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CENTER FOR DRUG EVALUATION AND RESEARCH

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JOINT MEETING OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE AND DRUG SAFETY & RISK MANAGEMENT ADVISORY COMMITTEE

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OPEN SESSION

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TUESDAY,

MAY 6, 2008

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The Committees convened at 8:00 a.m. in the Grand Ballroom of the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland, Sulpicio de Guzman Soriano, III, M.D., Acting Chair, presiding.

ANESTHETIC AND LIFE SUPPORT ADVISORY COMMITTEE MEMBERS (voting) PRESENT:

KANAWALJEET J.S. ANAND, M.D., Ph.D.

JEFFREY R. KIRSCH, M.D.
NANCY A. NUSSMEIER, M.D.
DONALD S. PROUGH, M.D.
ATHENA F. ZUPPA, M.D.

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBER (voting) PRESENT:

TIMOTHY S. LESAR, Pharm.D.

TEMPORARY VOTING MEMBERS PRESENT:

SULPICIO de GUZMAN SORIANO, III, M.D., Acting Chair
DIANE ARONSON, B.S., Acting Consumer Representative
WARREN K. BICKEL, Ph.D.
CHARLES CORTINOVIS, M.D.

RUTH S. DAY, Ph.D.
JACQUELINE S. GARDNER, Ph.D.
THOMAS KOSTEN, M.D.

SUSAN KRIVACIC, Patient Representative
JANE C. MAXWELL, Ph.D.
LEWIS NELSON, M.D.
LEONARD J. PAULOZZI, M.D., M.P.H.
FRANK VOCCI, Ph.D.
SIDNEY WOLFE, M.D., Acting Consumer Representative (DsaRM)

MICHAEL YESENKO, Patient Representative

ACTING INDUSTRY REPRESENTATIVE (non-voting) PRESENT:

CHARLES McLESKEY, M.D. (ALSDAC)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

PARTICIPANTS AT THE TABLE (non-voting) PRESENT:

HENRY FRANCIS, M.D.
SHARON HERTZ, M.D.
BOB RAPPAPORT, M.D.
CURTIS ROSEBRAUGH, M.D.

DOUGLAS THROCKMORTON, M.D.

GUEST SPEAKER (non-voting) PRESENT:
JUDY K. BALL, Ph.D., M.P.A.

DESIGNATED FEDERAL OFFICIAL PRESENT:

TERESA WATKINS, Pharm.D.

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(7:59 a.m.)

ACTING CHAIR SORIANO: Good morning. My name is Sul Soriano, and it's my distinct privilege to serve as the acting chair at this morning's Joint Meeting of the Anaesthetic Life Support Drug Advisory Committee, as well as the Drug and Safety Risk Management Advisory Committee.

I would like to read a statement from the FDA. 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 today 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. This is a gentle reminder individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting. Thank you.

At this time, I'd like to have each member of the Joint Advisory Committee introduce themselves, starting with Mr. Yesenko.

MR. YESENKO: Michael Yesenko, Patient Representative.

DR. GARDNER: Jacqueline Gardner, University of Washington School of Pharmacy.

ACTING CHAIR SORIANO: Jane?

DR. MAXWELL: Jane Maxwell, Senior Research Scientist, Addiction Research Center, University of Texas at Austin.

DR. ZUPPA: Athena Zuppa, Pediatric Critical Care Doctor and Clinical Pharmacologist at the Children's Hospital of Philadelphia.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center in Albany, New York.

ACTING CHAIR SORIANO: Sul Soriano, Neuroanesthesiologist at Children's Hospital, Boston.

DR. WATKINS: Teresa Watkins, the Acting Designated Federal Official for these committees.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

DR. KIRSCH: Jeffrey Kirsch, Professor and Chair of the Department of Anesthesiology at Oregon Health Science University.

DR. PAULOZZI: Len Paulozzi, Centers for Disease Control and Prevention.

DR. PROUGH: Don Prough, Chair of Anesthesiology at the University of Texas Medical Branch.

DR. BICKEL: Warren Bickel, University of Arkansas for Medical Sciences.

DR. KOSTEN: Tom Kosten, Professor of Psychiatry and Neuroscience, Baylor College of Medicine.

DR. NELSON: Lewis Nelson, Emergency Medicine and Medical Toxicology at

New York University.

DR. NUSSMEIER: Nancy Nussmeier, Chair of Anesthesiology at SUNY Upstate Medical University in Syracuse.

DR. VOCCI: Frank Vocci, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute of Drug Abuse, Bethesda, Maryland.

MS. KRIVACIC: Susan Krivacic, Patient Representative, Austin, Texas.

