liking, high, and take drug again as a combination to provide context for that finding.

So I think the quotient is an important analysis when evaluating properties of a controlled substance. But when looking deterrent effects, it might not be the most relevant of the outcomes

available or analyses available.

DR. BROWN: Dr. Morrato?

DR. MORRATO: I had a similar question to Dr. Craig's, so I thought it was very helpful what you said, Dr. Tolliver. No, you don't have to go back up. I just wanted to thank you because it helps I think interpret the clinical meaningfulness of the data.

My question was actually for Dr. Stevens. I want to commend you. I thought you really helped walk us through not just the data but how to think about and interpreting it, so it was very helpful. And I was wondering whether or not -- you made a very compelling argument with the chemicals and methods that were being tested, but had the FDA considered enzymatic challenge as well?

I know Dr. Emala brought earlier pancreatic enzymatic mixtures. The sponsor answered in response to one that they have data on singular enzymes. And I was wondering if you considered any of that in sort of the totality of your assessment of ease of circumventing the abuse-deterrent.

DR. STEVENS: Yes. I think the answer to that in general is no. I think the reasoning for that is that the condition that we typically ask for and that are requested in the guidance tend to focus on things that would be commonly used that we think the vast majority of common abusers might try or use or find available.

I certainly don't think that means that you wouldn't see very interesting results with enzymatic processes, and, again, who knows, there may be a response once the products comes unto the market and developing novel conditions that we may not have looked at during the submission.

But overall, the answer is no. We don't usually ask for that, and we don't usually look at it.

DR. MORRATO: Was there any data in the application, though, that came from more of the analytic chemistry kind of profile?

DR. STEVENS: Certainly not as part of the abuse-deterrent studies. There may have been under, for example, the clin-pharm sections or PK

sections, but I would not have reviewed those very carefully.

DR. MORRATO: Okay.

DR. BROWN: Thank you. We will now break for lunch. We're going to reconvene again in this room in one hour -- or actually at about 1:30, if we could be back by 1:30.

Please take any personal belongings you may want with you at this time. Committee members, please remember there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any other member of the audience. Thank you. See you at 1:30.

(Whereupon, at 12:38 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

Open Public Hearing

DR. BROWN: If we could return to our seats and let's get started. This is the open public session.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the 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 speakers, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your

attendance at the meeting. Likewise, the 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 the 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. With that said, in many instances and for many topics, there will be a variety of opinions.

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

Will speaker number 1 step up to the podium

and introduce yourself?

(No response).

Speaker number 1?

(No response.)

DR. BROWN: Speaker number 2?

MR. PHILLIPS: As there are two of us, I guess I get to speak for number 1 and number 2.

First off, unfortunately, I do not have any financial incentives or anything from the founder -- the sponsor. My name is Julian Phillips. I'm with the U.S. Pain Foundation, which is an organization, and it has become the largest pain organization in the country with approximately 100,000 members nationwide. Our mission is to try and advocate and support people with pain no matter the cause or reason.

I have lived with pain for the past 34 years. I have what's called RSD, reflex sympathetic dystrophy. I'm sure you're all aware of it or chronic regional pain syndrome as some people like to call it. It started 34 years ago, as I said, when I simply dislocated my finger, and

it's become a problem ever since.

I came up to Pennsylvania, having first came over to Florida, because as you can gather from my accent, I'm not from here originally. I moved up to Pennsylvania. I thought I had a great job, but the job caused me to keep using my hand, which ultimately ended up causing me to have to go on disability, which I detest.

I do also have to use opioid medications, which again I rather detest having to use because they cause other problems such as OIC. The medication, though, has at least made it possible for me to have some kind of life. Before, I didn't have a life. I was just in bed basically rolling around in pain.

My situation is typical of thousands of members who live with severe debilitating pain. Everyone who lives with pain must find their right combination of treatment options that help reduce their level of daily pain.

The IOM has reported that a 100 million Americans live with pain, and at least 10 percent

of those, or 10 million Americans, have pain so severe that they are disabled by it. Just this past August, the NIH reported on a study that found 40 million experience severe pain every year and 25 million experience daily pain. These numbers are absolutely staggering.

Opioids, analgesics do not help everyone who live with chronic pain, but they do help many thousands of Americans to function and have some quality of life. For these people, their medication is often a lifeline that can make the difference between a life worth living or not.

The purpose of this meeting today is to consider whether a new formulation of hydrocodone/acetaminophen short-acting immediate-release opioid product has abuse-deterrent properties sufficient to support such labeling.

Hydrocodone/acetaminophen combination products are the most commonly prescribed medications in the country and for good reason. They're highly effective for both acute and chronic

pain. They are useful and appropriate for a wide range of painful conditions and diseases and have relatively few side effects.

The combination presents addictive and synergistic pain-relieving effects, thereby reducing the amount of opioid and non-opioid required with pain relief while decreasing the chances of adverse events.

Approximately 47 million Americans use hydrocodone containing analgesics in 2011 because they provide excellent pain relief. It's essential that these combination medications remain available to millions of Americans that need them to manage both acute and chronic pain. At the same time, we know that these medications are highly abused, so it is critical that we do all we can to deter such abuse.

The KemPharm product being considered today uses a novel approach such that active hydrocodone ingredient in the medication remains inert until it is broken down in the patient's gastrointestinal tract. So the usual methods of abuse such as

crushing or melting the pill to readily access the opioid substance will not produce any euphoria.

Consequently, if this product labeling is approved, prescribers will have a safer therapeutic option with novel abuse-deterrent technology available for their patients who need pain relief. Prescribers will be able to have a level of comfort --

DR. BROWN: Mr. Phillips, if you could wrap it up, please, sir?

MR. PHILLIPS: Certainly. Prescribers will be able to have a level of comfort not now possible with the medication they are prescribing is highly likely not to be used. And currently, there are obviously a lot of pain management doctors who are no longer prescribing these medications because of the state and federal, as well as media actions against them. Thank you.

DR. BROWN: Thank you. Speaker number 3?

DR. TWILLMAN: Good afternoon. My name is Bob Twillman. I'm the executive director of the American Academy of Pain Management. I have no

financial conflicts to report.

The Academy espouses a model of integrative pain management recognizing the important role played by traditional biomedical treatments for pain, such as medications and procedures, but also advocating for additional treatments that may supplement, complement, or even replace them and the service of providing maximal improvement in pain and functional status for people with pain.

The Academy is keenly aware that opioid pain relievers and other controlled substances have become controversial because of their prominence in prescription drug abuse. We've been active in a variety of policy advocacy efforts related to these two major public health concerns.

One subject of these efforts is the development and uptake of so-called abuse-deterrent technology for controlled substances. We believe that this technology in general, and particularly the technology incorporated into this specific product, represents a significant incremental advance in efforts to protect people from

unintentional overdose, and that these products as a short-acting opioid is especially important given that we've seen a shift where short-acting opioids as the primary drugs of abuse since the introduction of ADF long-acting opioids.

The experience to-date with the one long-acting product that has a sufficient history of use to permit evaluation demonstrates that ADFs may very well prevent a significant number of individuals from engaging in this dangerous behavior, thus providing a meaningful benefit.

There have been questions asked about how many people abuse hydrocodone by snorting, but there is no question that it is a route of abuse. Approving this product then is a win-win. It will prevent some abusers from accidentally overdosing and it will ensure access for people with pain.

We're grateful to the FDA for its efforts to support the ongoing development of ADF technology. We also recognize, as I'm sure everyone here does, that this is not a static process with a well-defined endpoint.

People who tamper with these products in order to abuse them are very creative, and history has shown they are adept at overcoming efforts to thwart them. Thus, we find ourselves in sort of a continuing arms race, either to constantly develop new and better technologies in order to stay even a few steps ahead.

For that reason, I want to take this opportunity to encourage both manufacturers and FDA to continue innovating in the ADF space, developing new approaches that may be even more impervious to or discouraging of alternation, even if those new approaches only buy us a few years of relative success.

Our policy advocacy efforts related to ADFs also are focused on one of the troubling aspects of this form of innovation, namely the burden it places on people with pain who have no intent whatsoever to do anything other than use their medication exactly as prescribed in order to obtain pain relief.

Unfortunately, research and development

process that produces these valuable new products is expensive. The cost of that process inevitably is passed along to consumers. The end result is that people with a legitimate medical need for opioid analgesics, using them exactly as prescribed for pain relief, are forced to foot the bill for protecting others who are using the medications illegitimately in dangerous ways that were never intended.

It's patently unfair that this happens, and while many patients can understand why it's a sort of necessary evil that enables them to have access to their medications, we need to find ways to ensure that this unfair burden does not result in patients foregoing pain relief for financial reasons.

We'll continue working on this issue in federal and state legislative bodies and regulatory agencies, hoping that more will emulate success as seen today in Massachusetts and Maryland. While we do that, hoping that others will join us to overcome opposition derived from the fiduciary

interest of the insurance lobby, we hope that FDA will continue to encourage and that manufacturers will continue to pursue innovations that will bring us a few steps closer to the ultimate goal of being able to provide pain relief while minimizing risks to those who misuse these vital medications.

Thank you very much for the opportunity to speak.

DR. BROWN: Thank you. Can we have speaker number 4?

MS. KULKARNI: Good afternoon. I'm Shruti Kulkarni, and I'm a policy advisor to the not-for-profit Center for Lawful Access and Abuse Deterrence, CLAAD. CLAAD's funders include treatment centers, laboratories, and pharmaceutical companies and are disclosed on our website at CLAAD.org. Thank you for the opportunity to provide CLAAD's input on the abuse-deterrent properties of the proposed immediate-release formulation of benzhydrocodone and acetaminophen, KP201.

CLAAD works to reduce prescription drug

fraud, diversion, misuse and abuse, while also ensuring that individuals with legitimate need have lawful access to medications that safely and effectively treat their health conditions.

Our organization has taken an active role in encouraging a market transition of all commonly abused medications to abuse-deterrent forms. We're pleased that industry is responding to our coalition's call for research and development of safer medications to reduce prescription drug abuse.

Medications like KP201 can satisfy patient needs and improve public health and safety. In assessing KP201, we urge the committee to consider the following.

Elderly individuals and others with pain who have difficulty swallowing may benefit from an opioid pain reliever that may be crushed or ground into apple sauce, for example, without additional risk of harm.

With respect to intranasal abuse, data presented by the Centers for Disease Control and

Prevention at the recent National Prescription Drug Abuse & Heroin summit showed that the most common transition pathway for oral opioid abuse to heroin use is starting with oral ingestion of pills, moving to crushing and snorting of pills, continuing to snorting of heroin, and finally injecting prescription opioids and heroin.

The ability to make intranasal or any other form of abuse more difficult or less rewarding is a desirable feature in any opioid. This fact is underscored by yesterday's headline that even anti-diarrhea medications are being misused for their opioid ingredients.

Prodrug technology that limit the availability of active pharmaceutical ingredients when medications are manipulated can reduce the appeal of such drugs for purpose of abuse. For example, if a novel medication, when manipulated, makes over 50 percent less hydrocodone available for abuse per pill as compared with a traditional formulation, or it takes longer to abuse than the traditional formulation, then the novel formulation

effectively increases the cost of drug abuse, which can lower the demand that fuels drug diversion.

Abuse-deterrent opioids, therefore, can disrupt the market of medications sought for purposes of abuse, which can then provide meaningful opportunities to intervene and refer individuals with opioid use disorders to effective treatment.

Finally, every time an abuse-deterrent medication enters the market, it increases the likelihood that we can improve the quality of healthcare, spur competition, fund additional research and development, and eventually provide patients with effective treatments that pose minimal risk of addiction and overdose.

For these reasons, CLAAD urges the committee to consider the value of abuse-deterrent opioids to both patients and the public as it considers KP201 today.

Thank you for this opportunity. Please contact CLAAD if we can be of service to you.

DR. BROWN: Thank you very much. Speaker

number 5?

MS. McLAUGHLIN: Members of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, good afternoon. My name is Heather McLaughlin. I'm the corresponding secretary of the National Association of Drug Diversion Investigators, otherwise known as NADDI, a position I've held for over 20 years. I have no financial relationship.

I currently work for the Maryland Department of Health and Mental Hygiene. For over 25 years, I held positions at the Maryland Board of Physicians, and I'm currently working for the Maryland Board of Pharmacy. I am here today representing NADDI.