MS. ARONSON: Diane Aronson, Consumer Representative, Cambridge, Massachusetts.

DR. WOLFE: Sid Wolfe, The Health Research Group at Public Citizen and the Acting Consumer Rep on the Drug Safety and Risk Management Committee.

DR. MCLESKEY: Charlie McLeskey, Acting Industry Representative on ALSDAC.

DR. CORTINOVIS: Charles Cortinovis, Anesthesiologist, University of Pittsburgh, VA Medical Center.

ACTING CHAIR SORIANO: And Dr. Anand, Pediatric Intensivist at University of Arkansas. And now I'd like to have the members of the FDA introduce themselves, please.

DR. HERTZ: Sharon Hertz, Deputy Director, Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. RAPPAPORT: Bob Rappaport, Director of Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. ROSEBRAUGH: Curt Rosebraugh, Acting Director, Office of Drug Evaluation II.

DR. THROCKMORTON: Doug Throckmorton, Deputy Director, Central for Drug Evaluation and Research.

DR. WATKINS: Thank you. Good morning. I would like to first remind everyone present to please silence their cell phones, pagers, and Blackberries, if you haven't already done so. I would like to identify the FDA press contact. Ms. Cruzan,

if you're here, please stand. Okay.

Now with the conflict of interest statement. The Food and Drug Administration is convening today this joint meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members 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 the committees' compliance with federal ethics and conflict of interest laws covered by but not limited to those found in 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act 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 the federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special and regular government 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. Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees or regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

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 the purposes of 18 U.S.C. 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 discussion of supplemental new drug application sNDA 21-947S005, fentanyl buccal tablet, trade name Fentora, Cephalon Incorporated, and its safety for the proposed indication of breakthrough pain in opioid-tolerant non-cancer patients with chronic pain. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. 208 B1 and 712 of the FD&C Act for Dr. Thomas Kosten for his stock ownership in a competing firm worth between $25,001 and $50,000. The waivers allow this individual to

participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. McLeskey is serving as an industry representative acting on behalf of all regulated industry. Dr. McLeskey is an employee of Baxter Healthcare Corporation.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed

financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with any firms at issue. Thank you.

ACTING CHAIR SORIANO: All right. Dr. Francis, you want to introduce yourself?

DR. FRANCIS: Good morning. Dr. Henry Francis, Deputy Director of the Office of Surveillance and Epidemiology.

ACTING CHAIR SORIANO: At this time, I'd like to invite Dr. Bob Rappaport to make opening remarks for this session.

DR. RAPPAPORT: Good morning, Dr. Soriano and members of the Anesthesia and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, invited guests. Thank you for joining us today and welcome back.

As I noted at the opening of

yesterday's meeting, we are faced with many difficult decisions regarding the risks and benefits of new formulations and new indications for opioid drug products due to two separate but equally important public health concerns. First, there has been a clear increase in misuse, abuse, and diversion of these products occurring in the United States over recent years, and there has been a resultant increase in cases of addiction, overdose, and death. Second, while enormous strides have been made over the past few decades in the treatment of pain, millions of Americans have acute or chronic pain that remains under-treated even today. Both of these problems result in significant public health burdens, and it is essential that we address how can we balance the unmet needs of patients living with inadequately treated pain with the potential for the very treatments for that pain to be diverted, misused and abused, and to lead to addiction, overdose, and death.

Today you will be presented with important information concerning the abuse and diversion of prescription opioid drug products in the United States. However, today we will focus on the abuse and misuse of fentanyl and fentanyl drug products in particular.

The sponsor has submitted a supplement to their approved new drug application for Fentora, a transmucosally-absorbed lozenge formulation of fentanyl, to expand the indication from the treatment of breakthrough pain in opioid-tolerant cancer patients to the treatment of breakthrough pain in opioid-tolerant patients with chronic pain not due to underlying malignancies.

Fentora was initially approved in 2006 with a risk management plan that was modeled after the one originally implemented for Actiq in 1998. Actiq is also a transmucosally-absorbed formulation of fentanyl but is different in that it is designed as a lozenge on a stick, or a

lollipop. It was because of this lollipop formulation and the potential for accidental or inadvertent exposures to a potentially lethal dose of fentanyl by young children that the Agency insisted on this extensive and comprehensive risk management plan at the time of approval. However, that plan has only been partially successful. While there have been relatively few post-marketing reports of Actiq being prescribed to patients not already on background opioid treatment and relatively few accidental exposures to children, there has been increasing off-label prescribing of Actiq for non-cancer related pain, including for the treatment of conditions such as migraine.

Fentora has been marketed for less than two years, but we have already seen more reports of serious and life-threatening adverse events in both properly-prescribed and mis-prescribed patients then we have ever seen for Actiq over similar periods of time.

An expansion of the indication for

Fentora to non-cancer patients would clearly lead to an increase in the prescribing and use of the product. The new and expanded indication would allow Cephalon to promote and market the product to a much wider patient population.

We at FDA are concerned that increased prescribing might also lead to an increased level of abuse, misuse, and diversion of this drug product. Due to the potency of this product, if this were to occur the results may be an even more tragic public health crisis of increasing addiction, overdose, and death than we have seen with the currently available products and indications. And based on the experience with Actiq, we are not convinced that the risk management strategies that have been used to date can mitigate these particular risks. This must also be balanced against the possibility that new and more restrictive risk management strategies and limiting prescribing might lead

to the product being less available to legitimate patients.

Is it possible to find a path forward that will result in labeling that indicates for Fentora patients with breakthrough pain due to chronic painful conditions other than cancer while avoiding the potential widespread abuse and misuse of the product due to more extensive marketing and prescribing? This is certainly one of the most challenging questions that we have faced at FDA.

In order to make the most informed and sound decision possible, we will be asking you to address a number of questions today. First, we will ask you to discuss whether breakthrough pain episodes experienced by patients with chronic non-cancer pain actually require treatment with potent opioids, such as fentanyl, or whether they can be adequately treated with less potent opioid or non-opioid analgesics. Second, we will ask you to

address whether Fentora can be safely prescribed in a broad non-cancer opioid-tolerant patient population cared for by a variety of specialists and primary care physicians.

Fentora has attributes that make it particularly attractive for abuse and attributes that make it potentially dangerous for those who do abuse it. In light of the increasing abuse of prescription opioids and the fact that as prescription numbers have increased so has diversion with other narcotic agents and in light of the specific attributes of this particular product, we will ask you to discuss whether the increased availability of Fentora would likely lead to widespread abuse and the public health consequences of that abuse.

If there is a substantial risk for increased abuse of this product due to greater availability, can that risk be effectively managed? And if so, what specific risk

management tools would be necessary to mitigate the risks?

Finally, we will ask you to address whether the implementation of risk mitigation strategies might lead to limitations to access for legitimate patients. We will then ask you to vote to either recommend for or recommend against approval of the expansion of the indication for Fentora to opioid-tolerant non-cancer chronic pain patients with breakthrough pain.

I think it became clear from the discussion at yesterday's session that finding a reasonable compromise that will provide availability and safe use of potent opioid drug products for patients who need them to avoid unreasonable suffering and that would still prevent the abuse and diversion of these products and the consequent addiction, overdose, and death that this may cause is an enormous challenge. This particular change to the Fentora indication is a case study for the

larger problem.

We hope that your varied expertise and your extensive experience will help us find a reasonable path forward and that we will be available to do so carefully, cautiously, and with as much transparency as possible. Thank you for working with us to address these complex and difficult but extremely important public health challenges.

ACTING CHAIR SORIANO: Thank you, Dr. Rappaport. At this time, we will proceed to the sponsor's presentation for today's meeting. Before Cephalon's presentation, I would like to remind public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Now, the Joint Committee now recognizes Dr. Eric Floyd to make the introductions for Cephalon.

DR. FLOYD: Good morning to Dr. Soriano, members of the FDA Review Division,

panel members, and guests. My name is Eric Floyd. I'm Vice President and Worldwide Head of Regulatory Affairs for Cephalon. We are here today to discuss the proposed indication for Fentora for the management of breakthrough pain in patients who are taking around-the-clock opioid medication for their underlying persistent pain.

To provide some background, clinicians have been prescribing fentanyl for more than 40 years. In 1990, the fentanyl patch Duragesic was approved for the management of chronic pain in opioid-tolerant patients without a restriction to cancer. Eight years later, Actiq was approved with a limited indication for the treatment of breakthrough pain in opioid-tolerant cancer patients. It was the first C-II opioid approved with a risk management plan which was designed in consultation with the FDA. In 2006, Fentora was approved for the same indication with an expanded risk management

plan.

One of our goals in our current RiskMAP was to limit the prescribing of both Actiq and Fentora to cancer patients. And we recognize that we have been unsuccessful in meeting this goal, as the majority of our prescriptions were written for patients without a diagnosis of cancer. Therefore, we pursued a proactive clinical development program to systematically evaluate the efficacy and safety of Fentora in non-cancer patient populations. And as we continue to develop to Fentora, we will also refine our RiskMAP, which you will hear about today.