Relief from pain is important to millions of individuals who suffer from chronic illness and prescription drugs such as opioids -- have proven a valuable tool in the relief process. However, the potential for the abuse of prescription drugs, especially opioids, presents a significant risk. And as we are all aware, the misuse and abuse of

opioids has reached epidemic levels in many of our states.

Prescription drug abuse is the fastest growing drug problem in America, one that does not discriminate by region, socioeconomic status or age. The Centers for Disease Control and Prevention have identified prescription drug abuse as an epidemic, reporting more than 15,500 American deaths each year from prescription pain killers.

An important step in the abuse prevention process for both new and chronic pain sufferers is the development of tamper-resistant formulas for opioids.

NADDI is a nonprofit membership organization that works to develop and implement solutions to the problems in prescription drug abuse and diversion. It advocates for the responsible use of prescription drugs by people who need them and at the same time aggressively works with law enforcement and regulators to pursue those involved in related criminal activity.

Our primary focus is training and education

for our members, which include law enforcement personnel, regulatory agents, health professionals, healthcare fraud investigators, and pharmaceutical companies.

Continuing progress in the field of pain management involves a juggling act that balances the needs and interests of those involved. The development process involves all the stakeholders in the medical treatment of pain, clinical, legal, regulatory, law enforcement, industry, commercial, personal, and societal.

NADDI recognizes that no one approach to maintaining this critical balance will succeed unilaterally. Therefore, NADDI supports ongoing interaction and cooperation among all who can impact the access to and provision of competent healthcare and who can affect diversion and abuse of medications.

A scientific approach was taken to reduce illegal street activity. In speaking with and surveying NADDI law enforcement members at our trainings throughout the country, it appears likely

that the rates of diversion decreased dramatically after the introduction of reformulated opioids.

In October 2014, hydrocodone combinations were rescheduled as class 2 controlled substances. The rescheduling of hydrocodone combinations had a dramatic impact on their prescribing. According to the U.S. Department of Health and Human Services, 26.3 million fewer hydrocodone combination prescriptions were written in the first year after rescheduling, amounting to approximately 1.1 billion fewer dosage units.

Adding new physical and chemical features to prescription opioids to deter abuse could also reduce misuse of these drugs and the sometimes deadly consequences. These products can be part of a comprehensive approach, which should include prevention, interdiction, prosecution, and substance abuse treatment.

While the first generation of abuse-deterrent formulations have reduced diversion, any advances in this technology would further erode the street value of opioids and

maintain access to the individuals who would benefit from their relief would be welcome.

Due to the ongoing problems with pharmaceutical drug abuse and diversion in the United States, NADDI is a strong proponent of new abuse-deterrent medicines that make it more difficult for an abuser and reduce law enforcement involvement in healthcare. NADDI has a strong belief that the illegal diversion of prescription medication has a direct negative impact on legitimate patients, the vast majority who use controlled substances. Thank you.

DR. BROWN: Thank you. Speaker number 6?

DR. SCHATMAND: I'd like to start by thanking you for allowing me to testify before this committee today. I'm Dr. Michael Schatmand. I'm here as the director of research for the U.S. Pain Foundation, where much of my pro bono work includes advocating for patients with pain. In order to fully disclose, I'm not being paid by KemPharm to promote their product, although they were generous enough to pay my way to Washington for today's

meeting. Seattle is a long way.

I worked, although trained as a clinical psychologist, for the past 31 years in pain medicine. I still see patients half time, so I'm in the trenches, but I also train physicians. I've been a researcher, an author. I'm currently the editor-in-chief with the Journal of Pain Research.

I think importantly, in the context of this meeting, I'm also a pain bioethicist and likely have the strongest publication record in the world regarding ethical issues in pain management over the past decade. And I see, and some of my colleagues with whom I'm spoken, the approval of hydrocodone as a moral imperative.

Despite the protestations of anti-opioid zealots and health insurers frequent refusals to cover them in their efforts at cost containment and profitability, abuse-deterrent and tamper-resistant formulations of opioids need to be considered the future of opioid analgesia.

Accordingly, their use in appropriate patients in appropriate situations needs to be

encouraged and even incentivized. Even without completely clear data supporting the extent of the problem, as a practitioner, I've seen too many patients and far more often their friends and family members abuse hydrocodone nasally and intravenously over the years, and the lack of availability of abuse-deterrent formulations for short-term use will perpetuate this problem.

I emphasize "short-term use" as I believe the chronic opioid therapy ought to be considered only among well-selected patients for whom no other pain management approach is likely to be effective or accessible.

Again, there's a moral imperative, and even if it's only an incremental improvement, I believe that this drug is going to save many lives, and I have not been able to identify a down side to this medication even if not perfect.

The relative safety of benzhydrocodone has been established and has been discussed in the recent articles by Dr. Gudin who spoke today and Dr. Machu [ph] in post-graduate medicine. Really,

what's left is only to determine the extent of the efficacy of this prodrug formulation. While abuse deterrence in terms of nasal and intravenous administration have been established, there are also some signs from the research, as I read it, that enzymatic saturation in the GI system may limit the drugs' absorption if taken at ultra-high doses as well orally.

The only way that the FDA will have the clear epidemiologic evidence of benzhydrocodone's full abuse deterrence potential will be if the medication is approved with KemPharm planning an aggressive postmarketing surveillance as discussed by Dr. Mickle. At that point, we'll know just how effective it is in terms of preventing abuse, diversion, addiction, overdoses, and deaths. But again, what is the downside?

Let me conclude by telling this committee I've seen grandmothers in their late 70s and 80s undergo routine hip and knee replacements and to be sent home with short-acting, non-abuse-deterrent and non-tamper-resistant formulations of opioids.

A few would suggest that opioids are not appropriate in such situations, even the zealots, as no one should have to suffer from post-operative pain without analgesia. Furthermore, data indicate that rehabilitation among these patients progresses better if analgesia is provided on a short-term basis such as the maximum two-week period of time for which benzhydrocodone is being recommended for use by its manufacturer.

While the grandmothers themselves may not necessarily be at high risk for inappropriate utilization, their children or grandchildren perhaps may be at such risk with Dr. Gudin presenting the particularly high risk for nasal administration among adolescents.

So although a solid body of data on this medication's likeability has not yet been collected, it seems relatively obvious that it's going to be considerably less likely to be abused because it's more of a problem to do so, and that those with problems with addiction will seek other non-abuse-deterrent or tamper-resistant

formulations, which, as Dr. Darnell and I wrote in 2014, remained far too easily accessible.

In conclusion, benzhydrocodone is not a panacea, nor will it completely cure the nation of the scourge of prescription opioid abuse. However, given the likelihood that it will represent a significant improvement without a downside, please give this medication some serious consideration for approval. Thank you.

DR. BROWN: Thank you. Speaker number 7?

MR. BRASON: Good afternoon. My name is Fred Brason. I represent Project Lazarus as CEO, and I'd like to thank the committee for giving me this opportunity to share.

We are a nonprofit organization that basically is taking a public health approach to reduce and prevent overdoses from prescription medications, but also at the same time to present responsible pain management and promote substance use treatment and support services; basically being a person-first organization so that the person with pain gets the care and treatment that they need and

the person with substance use disorder gets the care and treatment that they need within our communities in North Carolina and elsewhere, and making sure that there's a balanced approached with that.

Well, I come from Wilkes County, North Carolina, and unfortunately, in 2007, we were the third worst county for prescription drug overdoses in the country based on CDC data. We had many different social determinant factors within our rural community from poverty and trauma and other issues to where we got the marvelous M's: the moonshine, marijuana, meth, and medicine issues that create a sort of an underground economy because of the desire for the medications from individuals that have substance use issues.

This just a quick listing, over the past year and a half or so, of arrests within our county for roundups from those who are diverting prescription medications mainly, though some of this is marijuana, and meth, and cocaine. But just recently in April, there were 73 people in one

roundup from undercover work, mostly prescription medications and mostly obtained from outside of Wilkes County because we've been doing so much work among our practitioners.

But when we see now that Wilkes was second in the United States of all the counties for income loss from the year 2000 to 2014, we see some of the social drivers why it becomes a public health issue. And abuse-deterrent formulations help us take those steps in order to stop the pervasive diversion, but also to stop the overdoses and hopefully stop the progression of individuals falling into substance use disorder and addiction.

Though it's hard to read and there's a lot on there, these are 13 individuals from January of 2015 to October of 2015 that died from an overdose in Wilkes County. These were Wilkes County residents, and you can see the amount that was found in the toxicology testing that was done from those overdoses.

So you can see what we're up against within the communities in the Appalachian region and

elsewhere, and why we need every tool in our toolkit to be able to combat this, because the social determinants, we can't turn around over night; that takes much more time. But when we reduce the availability and the access to those that can be obtained from medicines and having them abuse-deterrent makes a huge difference.

As I talk with our substance use providers, both in Wilkes County and other places, and I talk about the progression, help me understand that, ingestion and moving on from snorting to injecting, when I talk about that, they say it's now more than ever and it's just commonplace because that's what individuals are doing. Anything that has a time delay, they want the instant response to the ingestion or the snorting and injecting that they're doing, and it's important to deter that because that's what they don't want, then.

We realized early on with abuse-deterrent formulations, when they first started to come out onto the market, you couldn't give them away in my town. People didn't want them. They want

something that's more immediate, more now, and can be present in that situation.

So we do reach out to the prescribers to make sure that they are doing best practice. We present that. We make sure that they're doing assessments looking at all the different aspects with pain, and substance use, and mental health issues.

This is our one quote from our narcotic officer. Our docs are doing a bang-up job doing the right thing. And, of course, in that now is abuse-deterrent formulations so that it can't be diverted. We dropped over five years -- a 50-percent drop from the years 2009. We work with Fort Bragg, and they use abuse-deterrent formulations for every single refill now, and they've dropped their overdoses. They've dropped their events also. We've dropped school incidences.

All of those factors from a public health approach work, and now that we're statewide, we've got a 27-percent drop in emergency department

visits based on those coalitions in those counties that adopted the model that we created and using appropriate training and best practices for prescribing.

The abuse-deterrent formulations that we're talking about here today can be frontline for we in the communities that have had adverse events and the adverse effects from medications being misused and abused across the populations that are driven by the social determinants that unfortunately bring about that behavior. Thank you very much.

DR. BROWN: Thank you. Can we have speaker number 8, please?

DR. IWANICKI: Good afternoon. My name is Dr. Janetta Iwanicki, and I'm a medical toxicologist and emergency medicine physician who conducts research on opioid abuse with the RADAR system.

The RADAR system is independently owned and operated by the Denver Health and Hospital Authority, which operates the public hospital for the City and County of Denver, and the system is

supported by subscriptions from pharmaceutical companies that produce prescription opioids and use our data for risk management and postmarketing surveillance reports that are given to the FDA.

Subscribers have no role in the conception, execution, or reporting of the analysis that I'll be discussing today, and I have no personal financial disclosures.

I'm here today to talk with you about the data from our research program that shows that hydrocodone is not only abused by non-oral routes such as nasal inhalation, but also that abuse by these routes is associated with high risks of life-threatening complications and deaths.

The opioid abuse epidemic remains a serious public health concern associated with high risks in mortality impacting millions of Americans every year. We know that there's a proportion of the population that is at risk for developing opioid addiction due to a combination of risk factors that include genetic, psychological, and social components. This means that even though

individuals may initially receive an appropriate prescription for opioid pain medications to treat an acutely painful condition, a proportion of these individuals will progress towards addiction.

In the United States, 90 percent of all prescriptions for opioids are for immediate-release formulations. And this means that for the vast majority of first-time exposures to prescription opioid medications are to these immediate-release medications. This includes medications such as hydrocodone/acetaminophen combination products.

Additionally, previous research has shown the majority of prescription opioid abusers initiated their abuse with immediate-release products. This leads to the fact that hydrocodone/acetaminophen is actually the most commonly reported opioid to poison center calls across the United States and is responsible for almost half of all opioid-associated calls.

Once an individual has begun to abuse a prescription opioid by mouth, some will progress to abuse it by another unintended route such as nasal

inhalation. Indeed, data from the RADAR's poison center program as gathered from across the United States shows that when hydrocodone/acetaminophen products are used intranasally, it's associated with a relative risk of severe life-threatening symptoms or death of 1.66.