We are here to address today the following: the need to expand the indication; the safe use of Fentora in the expanded patient population; the potential for increase in overdose, abuse, and diversion; and our proposal on how we plan to mitigate these risks in partnership with the Agency.

Now, we agree with the FDA that a

stronger RiskMAP is warranted to reduce the risks of overdose, abuse, and diversion. And today we will share our proposal for an enhanced RiskMAP that includes a registration system and a controlled launch strategy. This RiskMAP is significantly more comprehensive and robust than that reflected and described in the briefing document, and we feel will more effectively mitigate the risks of overdose, abuse, and diversion.

In order to provide a more detailed review of our clinical development program, our proposal to address safety concerns with our enhanced risk management strategies, coupled with a proposed staged launch plan, I would like to introduce today's presenters. Dr. Perry Fine, a pain care specialist from the University of Utah, will discuss the medical need for an effective treatment in breakthrough pain in opioid-tolerant cancer patients. Dr. John Messina will discuss efficacy of Fentora and how we

plan to mitigate the risks of abuse and diversion. Dr. Juergen Schmider will discuss safety and how we plan to mitigate the risk of overdose. And Dr. Lesley Russell will provide closing remarks. We also have several consultants here today to address any outstanding questions which the Committee or the Agency may have.

At this point, I would like to introduce Dr. Fine.

DR. FINE: Good morning, Dr. Soriano, Dr. Rappaport, members of the advisory panel, and all those in attendance. My name is Perry Fine. I'm a clinician and researcher at the University of Utah, where I've been investigating and treating pain in both cancer and non-cancer patients for the last 25 years. And in appreciation for the diversity of experiences and various steps of knowledge and expertise around the table here, I think it's very important, critically important in fact, that we all have a firm

understanding of breakthrough pain and the high impact as a clinical condition it has for which conventional therapies, unfortunately, do not adequately offset and manage the debility that can be caused by this problem in those patients on around-the-clock opioid therapy for control of their chronic non-cancer pain.

Positioning opioid therapy in these patients, of course, is a process that involves evaluation, risk assessment, and stratification. And in those patients who are effectively and safely managed on chronic opioid therapy, there emerges in a select number of these patients this phenomenon of breakthrough pain that has become an emerging phenomenon that's been observed over the last 20 years, originally in cancer patients and now, as we've continued on with clinical investigations, in chronic non-cancer patients on continuous opioid therapy where their pain is otherwise safely and effectively managed

but then requires supplemental opioid therapy to control these episodes of breakthrough pain.

This is not a new problem, as I've intoned. This goes back in the literature, certainly in the pain and palliative medicine literature, about 20 years and, as an emergent phenomenon, has become normalized within the pain field and also, in a regulatory sense, as can be seen in the approved language in prescribing information, package insert material, that advises clinicians who are prescribing continuous or modified-release opioids for the control of chronic pain, again both in cancer and non-cancer patients who are effectively managed where their baseline pain is effectively managed to do further assessments in specifically evaluating for breakthrough pain and then, in fact, to treat those breakthrough pain episodes.

The formal definition now comes to the forefront as breakthrough pain being

typically defined as a transitory exacerbation of pain that occurs on a background of otherwise well-controlled chronic pain. And this definition has been operationalized in the clinical programs and controlled trials of Fentora where the patients entering these trials have pain for at least three months and are opioid-tolerant, as defined by using at least 60 milligrams of oral morphine or oral morphine equivalents for at least one week.

If we compare and contrast now this evolving literature and trial studies and surveys over the last 20 years starting with cancer patients, we can see that, in fact, there's great consistency actually between the population of patients with cancer and those with chronic non-cancer pain in terms of how the characteristics of breakthrough pain go. As you can see, about two-thirds of patients with cancer-related breakthrough pain experience this, about up to four episodes a day on average. And most importantly,

breakthrough pain, as this emergent phenomenon, is a very rapid onset problem for which the pharmacokinetics and the secondary dynamics of the usual short-acting opioids do not match up well. And in the cancer population, the average duration of these episodes is about 30 minutes but has significant impact on patients nonetheless.

And so when compared with the non-cancer chronic pain population, similar numbers are seen with maybe an average of two episodes, rather than four, per day, at least in survey data. And, again, onset time is a matter of minutes and perhaps lasting up to an hour.

Similarly, if we look at the path of physiology of pain and the etiology or causal nature of these pains in the cancer population and compare those to now what we've observed in the non-cancer chronic pain patients, there seems to be this final common pathway with nociceptive or somatic pains,

nociceptive visceral pains, and neuropathic pains being actually quite similar with a larger number of patients with mixed disorders in the non-cancer population. So, actually, as we studied this and this field has evolved in the last two decades, we actually see there's less differences in the expression of this pain syndrome amongst these two populations of patients.