What this means is that compared to simply taking the medication by mouth, the risk of life-threatening complications and death increases by 66 percent when hydrocodone/acetaminophen medications are taken intranasally.

Not only is the risk associated with this use high, but in all RADAR's research data set of patients entering methadone treatment programs and other substance abuse treatment programs, nearly 25 percent of patients who use hydrocodone/acetaminophen state that they do so intranasally.

Making a product such as hydrocodone/acetaminophen abuse-deterrent has several major benefits. Decreasing abuse amongst those who are newly exposed and just beginning a

progression down the spiral from simple oral misuse to crushing and nasal inhalation has the potential to impact a large number of individuals early on before their addiction becomes severe. Additionally, it has the potential to decrease the very high risk of these life-threatening outcomes and deaths associated with nasal inhalation.

Finally, if only extended-release products have abuse-deterrent formulations, abusers will likely simply switch to non-abuse-deterrent immediate-release options.

Not all abuse-deterrent formulations are created equal. The more difficult it is to defeat a mechanism that provides this abuse deterrence, the less likely somebody is going to invest the time and the effort that's required to defeat that mechanism and the fewer individuals that will be impacted by these high routes of abuse.

In order to preserve the availability and safety of opioid medications for those patients who so desperately need them for treatment of their severe pain, abuse-deterrent formulations for

immediate-release opioid such as hydrocodone should be considered very strongly by the FDA.

In summary, our data show that not only are hydrocodone/acetaminophen products abused by non-oral routes such as nasal inhalation, but that abuse by these routes is associated with the high risk of life-threatening complications and deaths and an abuse-deterrent formulation that provides a high barrier to defeat has the potential to save many lives. Thank you for your time.

Clarifying Questions (continued)

DR. BROWN: Thank you very much. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from audience. The committee will now turn its attention to address the task at hand, a careful consideration of the data before the committee, as well as public comments.

We're going to, at this point, renew our -- we're going to continue working on some of the questions that the committee members had about the sponsor's presentations.

Dr. Gupta?

DR. GUPTA: So I've had this question all morning for the sponsor. The graphs that were presented on the various pharmacokinetics throughout your presentation, particularly Dr. Webster's presentation, is there any way to reconstruct them from 0 to 30 minutes to see how the pharmacokinetics, the absorption actually occurs at the time that we're most interested in, on onset of absorption?

DR. MICKLE: Could you clarify perhaps which study you're most interested in or studies?

DR. GUPTA: Give me a minute. I'm pulling it up.

DR. MICKLE: No problem.

DR. GUPTA: This was on CO-55, CO-58, and CO-66 -- I'm sorry, CO-65. So those were the three that I was interested in just seeing, getting it very closely to see that window of time between at just 30 minutes. I think that'll be really important to assess what actually happens in someone that's trying to use it for a rapid onset.

I know we've discussed it. Many of the other individuals had the same question. If there's any way to emphasize that or to see exactly what's happening, it'll be really helpful.

DR. MICKLE: Sure. Are you more interested in the liking or the pharmacokinetic data?

DR. GUPTA: All of them.

DR. MICKLE: All of it.

DR. GUPTA: I think because the time window that you presented are between 2 to 4 hours. I'm not really interested -- I mean I am, but not so much in the elimination kinetics. I'm very much interested in the absorption and the peak onset, and what is happening in that window.

The FDA clarified many of those points in demonstrating what the statistical significance is, but clinically, it would be significant to know what happens as well.

DR. MICKLE: Sure. I'll talk about the pharmacokinetics and let Dr. Webster, who is an expert in this field, talk about the pharmacodynamic measures that were done during the

early time points. And I'll start with study A02.

So looking here again at study A02 -- if we could bring up the forest plots for the early time points for the pharmacokinetics?

As you have seen before already that there's early time points, we measured 5 and 15 minutes, as well as 30 minutes. If I bring up the forest plots looking at those early time points, you can see in study A02 at the early time points -- and we didn't do the 5 minutes for AUC here, really looking at half hour -- that was roughly half of the area under the curve for study A02 for that first time point.

We do have the early time data for the area under the effect curve, and that was, I believe, AA2. So I'll let Dr. Webster come up and speak about that.

DR. WEBSTER: I think this was a response -- this will be a response also to one of the earlier questions, I think your question about the p-values. This is the drug liking for the intranasal administration comparing Apadaz to Norco

at early time points. You can think about this, Dr. Gupta, as superimposed on the PK that he just showed you. They very much correlate. That's why the AQ actually correlates as well. But you can see the statistical difference -- okay, now it's up.

Sorry. I was talking to this slide that you now see. You can see the statistical difference up to and through 30 minutes. We don't have a 45-minute period here but you can see the trend. And as I say, this is -- all right. So now, we've got the drug liking that really does superimpose very much on the previous slide earlier on this statistical difference.

I want to just comment that Dr. Hertz had said earlier today that when we do these human abuse liability studies, we're really looking at a profile, and we're using endpoints like Emax and take drug again. But we really have to see the whole picture in order to really know what that drug might do.

Regardless, they're all surrogates for the

real world. They're not really telling us what's going to happen; they're just surrogates. I would say, though, that in the real world, we have a unique situation, because in the real world, we know hydrocodone is snorted, and this is the impact of snorting hydrocodone. You get an effect within the first 30 minutes that's significant enough to drive that behavior. That's what Apadaz prevents from occurring.

DR. BROWN: Can I ask a question of Dr. Tolliver? I'm really uncertain about this curve that we just looked at and the difference between this curve and the data that you presented about drug liking. If you could speak about the differences in the analysis.

DR. TOLLIVER: Well, a lot of what I stress was the fact that there's more than just drug liking. There are a variety of other scales that are also used as other means to look at the abuse potential under certain treatments.

So yes, with drug liking, there is an early increase in drug liking with Norco compared to

KP201/APAP.

DR. BROWN: Dr. Tolliver, can we get that slide back up that we were just looking at? Right.

DR. TOLLIVER: I think you see it there with Norco versus Apadaz. If you look at the oral versus the intranasal, you're seeing the difference with Norco versus Apadaz.

However, one of the things that I note is that with respect to the overall -- for the take drug again, which is an assessment that is taken at the end of the treatment, there was no difference. In fact, there was less than one point when people were asked, if you had the choice to take Norco or if you had the choice to take Apadaz again, would you be willing to do it? And it had almost the identical score.

Now, I'll take it a step further. What data that I did not show you, which was provided by the sponsor, is there's another VAS scale called the "overall drug liking." Again, this particular scale is taken at the end of the treatment or at some point -- to say 12 hours and 24 hours just

like the take-drug-again scale is.

When that scale was used and these people were given it, again, there was no difference with Norco versus Apadaz.

DR. BROWN: And that was with snorting?

DR. TOLLIVER: Sorry?

DR. BROWN: That was with snorting? Intranasal?

DR. TOLLIVER: Yes, with intranasal.

DR. BROWN: Thank you. Dr. Gerhard?

DR. GERHARD: My questions have since been clarified in the following discussions.

DR. BROWN: Dr. Morrato?

DR. MORRATO: I want to go a little further and kind of understand the chemistry a bit.

DR. MICKLE: Sure.

DR. MORRATO: Could you put back up -- you had shown a slide, I think it was number BF-26. It was the extended one of -- the 58 that I think Dr. Michna was asking.

DR. MICKLE: Was it this one?

DR. MORRATO: Yes. Okay. Let me see if I

understand. So in this particular study, there is no manipulation, correct?

DR. MICKLE: In this particular study, the products are both crushed finely so that they have a fine powder. So there's nothing else done to it.

DR. MORRATO: But no extraction or any of those methods, right?

DR. MICKLE: Right.

DR. MORRATO: So I could also look at it as they're pretty darn close. Without any manipulation, we're kind of debating the first 30 minutes that they're very similar. So I know part of the ease of deterrents is, well, how hard is it to overcome the mechanism that's in place? In this case, it's a prodrug.

You mentioned in response to Dr. Michna that you do have data on singular enzymes, and I'm trying to understand another way to interpret this instead of just saying they swallowed it and they're ingesting it.

What are exactly the enzymes that are breaking it down? I know you made the claim that

these are enzymes that are found safely in the GI tract, but I'm also wondering if there's enzymes available because snorting it, I don't think, should be going through the GI tract. So I'm trying to understand that mechanism.

I guess do you have any clinical data that gets to understanding -- I'm sure you did in the development phase and the analytic chemistry phase -- the enzyme aspects.

DR. MICKLE: Sure. We did a full metabolic profile looking at all the different systems as I discussed earlier. But in this particular case, specific enzymes, I think is what you're interested in, correct?

DR. MORRATO: I want to understand what's in the -- if you can get a mixture over the counter, or you can get it in other ways, that's just another means by which someone can easily find a new recipe that overcomes what is already short a marginal difference, in my mind, in terms of -- between these formulations.

DR. MICKLE: We have data that we've

generated internally to understand that very mechanism. It has not been reviewed by the FDA. So with their permission, I can show it here.

So this is just a partial list of many of the different enzymes and family of enzymes that are commercially available that we investigated, looking at the percent of hydrocodone release from these.

As I said before about the esterases, esterases are very effective at breaking these down. You can buy commercially available esterases. They are very expensive. If you think about most of those samples between $40 to $120 for a very limited amount of esterase activities. And then on top of that, you have an esterase present in whatever you're going to abuse that product with.

I think fundamentally, the question should be, why would we go through that when I could just swallow the tablet intact and get 100 percent release in a bioequivalent fashion to the product that's already on the marketplace? There's no

incentive here, we believe, to use the enzymes that are more expensive to tamper with these.

DR. MORRATO: You could probably make the same argument then why snort if you can take it orally too, I mean, other than this time period.

So then tell me, then, when your claim is that this is broken down in the GI tract, what is the mechanism that's happening chemically that leads to an effect when you are nasally absorbing it?

DR. MICKLE: We know that when you have a high volume of material that's insufflated, a lot of that material actually does go down the back of the throat. There's a lot of complaints of throat irritation. We actually don't see much systemic prodrug being absorbed in either one of our intranasal studies, so a lot of that breakdown is actually what you see or would see -- I'll just use one example here from our study A03.

You actually see less exposure -- can we bring up the slide that does a relative comparison? We actually see less exposure compared to when

we've looked qualitatively to other studies comparing the amount of oral release that we've seen than what we saw with the prodrug itself.

This is a study done without all that bulk. So in this particular instance, it does seem that the most probable enzymes for breaking this down, the most probable mechanisms for breakdown of intranasal administration is actually orally after the product is passed down into the GI.

DR. MORRATO: Okay. So I guess -- if I'm using it under normal use conditions and I'm nasally snorting it, then I'm getting the same basic biological mechanism of action as if I had swallowed it, correct?

DR. MICKLE: That really has been our goal. There's no incentive for an abuser to snort the product because they'll get the exact same effect as if they swallowed it.

DR. MORRATO: All right. Thank you.

DR. BROWN: Dr. Stergachis?

DR. STERGACHIS: Thank you.

Andy Stergachis. This is for you, Dr. Mickle.

It's about esterases.

What mechanism of action is bond cleavage through esterases, but my question is whether you have any data or aware of the literature as to whether or not there is human genetic variability in esterase activity? And I'm really getting at the question of whether there's a pharmacogenomics dimension to any of this that might or might not suggest variance in esterase activity by race, ethnicity, gender, concomitant illnesses.

We've been given very little information about the characteristics of the patients, for example, in the studies. But that's a side question for you. But my real question has to do with to what extent are esterases different with respect to their properties or their rapidity of action based on genetics?

DR. MICKLE: We actually did examine this. When you look at esterases that are involved in digestion, there's not a lot of variation between people because, again, those are required for proper digestion of food.

There are a few rare diseases that have issues related to this as far as what the propensity for those esterases, but it doesn't seem to be specific to one type of esterase. So we know there's a host of esterases found in the GI tract and different types that could be involved in the break down.

What I'd like to just quickly show is the coefficient of variance for our bioequivalent studies and some of our PK studies that we did in healthy volunteers because we didn't do an efficacy trial because, again, we're bioequivalent to the references to drug.

This not a surrogate for any means to show the different populations that may be affected here. But if you look at just the coefficient of variation between the different parameters of Cmax and AUC last, they're very, very similar to Norco. So there wasn't a lot of variation in our studies, both for Norco and Apadaz. We saw a breakdown that was very, very consistent.

One thing, just to recall, is the

hydrocodone is nearly 100 percent bioavailable. So it'd be difficult for us to -- I believe it'd be difficult for us to achieve bioequivalence if there was a lot of genetic variation because, again, you have such a high bar to try reach to obtain exactly the same exposure to the drug when taken as intended.

DR. BROWN: Dr. Shaw Phillips?

MS. SHAW PHILLIPS: I wanted to go back to your slides about extraction of hydrocodone, slide CO-26. They seem to be maybe showing something different or trying to paint a pretty picture because it seems to me they're inconsistent with the later slides or your later discussion when you're talking about extraction maybe 60 percent.

So one of the questions is, are you extracting the prodrug rather than hydrocodone? So what are you measuring in this slide? You're purporting to say you're not extracting anything, but that's really not true, right?

DR. MICKLE: That's right. And that was not our intension to say that. We're not releasing any

hydrocodone from these extraction methods. So these common methods that abusers would use first -- because it's in everybody's kitchen; these are the first things you would probably encounter -- all they do is actually extract out the inactive prodrug. So I actually have those levels here, too, just not on the same slide, unfortunately.

Here, you see, you do get the prodrug in this particular instance out with most of these commonly ingestible solvents.

MS. SHAW PHILLIPS: Because I'm really trying to wrestle with what the advantage of this agent is, the likeability, the high and everything, even with very high oral doses is pretty consistent with the comparator product. And then somebody that was trying to abuse larger doses and was a little more sophisticated, that wanted to try and separate out the acetaminophen, it looks like it would not be that difficult to get at least clinically significant amounts of separated acetaminophen so they could safely give larger

doses without liver toxicity.

So it just seems to me that the clinical advantage of your abuse-deterrent is extremely small.

DR. MICKLE: I'll just touch on a couple of points that you made. First, we did see differences, and the FDA agreed with us, in the exposure to the hydrocodone that was released from Apadaz.

This, again for some perspective here, at least from my perspective, is pretty unique. We've never seen an opioid that self-limits at high doses, even a little bit. Now, that may have led to the same liking, but we all know that drug exposure is really the ultimate risk. And when you talk about high doses, maybe the difference here could have something. We have more work to do with this. It's a very interesting finding.

I think the other part to that question is the A03 data, if we could bring that up as well. When you remove -- the PK data, please?

When you remove the acetaminophen, you

actually make this a better abuse-deterrent product. So the removal of the acetaminophen actually made this less exposure to the hydrocodone than when you took it with the acetaminophen present.

Again, that was because of the bulk of the material that went down the back of the throat. Here, there was far less of it. It eventually took longer, and not as much of it made it down there and is effectively broken down.

So I think there is an incremental benefit. I will agree that it's not tremendous, but right now, there's no other abuse-deterrent products in this space. Immediate-release combination products are very, very difficult to make an effective pain medication and have it be abuse-deterrent because you need that drug to come off immediately.

DR. BROWN: Dr. Perrone?

DR. PERRONE: Thank you. This might be so obvious. It's a question for the sponsor, slide 40. My question is nobody has really addressed the product, benzoic acid, and for this,

if you imagine somebody got a whole bottle of this product and did the derivatization to make it soluble to inject it, there was an epidemic of something called neonatal gasping syndrome in the 1980s, where benzyl alcohol was a diluent in heparin flushes, and the babies were getting a build-up of benzoic acid leading to a metabolic acidosis.

What happens to the benzoic acid in these as the prodrug is cleaved off? Do we know that in cumulative IV dosing somebody isn't also going to get sick in another way?

DR. MICKLE: I don't think that's fully known, again, for IV injection for this particular product. And we did a simulation here, so we don't know ultimately what this product looks like in a human.

What we do know is that benzoic acid has been shown to be safe for injection, so there's a product that's a mixture. It's used, again, already in the pediatric setting.

The other things that we do know about

benzoic acid -- I'll just give you a second to go ahead and read that slide -- is that this has generally been recognized as safe by most, if not all, regulatory bodies as far as what the amounts could be. There's very little of it in our actual product, 1.85 milligrams per tablet. If you take 4 to 6 of those a day, again, you're probably in a very modest range for intake.

There's more benzoic acid, sodium benzoate, its salt form, in those carbonated beverages we've all been consuming all morning to keep us awake. So here, benzoic acid is, again, something that we're not terribly concerned with safety.

DR. PERRONE: That's PO. But if you go back to the slide that was parenteral?

DR. MICKLE: It was.

DR. PERRONE: Okay.

DR. MICKLE: So I'll bring that back up.

DR. PERRONE: Thank you.

DR. MICKLE: Yes. This is an injectable product.

DR. BROWN: Dr. Craig?

DR. CRAIG: Thank you. Just a quick question about numbers. On slide 65 of the company, the N's are just not matching up for me here. You have an N of 24 on the right, and then on slide 67, slide 68, you had an N of 51. Can you help me understand why those N's are different?

DR. MICKLE: Sure. I think Dr. Tolliver actually went through the reasoning behind here. But if we could bring back up the PK slide, A03?

So in this particular case, we actually did two cohorts, and it was unfortunate there was a laboratory error in processing the pharmacokinetic samples once they were analyzed.

But during the course of this study, every subject was done in the exact same fashion. So we were actually able to take blood, do the liking measurement, take the ease of snorting measurements, all the, really, four information measurements that we took, we were able to do that for both cohorts.

So the N value differences that we're showing are, one, we analyzed the pharmacokinetic

data for, and the second, we analyzed all of the collected pharmacodynamic measures during the study.

DR. BROWN: Dr. Donovan?

DR. DONOVAN: Actually, my question previously was answered, but I do have a follow-up back on CO-55, the famous slide we've gone through numbers of times.

My somewhat basic question is, we're all very impressed with a higher number because we all just are used to thinking higher is better. But really, what's the threshold concentration for effect or liked effect? And if it's only 10, the differences between these products are pretty minimal.

DR. MICKLE: So I don't think that's well-known. Dr. Webster, maybe you want to talk about clinical relevance of the PK here?

DR. WEBSTER: I can speak more to the PD than the PK. We don't really know what is clinically relevant with regard to differences in liking.

Remember on a bipolar scale, you've got 50 points. There's literature that says on a unipolar scale, a difference of 10 is probably clinically significant. And I don't think you can say in half because of it being a bipolar that 5 is clinically significant.

I would say, though, that -- I go back to what I mentioned earlier. We know the behaviors of people who want to snort hydrocodone is reflected in the difference that we see with intranasal versus oral. That is well-known in the community.

So whatever that difference is, it is driving people, at least a subset of the population, to use hydrocodone intranasally.

DR. MICKLE: And maybe Dr. Gudin, you would want to give your physician's perspective here as well.

DR. GUDIN: I don't have much to add to what Dr. Webster said. But I could tell you when I look at this curve on liking, and I look at the difference between Norco oral and Norco snorted, as Dr. Webster mentioned, this graph that we're

looking at here is the primary reason that people progress from the oral route to the intranasal route. That is the gateway; that's the progression of substance abuse that we see clinically.

So patients start out taking it orally and then to gain more reward, financially and more kind of bang for the bucks so to speak, then they go to use it intranasally as you see there.

So from a clinical perspective, to me looking at this slide, as well as when you look at the likeability data, this is what drives home to me the -- or what imparts the abuse-deterrent features of Apadaz versus Norco, is that there is no difference that we see there between liking.

As far as the number, I've looked at a lot of the -- or all of the literature, I can safely say, on the human abuse potential studies, and I just don't think we know, whether it's a 5-point or a 25-point difference, that's the clinically meaningful difference in likeability.

But remember, as Dr. Webster said, those are bipolar scales, so that 10-point difference is not

on the 0 to 100. That point different is on the 50-100.

DR. BROWN: Dr. Donovan?

DR. DONOVAN: Can I follow up the question with another comment? Because I don't really -- the likeability scales are a little too squishy for me, so I like real concentration numbers, and that's what I'm looking for.

What's the minimum effect of concentration of hydrocodone or the minimum concentration in the plasma where somebody will report an effect?

DR. GUDIN: I think that's a difficult question to answer because we're dealing with a lot of different factors. Everyone is going to respond differently. We know this even with liking.

So if you're talking about analgesia versus liking -- when we do human abuse liability studies, we have a lot of placebo responders that are going to, at no level, have a tremendous response. And then we have people that have a very high level who have no response.

I think that genetics plays a role in that,

but there are a lot of factors that contribute to one's experience with a drug. So the nanogram level, or picogram level or milligram level is very much individualized. And we can look at a clinical trial and look at what the mean is that has generated an effect, but otherwise, I think it's hard to give you a number.

DR. MICKLE: Dr. Webster, maybe you want to talk a little bit here because this is a PK-derived function of the AQ as rate of rise into the brain, really probably being a surrogate here for exactly what you're looking for.

DR. WEBSTER: Yes. This is the quantitative; this is the number. Maybe this isn't what you were looking for, but let me just say, though, that Cmax is not the only factor that determines liking.

I mean, everybody knows that people like to shoot up to get the fast response. The non-opioid effect analogy is a cigarette versus a nicotine gum. Nicotine gum does not get you the same effect as a cigarette, not as fast and not as high. And

that's kind of what we're looking at with the abuse quotient. The rate of rise and the level that it gets to have to be combined in order to really have the full appreciation of the abuse potential.

DR. BROWN: Dr. Higgins?

DR. HIGGINS: I'm particularly interested in age. I see that the data are really truncated at 18, and that's awfully young. I'm wondering if you have any experience with the likeability, nasal use, first time using IR? Any of that would be really helpful for me to hear.

DR. MICKLE: Are you looking for clinical experience or just epidemiologic data?

DR. HIGGINS: Either.

DR. MICKLE: Either. Maybe Dr. Webster, you can talk about the clinical experience with anybody younger than 18 in our human abuse liability study?

DR. HIGGINS: Older than --

DR. MICKLE: Older than --

DR. WEBSTER: So these clinical trials obviously have to be 18 and above. But most of the individuals that enter the studies are between 20

and 30. And if they're entering an intranasal study, they'd been recreationally intranasally using drugs. That's a criteria. So there's an abundance of young people between 20 and 30 who are intranasally using opioids.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Yes. I have two questions. One is just a factual question about the A03 study, where you were doing the active product. Was that dose supposed to equivalent to the 2 tablets that were crushed? Because that was a little unclear.

DR. MICKLE: Yes. The dose was intended to be equivalent because we already had data that was directly comparable from that.

DR. SHOBEN: Okay. And then I know that there were two different groups of subjects, but certainly the abuse quotient, the measure that you're trying to advocate for is perhaps more relevant than the Emax.

You saw a huge difference in terms of the 87 versus 17 -- this is on slide 66, yes -- but then you don't see that correlating with anything else.

So in fact, it seemed like the drug -liking measures were in fact lower, on an average, in the study than in A02.

DR. MICKLE: Probably Dr. Webster will be great at answering the pharmacodynamics here. I think in this particular case, since we saw the delay in the Cmax with the A03 study, as well as the truncated Cmax, that's why you get the much lower number. It, again, essentially didn't break down as quickly as hydrocodone went in very, very rapidly. And actually, abuse quotient is actually a very good way to compare across studies.

Now, for liking data, I think you can't compare across studies, correct, Dr. Webster?

DR. WEBSTER: [Inaudible - off mic].

DR. MICKLE: He said no, if you can make him stand up again.

DR. WEBSTER: You can't because it's really about that subject population. In doing the comparison, there are always double-blind crossover, so everybody gets all doses and a placebo. And it's very unique. The response is

very unique to that particular person, so you really can't compare from one study to another, the liking.

I would say that with this A03 though that, the study, we didn't -- as FDA had indicated, we did not put them through a discrimination phase, which is an enrichment process to find people who are most sensitive. And that actually made, as I said, I think the results more dramatic because, normally, we recruit individuals who like the drug and like that particular molecule, and have to like it to a certain minimum level to even get into the study. And we didn't do that with this population. And despite that, there was a huge separation.

DR. MICKLE: And maybe one point again why we designed the study the way we did, in this particular instance, it was entirely meant to be a pharmacokinetic study because nobody has ever put a pure prodrug in somebody's nose to see how it breaks down. We really wanted to know happened when that occurred, so we really were focused on the pharmacokinetics.

Using the secondary measures here as liking, with this particular product, I think it was very much trying to mimic a real-world scenario, just like the FDA said, where somebody is able to get rid of all the acetaminophen.

So what would happen if they tampered it to the extreme, got rid of all the acetaminophen, and then try to abuse it? And we know that it's going to actually produce a much lower exposure to the drug than what we saw before.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: This question is, again, for Dr. Webster, and maybe we can put up FDA's slide 15, Dr. Tolliver's presentation. Thank you.

For the sponsor, I'm just trying to reconcile, if the abuse quotient or time to Cmax are really what drive the likeability of the drug when ingested via the intranasal route, how do you reconcile your data showing a delay to Cmax and a different abuse quotient with the fact that the take-drug-again VAS are essentially the same in Norco and KP201?

DR. MICKLE: I'm going to ask Dr. Webster to get up again. He really wanted this exercise today.

(Laughter).

DR. MICKLE: So we're going to continue this. But I think a couple notes about take drug again, one thing, at least from my perspective when I look at this measure for other products, I look most closely at the product that was before this committee last year, or late last year, was Xtampza.

That product showed dramatic differences in Emax. Again, it's an ER product versus an IR product. There was substantial differences in the pharmacodynamics and the pharmacokinetics involved with that. But there was no statistically difference in take drug again.

That product is a 12-hour product, extended-release, and they're taking measures at 12 and 24 hours. So it's, really, real time for them. This happened -- the peak effect happened at 30 minutes for the abuser. How are they going to

remember how they felt about that product 12 and 24 hours after that?

So maybe, Dr. Webster, you have more to add about this scale because you've been a bigger part of this.

DR. WEBSTER: Well, as I said earlier, the scales are obviously important, but we can't overstate the value of any one of them.

Remember that they're still going to like the drug. These are individuals who like taking drugs. They're recruited because they like drugs. And some of them actually begin to salivate knowing that tomorrow is the day they get to have their fun.

The psychology about all of this has to be taken into account. They're still getting an effect. So take drug again, does that really measure the intranasal difference of the effect or that they received an effect, they benefited from the high, the rewarding, the liking properties sufficient that they would say, I'll take it again?

DR. BATEMAN: But this isn't being measured

on a binary scale, right? This is a continuous measure. So wouldn't you expect if they were getting a better high, that it would push the difference in some way?

DR. WEBSTER: I think that that's a fair question. I think that's a research question, why they don't separate.

DR. BROWN: I have two questions before we move on. One is that apparently grapefruit juice inhibits the gut esterases. Have you looked at the effect that that has on the activity of this analgesic?

DR. MICKLE: We have not investigated that.

DR. BROWN: To your knowledge, are there any accelerants to the analgesic? I'm thinking back to genomic properties of drugs like codeine that have accelerated metabolism. This is not what I'm asking about. But I'm thinking about food products that may accelerate the esterase metabolism of this prodrug.

DR. MICKLE: No, and I think the point here to bring up is that since hydrocodone is already

close to 100 percent bioavailable and we're equivalent to that, there is no way to accelerate that further because you have a complete mass balance with this product.

Every molecule that went in breaks down very readily in the GI tract before being absorbed. So we don't see prodrug at all systemically. There's no exposure beyond that in the GI. So I don't know if that helps answer your question at all.

DR. BROWN: Yes, it does. The second and last question actually is, in the oral studies that were done, the treatment group received almost 4 grams of APAP at one time, and I just wondered how those patients did.

(Laughter).

DR. MICKLE: Actually, I don't believe there's any AEs related to liver effect.

Dr. Webster, do you recall?

DR. WEBSTER: No.

DR. MICKLE: Yes. Again, all these were opioid effects in that study. We looked at clinical, chemistries, and so forth.

DR. BROWN: All right. We're going to move on now --

DR. MICKLE: There was one question that I didn't get a chance to clarify from earlier. I don't know if you want to bring it up here. It's about the solvents and the differences. It'll take two seconds.

DR. BROWN: Absolutely.

DR. MICKLE: Thank you. So this is just a clarification. Again, there's nothing confidential presented here, just a clarification between the Solvent X and the Solvent G.

We called it Solvent X in this particular instance. It is an advanced buffer. What we saw with this particular stress condition is that, yes, at 4 hours, post-initiation of the extraction, you would get 60 percent hydrocodone. If you did it for any less or any more, you weren't able to get -- it actually reduced it quite substantially.

So there was a magic point here for some reason. Very early on in the extraction conditions, the whole solution turned black. And

one of the buffers that we added to this to make this buffer has actually been banned by the FDA as a food additive. So this is not an ingestible solvent in our view.

FDA Solvent G, from what we saw before, there was advanced laboratory equipment that was required to maintain this stress temperature. And then again, it still went for 3 hours.

So the statement I made previously regarding why would you do these things that take many, many hours when you can just swallow it to get the very full effect within an hour or 2 hours, I think, just hopefully is highlighted here with these two examples. Thank you for your time.

DR. BROWN: Thank you.

Dr. Hertz will now provide us with the charge to the committee.

Charge to the Committees - Sharon Hertz

DR. HERTZ: Thank you. As we proceed to the questions, I'd like you to consider several concepts along with the data that have been presented.

First of all, because these products are analgesics, they have to be able to deliver the opioid. So these are all going to remain abusable. "Abuse-deterrent" does not mean abuse-proof. It means that there's something about the formulation that makes it less amenable to abuse through a variety of either methods or routes. There's a big range of these products under development. But we don't expect "abuse-deterrent" to mean "abuse-proof." So that's number one.

We accept that there's an overall public health benefit to incremental improvements, so that makes it challenging for sponsors because the bar will continuously change potentially as new products come to market. But because there is no absolute value that we can declare for everything, incremental improvements are really acceptable.

We do encourage the development of immediate-release abuse-deterrent formulations, as well as the extended-release.

As described in the guidance for industry on the development of abuse-deterrent formulations of

opioid analgesics, when pre-market data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, those data, with characterization of what they mean, can be included in the labeling.

It's extremely important to understand the abuse-deterrent properties relative to a relevant comparator, and that's also in our guidance. In particular, the guidance directs the investigator that the standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products in the market at the time of that application.

So abuse deterrence is a relative phenomenon. It can be established only through a comparison to another product.

So as you can see, there's differences in the interpretation between our understanding of the results of these studies and the sponsor's. Dr. Webster is an expert, that's well-recognized,

and he presented a number of important and interesting analyses and interpretations along with Dr. Gudin.

We have a fair amount of experience with these now as well. We really do focus or weigh willingness to take drug again very much in conjunction with the other pharmacodynamic measures of drug liking and drug high. Because we don't have that nice PK/PD relationship that Dr. Donovan was looking for, we cannot rely on PK at this time, and we must have the PD assessments to go along.

So we're interested in products that these subjects really do find less desirable. And not only can willingness to take the drug again provide context for liking and high, which provide context for one another, it also provides context for adverse events because in some situations where we have abuse-deterrent products that have irritating qualities, they may produce very much the same liking and high, but there could be a big difference in take drug again when it is substantially irritating.

We've actually presented a product with that characteristic a number of years ago. The product had other problems, so it wasn't approved but we did see that type of separation.

So we don't feel that there are differences that meet the criteria. And I will also say that in the context of these pharmacodynamic outcomes, we have products where we have seen willingness to take drug again correlate, give context in a meaningful way, to differences in drug liking and high because we've approved six products with the modern language, the modern labeling as described in the guidance.

So there is an opportunity for these to correlate. We do know that there are circumstances where they separate where it's not just one of the three.

So our questions are going to ask you to discuss the relevance, first in general, of the intranasal route for products like Apadaz that have hydrocodone and acetaminophen as the active components and whether there are -- subsequently to

that question, we need to know if you believe that there are abuse-deterrent effects relative to the comparator.

So for any of the routes, are there differences relative to what's out there that would warrant choosing this because there is a belief that there will be a deterrent effect?

Then we'll go on to ask you additional questions about whether you think it should be approved, and if so, what the appropriate labeling would accompany it.

So once again, let me just thank you for your time, your commitment to helping us with these really important questions. I think that if we're going to support the abuse-deterrent products, the development of these, we have to make sure that we understand that we're maintaining a standard that when these products go out on the market, people can expect there to be some value added. Thank you.

Questions to Committees and Discussion

DR. BROWN: Thank you.

We're going to begin with question 1. Question 1, please discuss whether the data presented for hydrocodone and acetaminophen combination drug products support that the nasal route of abuse is relevant for KP201/APAP? And we want to get a very vibrant examination of this and get everybody involved in this.

Anybody have any questions about the wording of the question? Dr. Michna?

DR. MICHNA: Yes, I do. It's kind of a general question. If it's an active compound and the indication is going to be moderate-to-severe pain -- I mean, that's the indication, correct?

DR. HERTZ: Well, question 1 --

DR. MICHNA: For the vote. For the vote, I'm talking about.

DR. HERTZ: Oh, for the vote later on?

DR. MICHNA: Yes.

DR. HERTZ: About the indication?

DR. MICHNA: Yes. It says, should it be approved for the approved indication?

DR. HERTZ: Yes, the approved -- we don't

know exactly. We have this very large initiative going on for the immediate-release opioids.

DR. MICHNA: Okay.

DR. HERTZ: So there are going to be a number of changes in labeling that may overlap with indication. I don't know what the final indication for this product will be.

The proposed indication is, I believe, moderate-to-severe acute pain. We can consider it in that context. But basically, it would be a similar indication as Norco.

DR. MICHNA: So the question involves whether it meets that indication, not anything about the abuse deterrence?

DR. HERTZ: Yes.

DR. BROWN: Dr. Morrato, do you have a question?

DR. MORRATO: Just a follow up to that just to make sure I understand. So abuse deterrence is not a condition of approval of new immediate-release or new opioids?

DR. HERTZ: Okay.

(Laughter).

DR. HERTZ: We have about 18 reasons not to approve a product listed in our regs. Abuse deterrence wasn't even on the radar in that setting. But I think that we can think about it still in the context of our overall range of reasons not to approve a product.

Basically, we want to know if it's going to -- for the intended population, if it's going to work the way it's expected, if we understand enough about its safety, and if we think the balance is acceptable, if we have enough data from all the different disciplines, the CMC, the nonclinical, the clinical, facilities, all those basic things. And then we also have criteria based on if the labeling is accurate and supports what we know about the product.

So the question about whether we can approve an abuse-deterrent product if we don't think it has abuse-deterrent properties, or if we do, would be based on whether you think that there are any unintended consequences that would alter the

risk-benefit for the patient.

So in the fall, in September for instance, we had a product that -- we actually had a safety concern that was formulation-based that influenced our thinking, that influenced the committee. And the committee voted against approval even though it looked like it would effective, it was somewhat comparable to the comparator, and we had a full evaluation of the abuse-deterrent properties.

So we need to look at the -- so the question of should it be approved for the proposed indication really does try to take into account if we think it's safe, if it's effective, if the newness of the product under consideration offers any expected less safe aspects. So it's a huge thing.

It does get difficult, though, where there might be a difference in opinion between the effect in the intended population and the effect for the public health value. And that's what makes this whole area so challenging, is to understand how to integrate those two.

The best I can advise you is think about whether you think this product should be approved for that type of indication and if you feel that it -- we're going to ask you about the labeling anyway. But if you somehow are conflicted by your thoughts on these different aspects, you can express that when we go around and ask for an explanation for why you voted the way you did and what your thinking was there.

That's the best I can offer because we struggle with this as well.

DR. BROWN: Back to question 1, Ms. Shaw Phillips?

MS. SHAW PHILLIPS: I'll just break the ice on question 1. I think that the evidence is there that even though it may be a small percentage, that with the large availability and large uptake and large use of hydrocodone, that even if it's 5 percent of abusers and a potential pathway to increase abuse, that intranasal route is a significant one to be considered.

I think it's a whole different question from

whether there's a real incremental advantage with the product or not. But I think the intranasal route is a potentially significant route of abuse.

DR. BROWN: Dr. Israel?

DR. ISRAEL: Yes, I'm glad you started. I would agree that drug abusers versus drug users are two different kind of animals in a way, or maybe just in a different progression or different personality or whatever.

But if the intranasal route -- if this drug will help control the transition of people from oral to intranasal route -- which we do know that some drug abusers do run that whole progression of that slide from oral to intranasal to IV usage, that direction in terms of developing an addiction -- then I think the drug is worth giving it a shot because of that.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Toby Gerhard, Rutgers. Well, I take the opposite perspective here. Obviously, the data isn't very strong, but we have a very small proportion of abusers, not users -- the data

was based on drug abusers -- that either exclusively or preferentially have endorsed the nasal route. There's a larger proportion that uses the drug this way, but preferential or exclusive was in the rate of 5 percent of the drug abusers. So it's a pretty small proportion.

Then the big question, given that virtually everybody uses the drug orally, this wouldn't reduce abuse. It would only reduce the abuse through that specific route.

So then the question becomes, is there something that this specific intranasal route contributes that makes the problem worse? And we have been told about kind of this transition or progression from oral to intranasal to injection, but we really haven't seen any evidence that that's an issue. We have seen that it happens, but whether there's a causal effect or whether it's the result of increasing dependence, we don't know.

We have seen no evidence for this, so I'd be very skeptical to say that the intranasal route here really is a relevant target. So in other

words, if we would reduce it, would we have any effect on dependence and the ultimate adverse outcomes of overdose admissions, overdose deaths. So I don't know that we have evidence for this.

DR. BROWN: Dr. Kaye?

DR. KAYE: Alan Kaye, LSU. I think the nasal route is relevant, and I also believe that there is a gateway path from prescription pills and their modulation through nasal, and then intravenous, and finally to heroin.

So I think it is relevant, and I think clinically, I personally have been tricked by many people who come in different sizes, shapes, ages, genders, who were abusing prescription pills nasally for a very, very long time. And I'm sure that I am still being tricked by some.

So I think it's E, all of the above. All of these pathways and all of them are a problem. And at least there's some positive here on one piece of the puzzle. Thanks.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: Melinda Campopiano. I'm

either going to agree with everybody or disagree with everybody. I'm not quite sure which.

I do think the route of nasal abuse is relevant for the product, and I think I've heard people say that so far. But I also think that it's only relevant for the product.

I don't think we can say that having this product be less likeable is, in any way, going to prevent somebody with severe addiction from progressing to an intranasal route of administration or something, because the way we're analyzing this, the way it's constructed and the way it has to be, the discussion is comparing this to a comparable product as if it's a closed universe. The fact is people have options, and their option is not swallow this, or take it intranasally, or take it intranasally, or take its equivalent intranasally.

So while I think it's important to distinguish what we can say about the likelihood of this product being abused by that route, we can't say anything about whether or not it will change

the course of anyone's addiction based on that. And I think that kind of goes to what was being said, so I'll stop there.

DR. BROWN: Dr. Morrato?

DR. MORRATO: Yes, I just wanted to say I like the way the FDA was framing because I know this is new and thinking through what does relevance mean in terms of relevant to the route.

So I like the way they framed it as sort of scope of the problem and then the adverse outcome and severity, so how widespread is the route in total, as well as being preferred and exclusive and whether or not there was variance.

So I agree with Dr. Gerhard in terms of it may ultimately end up that it's not the most preferred route, but I did find compelling the data that says, among adolescents quoted 40-ish percent, adults past 30 days up to 23 percent. So there is a volume of patients that are going through it.

I was also compelled with the variation that was cited between urban and rural, and there may be different use patterns in different settings that

make a difference.

Then in terms of adverse outcomes, in addition to what was mentioned I think on the nasal tissue damage, I don't think we heard. But we did hear that public forum from the RADAR's data that maybe this route might actually be associated -- I don't know if it's causal -- with more serious adverse outcomes in terms of those that are using this route. I think they were quoting maybe more at risk of death or serious adverse events.

So I would say in total, when you look at that as the framework, I would agree that it supports a relevant route of abuse that we should target.

DR. BROWN: Mr. O'Brien?

MR. O'BRIEN: The difficulty -- as I indicated earlier, for the patient community that I am aware of, intranasally is not the preferred choice. However, in listening to everybody -- and clinically -- and I accept the fact that that is a route that individuals may take.

When I look at the data, I see that we had

62 individuals who are recreational users, whose preference is to take drugs intranasally. I did not see any data, though, that showed me, or any testing that said that there was a deterrence if in fact they took KP201. There was nothing to show me that they would change their preferential method routing.

So I'm not quite sure, from an objective standpoint, do I really have data that says that it's relevant that KP201 will in fact deter behavior? I'm not quite sure there.

DR. BROWN: So if there are no more clarifying questions or comments concerning this discussion topic, let me just say that the sense of the committee is that the nasal route is probably relevant even if there's only a small relevance.

There's some question in some people's minds about whether or not the nasal route after the oral route produces a progression to other drug abuse.

Dr. Kaye suggested that this may be a gateway path, that there are populations that might be especially at risk such as adolescents that

appear to have a large percentage that are abusing through the intranasal route.

It also appears, at least in the data from the Commonwealth of Kentucky, that there was a large number of rural folks that were using snorting as their primary method of abuse.

The question was raised about whether this was relevant for the product, did the fact that this was a relevant pathway imply that the product in it of itself was going to prevent a progression, and that is not known.

Any other additions to that summary of what's been said around the table?

(No response).

DR. BROWN: If not, let's go to question number 2, please discuss whether there are sufficient data to support a finding that KP201 has properties that can be expected to deter abuse, commenting on the support for deterrent effects for each of the three possible routes of abuse.

Dr. Emala?

DR. EMALA: I'll take each of these A, B, C.

A, I think, is it was never intended to be a deterrent for oral. C, I think I would refer back to the relevance issue. I think the data we've seen suggest that this class of drugs, the intravenous route is not relevant. So I think it focuses really on the potential for nasal deterrent.

I remain unconvinced, after looking at the data from study A02, that this product really offers any deterrent features over its comparator. And I do think the data in study A03 needs to be taken with a great deal of skepticism based on the shortcomings that have been outlined by the FDA.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard. Yes, I also think that it's pretty clear that the answer for A and C is no. I also don't think we've seen really compelling evidence for B.

So I think that at the end of the day, even if there is a little bit of data that suggest that maybe -- some PK/PD measures early in the follow-up might show a small difference, if at the end of the

day, you can't show any difference in overall liking of the drug, or level of high, or the likelihood of taking the product again, I think it would be hard to ascribe a deterrent effect to such a product.

DR. BROWN: Let me add to the discussion here by asking the committee if there were other issues that were not addressed by the folks that presented the product that might assist us in having a better understanding of whether or not this could be a deterrent.

Dr. Phillips? Dr. Higgins?

DR. HIGGINS: For me, it was methodological. I was challenged by the fact that the methods that were chosen were based largely on internet survey data. I also was having a difficult time with the fact that there was not representativeness of this sample.

I dispute the fact that all users are 18 years of age or thereabouts. I do see a lot of abuse even in the older generation, so those are challenges for me above and beyond the data.

DR. BROWN: Anybody else? Dr. Morrato?

DR. MORRATO: Two things. I was compelled by Dr. Stevens' evaluation of the chemistry of it. Part of the abuse-deterrent is how easy is it for someone to overcome, and I did not see compelling evidence that this is very hard to overcome.

Having been part of other meetings where we reviewed abuse-deterrent, the chemistry data in other products, we've gotten to see far more, I don't know, broad-ranging aggressive ways of trying to overcome it, and I didn't really see that same sense of, I've tried everything to overcome it.

It was nice experiments, but I think some of the logic others were using, putting things together and that, longer times were a little bit harder, it gave evidence that this might not be so hard to overcome in real world.

Then the second piece is if we're trying to interfere with the nasal pathway, I just had a hard time with the logic. And I'll see if I can say it right so it makes sense.

So if we say that Apadaz oral is

bioequivalent to Norco oral, and then we say that Apadaz snorting is largely having its effect because I'm swallowing it or it's somehow being ingested, then I'm basically saying my snorting route is just like my oral, and I said my oral is just like the thing I'm trying to prevent, which is immediate-release.

So I didn't see compelling evidence that something that was happening chemically, the story made nice, but was not happening in play. Then that reinforced in my mind, now, you look at the data that was referenced by Dr. Emala, and we see results that are similar. So the logic of it didn't seem to hang with me when you looked at all the data in total.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: So I just want to say that I agree with everything that's been said, that nasal abuse studies was best-case scenarios, people crushing the tablet without doing anything to it and then snorting it. And there's just not compelling evidence for me that that was enough of

a deterrent that someone wouldn't do that again even if this were the only product on the market.

The chemistry studies that Dr. Morrato just mentioned might suggest that perhaps it is actually, in some ways, easier -- certainly maybe perhaps just different -- to separate out the acetaminophen from the prodrug, which might make sort of unintended consequences of putting this in the market problematic in terms of potentially more oral abuse or other methods of ingestion.

DR. BROWN: Any other comments?

(No response).

DR. BROWN: To summarize, the panel seems to be unconvinced of the deterrent characteristics for snorting, which would seem to be the major reason to bring this drug to the FDA at this time. Folks said that there was no compelling evidence, and Dr. Morrato revealed to us that it didn't seem to be hard to overcome the deterrent properties of the drug. That's my take on it.

Anybody have any other comments that I might've missed?

Dr. Hertz?

DR. HERTZ: After two and three-quarter days in this room, I appreciate succinctness, but even if there is a sense of concurring with something that had been said, positive or negative, it's really helpful just to get a sense of the committee's thoughts about these questions.

We try not to force lots and lots of votes, because that does make everyone respond. But if anyone else would like to comment one way or the other, it's very helpful to hear from more folks, even if it's just to say you're on board with something that was said.

(Laughter).

DR. BROWN: Dr. Craig?

DR. CRAIG: Thank you. Thanks for the prompting, Dr. Hertz.

Yes, I think it is an approvable drug based on its availability. We don't have any other options. I think that the innovation and the prodrug approach is very neat. I think to have the option for something like this in certain patient

populations could be positive.

Again, comparative to what's currently available, it's clearly not perfect and many people have said that today. Should it be available? I think it should be. Whether the abuse-deterrent properties are enough, is the question, and I don't think it is. But I think it would be a nice option to have available.

DR. BROWN: Mr. O'Brien?

MR. O'BRIEN: I'm sort of echoing the same comments. I guess my question is that I see it as a -- what I saw was that it's a safe and effective drug that appears to be similar to the comparator that's there. I have a lot of questions about how it's going to be labeled and what it's going to be promoted as and its capabilities to do that. And that's where I really have a question in terms of its real deterrence value.

So if I'm being asked to say is it something that should be in the market, then yes.

Oh, that question?

(Laughter).

MR. O'BRIEN: Oh, I was answering the other question, the general question. Sorry.

DR. BROWN: Dr. Israel?

DR. ISRAEL: Yes, I just wanted to also say, it's kind of a confusing, the thing that we're looking at right now in terms of a multiple -- this whole idea of whether it's going to be useful and whether it's really going to have deterrence in terms of intranasal usage.

But even if it's slows down -- even if it's really a point, like Dr. Morrato was talking about, that it's just going to slow down the absorption so it acts like an oral IR and even deters a small percentage of those people that we don't normally see and the statistics, if it helps in any kind of way to slow down potential abuse, then I think it's something that's worth approving.

DR. BROWN: So does that mean that you -- because we've had people around the table saying that they're unconvinced, unconvinced, and then some say that they're convinced.

Are you saying that you're unconvinced or

convinced?

DR. ISRAEL: Well, it looks like the effect -- you know, from the data, it looks like the effect is small, and I'm not sure how much of an effect it's going to have, whether it should be -- I think the drug, it should be approved.

DR. BROWN: Dr. Tyler?

DR. TYLER: Thank you. My sense that the appeal of intranasal is because people want the rush or the high. So what I find interesting is the data that was presented was how it compares to oral, and it looks like oral will -- so oral is not known for quite the same rush or the high that people are seeking with the intranasal. And when we look at the data on drug liking and on the unipolar high scale, they measured it at half hour. So again, hard to assess -- or in one case, a half hour; in one case, in 15 minutes.

So I have challenges with did they measure it at the right time to catch what they were really looking for. And I think in some ways, how the data was presented made it hard for me to grasp if

that's what was going on. So I think that was the biggest thing for me in looking at the intranasal data, is you can't really tell that easily.

DR. BROWN: Dr. Tyler, does that mean that you think that the data had been presented in another way so that it would have provided you some clarity in making a decision about this?

DR. TYLER: Yes.

DR. BROWN: How would we do that?

DR. TYLER: So I think there are two things: One, how the data that they had was presented, so it was only very late that you presented it compared to the oral to get a sense there. I think the second one is the timing of the data points.

So that's where -- I don't know if they are some place. When somebody asked about it, they said, well, you know, we can't ask these people too many questions, but there -- we have to think about a design that captures it at the right time that we think differentiates it.

So the data probably wasn't collected to tell us what's happening in a way to give it

the -- or for us assess that when we think people have the -- or want to take it intranasally, what's the advantage of intranasally, we weren't measuring at the time points that tell us whether it's advantageous for them.

DR. BROWN: So incomplete granularity of the data --

DR. TYLER: Yes. Right.

DR. BROWN: Do you think that would be helpful?

DR. TYLER: Yes, I do think it would be helpful. I think we have a surrogate from the standpoint of it looks like oral. But then, it looks like oral, but we still don't have the data at the time points that might be most useful.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: If the standard for labeling for abuse deterrence can be expected to result in a meaningful reduction in abuse liability relative to relevant comparators, I don't think the data we've seen demonstrates that in a compelling way.

Far and away, the most important route of

abuse for this drug is via oral ingestion. There was some suggestion by the sponsor that there might be a ceiling effect, but I think that would need to be demonstrated in a much more robust way for us to really take that into consideration.

Then in terms of the data around intranasal ingestion, the overall findings from study A02, particularly the VAS take drug again, the overall VAS high and likeability all suggested that the drug is essentially comparable with Norco.

Regarding the intravenous route, that doesn't seem to be a major route of abuse for hydrocodones, less relevant here.

DR. BROWN: Dr. Hall?

DR. HALL: One unanswered question I had on the nasal route of administration was I sense to have the suggestion that this particular product had its limits in the quantity that could be effectively used by intranasal use, and I don't know how that would compare with Norco or other products. But I thought I heard a suggestion that there was only so much that a user could snort.

And if that be the case, that may be a reason, but I didn't hear really any clear evidence in it.

I also think that the intranasal route is almost a social norm, so that one group, in a social setting -- I mean, even similar to intranasal use of cocaine or methamphetamine, where groups teach each other and now teach other by drug forums online.

I found it interesting during the sponsor's presentation comparing the two products on intranasal use that -- I mean, I could almost translate that into an online forum discussion, yes, but not take the risk that this was a better product for intranasal snorting.

So in that sense, I had a sense that this does present some deterrent level, but I think if that clear comparison were available and also made more readily understandable to potential intranasal users, that may contribute to its abuse deterrence.

DR. BROWN: Dr. Perrone?

DR. PERRONE: Jeanmarie Perrone. I'm just remembering back to I think it was the hydrocodone

scheduling meeting, where we were presented a lot of data about why hydrocodone was or wasn't abused as much as other opioids. The acetaminophen was clearly an abuse deterrent.

So perhaps this product or this modality could be looked at in comparison to a pure hydrocodone product, which I guess is Zohydro, which is on the market.

I think when we first listened to this, we heard there wasn't another pure hydrocodone product, but there is. And maybe that's where we need this kind of abuse-deterrent formulation because by comparison, hydrocodone/acetaminophen, the existing product, it doesn't seem like it's very different from what we have already.

DR. BROWN: Dr. Stergachis?

DR. STERGACHIS: Thank you. Stergachis. Yes, when listening to the FDA critique of the human abuse potential studies, and of the three, two failed to meet the primary endpoint, and one was considered flawed or had significant deficiencies, that's compelling in terms of not

supporting a labeling with respect to the deterrent aspects with respect to this product.

The one positive aspect that I pulled from slide 12 from the FDA is that there is nothing to be gained in terms of mean plasma hydrocodone for nasal route versus oral. So that would, in effect, reduce the importance of going the nasal route with the fact that there's equivalency between intranasal and oral in plasma mean hydrocodone.

But on balance, I think that the concerns with the study designs and the lack of meeting the primary endpoint are concerning.

DR. BROWN: Dr. Donovan?

DR. DONOVAN: Somewhat in keeping with what Dr. Perrone had said also is that, yes, probably the APAP in both of these is acting as a deterrent plus too much of a bulking agent, in essence. Really the goal with the intranasal absorption is when it works best, it works within 2 to 5 minutes.

Even in the comparator product, we're looking at about a 15-minute peak. And it's got limitations, too, which is probably why only about

25 percent of people actually inhale it nasally and usually just prefer to use it and abuse it potentially orally.

But then I start to think about, okay, so I have this thing that really only works in 15 minutes, but I know why it only works in 15 minutes because it's a prodrug. And we had some pretty compelling evidence from the FDA about it's really not going to be that difficult to alter the prodrug and purify it into hydrocodone. And that will likely give you -- and then there's data, even from the sponsor, that you'll see rapid absorption from pure hydrocodone.

I was a little bit disappointed in the sponsor's data they provided about modifications to the chemical itself in that they only took one-step approaches, and with a prodrug, you always have two steps. You have both the extraction of the prodrug itself and then the conversion of the prodrug to the parent drug. And two-step processes were never addressed by the sponsor. They, I think, were somewhat slightly addressed by some of the work

that the FDA had started.

I think that's really the goal, a motivated abuser, two-step is -- and especially some of these would be pretty simple two-step processes to be able to purify enough hydrocodone to abuse. And that's where my concern is, and I don't think that this meets the mark as abuse-deterrent because those steps are actually probably a pretty low threshold.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: I just want to make a couple points about the sort of combining questions 1 and 2 in some sense. We said in question 1 about the scope of the nasal route, that it sort of was relevant in this context. But I think that its relevance certainly needs to be taken into context here when you're trying to figure out if there really is an abuse-deterrent effect.

In particular, Dr. Tolliver's slide 15, when you're comparing the drug liking between the Norco intranasal and the Norco oral and you see very little difference, it's very much consistent with

the epidemiological data, which is there's very few users who really are preferring the nasal route, and that they may like the nasal route every once in a while or just something different, but it's not like they're getting a dramatically sort of better high from the nasal route because that was not sort of supported, at least, in this particular drug-liking study.

So in that sense, in order to have a real impact on the deterrent of the nasal route, there'd have to be something that was really dramatically negative in my mind that there's just -- in this context, there may be slight pharmacokinetic differences between the two, but there's no impact on how much people are liking it. You'd really have to go for a negative effect for it to have a meaningful impact on the nasal route of abuse.

DR. BROWN: Dr. Kaye?

DR. KAYE: Yes, I think I've been spending the whole day trying to figure out what does the data mean, and I think it's a topic that's very complicated and multifaceted.

So I had two points. One is, having done some clinical pain research myself, it is a very difficult population to work with. If there's a data point that isn't exactly where at the right moment or minute, I think that's not a deal breaker for me.

Then the second thing is, looking at the data all day, I'm asking myself, is there anything that was presented to me today that would make a step backwards? And I don't hear that; I don't see that; I don't sense that. It's kind of a baby step forward. It's not going to solve every problem in the opioid epidemic, but I just don't see anything that tells me that we're going backwards. Thanks.

DR. BROWN: Dr. Campopiano?

DR. CAMPOPIANO: Melinda Campopiano. This will be a little bit summarizing because I'm hearing a couple of areas of challenge with regard to the analysis, one being analyzing the effect within the first minutes of taking it instead of at 15 and 30 minutes.

So that's kind of a valid critique of how

the study was designed. And because of it, because of what we expect immediate-release drugs to do and what we expect the substance user to want from them, we kind of miss the window, the really, really relevant window. So that point has been made by a couple of people.

The second piece is kind of the lack of innovation, if you will, in the manipulation and extraction experiments with regard to combinations, and the type of creativity that you might expect from the average drug user is a little bit lacking to make it really compelling that we've captured accurately how extractable or not extractable the product is and how easily manipulated the prodrug is.

So those concerns balance that against the numbers of people in pain who need safe options, the amount of hydrocodone being prescribed to the population at large, it's hard not to say, oh, I see a tiny incremental benefit here for at least a portion of people who will not misuse this particular product as a result.

So I'm thinking about that, and I'm comfortable with what Dr. Kaye just said, it's not a step back. And what I'm struggling with is, is it a big enough increment forward to be able to call it abuse-deterrent without either undermining our credibility, or raising questions about our intent of what we meant by that, or potentially --

It was raised earlier by one of the public commenters that, well, we'll see how it really works in the postmarketing surveillance. And I feel like, oh, are we going to use the entire population as research subjects without their permission? Is that where we're setting bar?

It's a tiny increment. We don't really know if it's going to work or not, but we're willing to experiment on the public. So I'm really conflicted in case you can't tell. So I'm going to be very surprised to see how I vote on question 3. But I'm interested to see if I provoked any other challenging thoughts.

DR. BROWN: Dr. Emala?

DR. MICKLE: Dr. Brown, can I just make one

clarifying comment very quickly?

DR. BROWN: Yes.

DR. MICKLE: Thank you. I just wanted to quickly clarify as far as it goes for the tampering studies, we did over 1600 different chemical extractions conditions. Most of those involve multi-steps, not just single-steps, two-steps, but multi-step conditions that needed to be done.

These were extremely harsh conditions. No sponsor yet to date has undergone that type of tampering conditions that we've seen. And the comparator in this case, you can drop into a simple everyday solvent and get out 86 percent in 5 minutes. In worst case that the FDA has presented, it took several hours for KP201.

So I just wanted to give that really brief perspective because I just didn't want you to leave here thinking what we know, and I think the agency knows as well, there's a significant barrier to tampering. Thank you. Sorry.

DR. EMALA: I just wanted to follow up on the last comment from the committee because maybe

we're jumping ahead a little bit talking about labeling concerns.

When we think about the size of the incremental step, I think we have to think about the impact that labeling would have on a prescriber, that a prescriber who would somehow interpret this drug as being a safer drug would be a little bit more willing to prescribe it, maybe even prescribe it in larger quantities because they had some sense that the FDA and this advisory committee believes that there was abuse-deterrent properties.

So I think we have to take that consideration very carefully about the unintended consequences of what such labeling might do.

DR. BROWN: We're going to take a 15-minute break. Please remember there should be no discussion of the meeting topic during the break amongst yourselves, and we're going to resume deliberations at 3:55.

(Whereupon, at 3:41 p.m., a recess was taken.)

DR. BROWN: If we could take our seats please. We have asked to add a second voting question to our deliberations, which will be question 4, if approved, should KP201/APAP be labeled as an abuse-deterrent product, which we will take vote on after we discuss and vote on question number 3.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and how

they voted into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all the questions have been answered or discussed.

DR. BATEMAN: Dr. Brown, can you describe what the second question will be?

DR. BROWN: Question number 4, it would just be an added question, if approved, should KP201/APAP be labeled as an abuse-deterrent product?

So we're going back to question 3. And question 3 is, should KP201/APAP be approved for the proposed indication? Are there any questions or comments concerning the wording or question?

DR. EMALA: Charles Emala. Could you clarify what "proposed indication" means?

DR. HERTZ: Let's use the working language for moderate-to-severe acute pain.

DR. BROWN: Up to 14 days. Any other questions or comments?

DR. CRAIG: Could we just clarify the indication once again? There's some mention about

time, about 14 days, which wasn't mentioned?

DR. HERTZ: I think at this point, you can just work on moderate-to-severe acute pain. I think that's really enough just to kind of think about it at this point.

DR. CRAIG: Thank you.

DR. BROWN: If there's no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote.

As you can see, it has "yes," and "no," and "abstain." You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken).

LCDR BEGANSKY: The vote was 16 yes, 4 no, zero abstain.

DR. BROWN: Everyone has voted. The vote is

now complete. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We can start down with Dr. Herring.

LCDR BEGANSKY: He didn't vote.

DR. BROWN: Oh, he didn't vote. Dr. Israel?

DR. ISRAEL: For the indication for moderate-to-severe pain, I think it meets the bar for that. It's similar to Norco. So am I supposed to say anything else to that other than that?

DR. BROWN: Please state your name --

DR. ISRAEL: Oh, sorry. Heidi Israel.

DR. BROWN: And how did you vote?

DR. ISRAEL: Yes. So the indication is for moderate-to-severe pain, and I felt comfortable with voting for that indication.

DR. BROWN: Very nice.

(Laughter).

DR. ISRAEL: All this discussion, what would you like -- three days of this, I'm sorry.

DR. BROWN: I understand completely. I've

been here with you. Next?

DR. DONOVAN: Maureen Donovan. I voted yes and based on the bioequivalence data with the comparator product.

DR. MICHNA: Ed Michna. I voted yes because I don't see any negative effects versus the reference product.

DR. GERHARD: Tobias Gerhard. I voted yes for the reasons that have been stated.

DR. HIGGINS: Jennifer Higgins. I voted no. I was not persuaded by the data.

MR. O'BRIEN: Joe O'Brien. I voted yes because of the similar things. To be honest, I almost abstained only because I don't think it had the strength of data that would normally be if someone was just presenting for a new drug.

DR. HALL: James Hall. I voted yes. I think it meets the indication.

DR. CAMPOPIANO: Melinda Campopiano. I voted yes.

DR. KAYE: Alan Kaye. I voted yes for the reasons stated.

DR. EMALA: Charles Emala. I voted yes because I believe it meets the indication for treating acute pain.

DR. PERRONE: Jeanmarie Perrone. I voted no really largely because I don't think that we could promote this as a safer product, and the unintended consequences that Dr. Emala referred to concerns me.

DR. BROWN: Ray Brown. I voted no. I'm unconvinced that this drugs offers robust deterrence, -- and it worries me to put another opioid on the market that does not have robust deterrence properties.

DR. CRAIG: David Craig. I voted yes primarily because of its clear use in the treatment of acute pain, which I think is pretty clear. I had questions about the second thing we're going to be voting on, but for this, it's a yes.

DR. SHOBEN: Abi Shoben. I voted yes, reluctantly, but I voted yes due to the bioequivalence data.

DR. MORRATO: Elaine Morrato. I voted yes,

also bioequivalence, didn't see evidence it would be more harmful. But I have the same concerns that were expressed by Drs. Brown and Perrone.

DR. STERGACHIS: Andy Stergachis. Yes.

DR. BATEMAN: Brian Bateman. Yes, based on bioequivalence with the reference product.

DR. GUPTA: Dr. Gupta. I voted no. I have a statement because I didn't participate much in the discussion. But I really do appreciate the work that the sponsor did and also the FDA on the diligence that they put forth and the detail that they've presented.

I'm certainly encouraged that there is progress in finding abuse-deterrent formulations and that there's initiatives in place to ensure patient safety. However, I did vote no for several reasons.

One, the findings demonstrate that the oral and nasal route were similar in drug liking, high intake drug; again, most notably in the first 30 minutes of intake; two, the lack of data on potential genetic and population variables was not

presented; three, the lack of clarity on how much added value the prodrug offers to prevent abuse deterrence; and four, the solubility characteristics that were presented demonstrated the ability to manipulate the product using simple solvents.

Unfortunately, in my opinion, the drug presented did not clearly appear to provide any compelling or incremental advantage over the current available product.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips, I voted yes. It's got evidence to show it's bioequivalent to the reference product, so it meets the minimum standard for coming on the market on that level. And similarly, I didn't see any concerns about either delayed released, or dose dumping is not issue obviously because it's immediately released.

So unlike some products that we looked at earlier this fall, there were not some safety concerns that would say it was not clearly safe and effective for treatment of pain.

DR. TYLER: Linda Tyler. I voted yes also based on the bioavailability profile.

DR. BROWN: We're going to move on to question 4, which is the new question, if approved, should KP201/APAP be labeled as an abuse-deterrent product?

Again, we will be using an electronic voting system. If there are questions or comments from the panel concerning this question, can we hear them now?

(No response).

DR. BROWN: Questions comments?

(No response).

DR. BROWN: No. So we're going to use the electronic voting system. Once we begin the vote, the buttons will start flashing and will continue flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

If everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen in to record.

Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

If there are no questions or comments concerning the wording or the question, we will now begin the voting process.

(Vote taken).

LCDR BEGANSKY: The result was 2 yes, 18 no, zero abstain.

DR. BROWN: We're going to start with Dr. Stergachis since he has to go to a plane.

DR. STERGACHIS: Andy Stergachis. No, for reasons cited earlier.

DR. BROWN: We're going to start back over here with Dr. Israel.

DR. ISRAEL: I voted yes. Baby steps --

DR. BROWN: Could you state your name?

DR. ISRAEL: Oh, sorry. Heidi Israel. I voted yes, baby steps in the process.

DR. DONOVAN: Maureen Donovan. I voted no, based on lack of evidence of clear distinction of abuse deterrence for both nasal and other routes.

DR. MICHNA: Ed Michna. I voted no because I thought the evidence was really not compelling at all for an abuse-deterrent indication. Unfortunately, it'll probably take us years to know what the effect is, and hopefully by then, we'll have improvements on this kind of technology.

DR. GERHARD: Tobias Gerhard, Rutgers. I voted no. I think we all would like to see an abuse-deterrent product for immediate-release that really has an effect. But we have to remain critical when being presented with data for such products. And I think here, we haven't seen the type of evidence that would suggest that this product really makes a difference compared to the available immediate-release product.

DR. HIGGINS: Jennifer Higgins. I voted no.

MR. O'BRIEN: Joe O'Brien. I voted no. I also have concerns for the same reasons. I also have concerns for labeling for some of the things that was mentioned, for example, crushing. I find that maybe confusing. I think that needs some attention in how is that potentially presented.

DR. HALL: I'm James Hall. I voted yes. I guess I believe in real baby steps, but also hopefully that if approved, this does send a message that we really believe that abuse-resistant is -- abuse-deterrent is a very important strategy, particularly with the opioids.

DR. CAMPOPIANO: Melinda Campopiano. I voted no because I feel that the evidence is equivocal enough that it would make it very difficult to provide effective guidance to prescribers and patients about just what exactly to expect.

DR. KAYE: Alan Kaye. I voted no just from remembering what I learned on Tuesday and Wednesday of this week. I don't feel labeling it as such

might communicate effectively with our prescribers, and I don't want to make things worse by stepping out and saying yes that it is a deterrent.

I think it is an improvement, a baby step, but I don't think you can label it as a deterrent because I think the prescribers might make things worse.

DR. EMALA: Charles Emala. I voted no for both Category 1 and Category 3 reasons. I think in Category 3, the A02 study was unconvincing that there was a difference to the comparator.

I'm also not convinced that it's not an easy extraction method. And I'm most concerned about giving a false sense of security to prescribers that I think could actually accelerate the volume and number of these pills prescribed.

DR. PERRONE: Jeanmarie Perrone. I voted no. Good thing Dr. Emala is here. I agree with him again.

DR. BROWN: Ray Brown. I voted no.

DR. CRAIG: David Craig. I voted no.

DR. SHOBEN: Abi Shoben. I voted no. I do

think that there's a place for these abuse-deterrent drugs, and I do believe that incremental improvement should be the bar, and we're looking for some sort of value added. However, in this case, I find the data just unbelievably unconvincing that this is even a little bit of an improvement.

DR. MORRATO: Elaine Morrato, and I also voted no. I agree the theory, the prodrug mechanism is there but it was not borne out by the in vitro, nor in vivo studies. And I also worry greatly about unintended consequences if we imply something is safer or better, especially, as we heard earlier, that this is a contextual thing and that this would be the first abuse-deterrent immediate-release. So it could lead to unintended consequences.

I might also add that I encourage the FDA to have very careful consideration of a launch marketing materials and the [indiscernible] mechanism of action data presented in those kinds of materials. And I would hate for it to imply

abuse-deterrent properties.

DR. BATEMAN: So I voted no for the reasons that others have indicated. I'm sorry. My name is Brian Bateman, and I voted no for the reasons that others have indicated. Particularly, the data from study A02 I think failed to show that it has abuse-deterrent properties relative to the comparator.

I agree with Dr. Morrato that when we do eventually have an immediate-release opioid that has abuse-deterrent properties around the nasal route, it'll be very important to communicate to physicians that that does not necessarily imply abuse-deterrent properties with respect to oral ingestion. And therefore, a physician shouldn't have a false sense of security about these medications.

DR. GUPTA: Dr. Anita Gupta. I voted no for the reasons already stated.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. I voted no. I think it's a small incremental step, that it's more challenging for a large scale drug

operation to try and extract large quantities of pure benzhydrocodone or pure hydrocodone from it if they wanted to do something on a large scale. But I don't want to send a message to patients and families or to prescribers that it would be less abusable for an individual patient who's going to take large quantities orally or even try to snort some.

DR. TYLER: Linda Tyler. I also voted no. And also, for baby steps, the term everybody else used, I want to recognize that the sponsor did an incredible job in the studies that they did, especially around the extractions. But this is where I think a certain degree they got caught in that the bar is rising.

I think Dr. Hertz's comments resonated with me, that we have to maintain the standard of what people expect for abuse-deterrent. And I think that's different, and some of us are getting kind of experienced on what's abuse-deterrent having been on a couple of different panels that have evaluated this.

So the bar is rising, got caught in that a little bit, and then what we expect as abuse-deterrent is also changing.

I think I'm concerned also around the marketing potential of that people will perceive that if it's abuse-deterrent, that that means it's safer. So that's something we'll have to struggle in the labeling because, clearly, those are two different things. But to the public, that may not appear to be two different things.

Then last, what we really want to know is does it make any difference in the abuse? Is it a product that helps us in the war, the public health crisis around opioids? What does it look like when this drug is used in the general population?

So to speak to that really is around our strength in our postmarketing surveillance, so are there opportunities to develop a really strong uniform postmarketing surveillance program as we consider these products going forward?

DR. BROWN: Before we adjourn, are there -- oh, question 5. Where did that come from?

(Laughter).

DR. BROWN: So question 5, if you think that the product should be approved, discuss the route or route or routes of abuse for which abuse-deterrent language should be included in the product label.

Why are we voting on this?

(Laughter).

DR. BROWN: Why are discussing --

DR. HERTZ: Because we added question 4, it doesn't mean with can delete the previous question that was there. So as we think about this, I guess I would like to ask you to consider in this discussion if there's anything further that you would like to say that you have not already expressed in the context of 4, this would be an opportunity to do so. Is that okay?

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I'll just make one point very quickly. So in the studies that the sponsor showed with larger doses of oral medication, there was some suggestion of a lower Cmax. And I think the

sponsor attributed that to a potentially saturation of esterases in the GI tract.

If they can develop a more compelling data there to really demonstrate a ceiling effect, that could be a very important step forward in proving the safety of these medications. So I think further development along those lines would be very helpful.

DR. BROWN: Dr. Hall?

Dr. Israel, you voted yes. Do you have any specific comments surrounding this particular discussion question?

DR. ISRAEL: No, I have no further comments.

DR. BROWN: Are there any other comments that anyone might have?

(No response).

DR. BROWN: I'd like to say that I think the sponsor did an excellent job in presenting the data. I'm not certain that this is the end for whether or not this can, at some point in the future with this technology, be considered.

I would like to see more information,

postmarketing information concerning this. I think it'll be very important, as has been said, for us to continue to follow that quite closely so that we can determine whether or not, in the future, the labeling could perhaps be changed to make it abuse-deterrent.

Dr. Hertz, do you have any questions, concerns, or comments?

DR. HERTZ: I just want to express my thanks again to the committee. We value your time, your comments, your thoughtfulness about this. We just really appreciate your taking the time out of your busy schedules.

Adjournment

DR. BROWN: Before we adjourn, panel members, please take all your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of.

Pease also remember to drop off your name badge at the registration table on your way out so that they may be recycled.

We will now adjourn the meeting. Thank you very much.

(Whereupon, at 4:20 p.m., the open session was adjourned.)