Whereas, currently, in the area of non-cancer chronic pain treatment, there are no approved medications, although there are avid attempts to treat these patients. But as I said, these are oftentimes ineffective with the conventional therapies at hand.

And, again, this is not a low-impact problem. This actually has a significant debilitating effect on patients. And these patients who, otherwise, are well controlled with the baseline pain, those breakthrough pain episodes have a serious impact on their health and well being. If we

compare, again, and contrast high-impact chronic conditions, such as congestive heart failure, recent myocardial infarction, affective disorder/mood disorder of major depression, we can see that chronic non-cancer pain with breakthrough pain actually, on this validated instrument, the SF-36 Physical Health Summary Score, actually has a greater impact than these other chronic kind of conditions. So this is clearly an issue for patients that should not and cannot be ignored.

So what is the evidence supporting the need and potential benefits of a new tool, Fentora, for the treatment of breakthrough pain? I think there are three lines of evidence, other than the high impact that we've now seen in terms of general health status. One arises from survey data, again showing about three-quarters of patients who are otherwise well managed on chronic opioid therapy who do demonstrate breakthrough pain

episodes that, in fact, it's effort to treat them with conventional agents that are currently available, the typical short-acting agents such as oxycodone or hydrocodone, etcetera, that two-thirds of patients are attempted to be treated in such a manner; but the same fraction demonstrate inefficacy or poor management of their breakthrough pain. This is translated into sort of the naturalistic experiment that we've seen amongst clinicians, practitioners, such as myself, who treat both populations who have had the advantage of having an indication for the transmucosal delivery systems of fentanyl for the treatment of cancer pain, have been involved in the clinical trials, have witnessed the benefits and the improved functional capacities of those patients with cancer, and have these similar problems in our non-cancer patients. And as a result of this, currently because of the larger population of non-cancer chronic pain patients, about 80-

percent of current prescriptions are being written for the non-cancer patients with breakthrough pain.

And then the clinical trials data, the third line of evidence, suggests that it's at study entry, those patients experiencing breakthrough pain with insufficient benefit from the short-acting agents they've previously tried have the opportunity to experience using Fentora. And, again, about two-thirds or more of these patients clearly define this as being a far more effective and beneficial therapy for the control of their breakthrough pain.

So now we've got I think an evidence base that suggests not only that this is a high-impact clinical problem that cannot be continuously ignored and also that there is an effective treatment that is feasible for these patients that we have to consider where we position a drug like Fentora in the schema of chronic pain management. And so we sort of

move up this conventionally pharmacotherapeutic approach to the management of chronic pain starting with non-opioid therapies and moving towards milder low-dose opioid therapies. And, again, in those highly-selected patients who clearly benefit and have efficacy and safety in use of chronic opioid therapy over time. Then the rapid onset opioids would be viewed as a supplement for those patients who do have this emergent phenomenon of breakthrough pain. So, again, this would be third-stage therapy.

So now let me talk to you about two patients, actually, of mine to demonstrate sort of the principles that I've been alluding to with the comparisons of cancer and non-cancer pain. These two patients, both women, both around the same age, have serious and significant pain problems secondary to their underlying diagnoses. One has a cancer diagnosis, actually metastatic breast cancer, with severe and debilitating bone pain. The

other has a disease, CREST syndrome, an autoimmune disorder, for which she also has severe and debilitating bone pain.

Both these patients, at the time they were referred to me, had pain that was largely out of control. It was poorly managed. And, ultimately, their baseline pain was able to be controlled on controlled-release opioids, one with transdermal fentanyl and the other with controlled-release oxycodone product, but, nevertheless, had this emergent phenomenon of breakthrough pain that equally and seriously impacted their ability to go to work, which they both continued to want to do as long as they could, their ability to take care of family situations or family matters. Essentially, their activities and functional capacities were significantly impaired. And the usual approaches to therapy, the immediate-release short-acting opioids, were simply not effective in managing them.

They have both been titrated and effectively managed with Fentora, but that's where the similarities end because our cancer patient has patient-specific information and educational materials that can be delivered to her. As a professional, I can receive information about principles and practice to create best practices around the use of this agent for the cancer patient. But without an indication, there's absolutely no such materials available for my non-cancer chronic pain patient. And, furthermore, this patient, the non-cancer patient, is burdened by the problem of not having this drug available on formulary without an indication and so presents her with a serious and significant financial burden, as well.

So with the similarities actually between not the diagnoses and the underlying problems which have to be managed independently but this convergent phenomenon of their chronic pain and their breakthrough

pain with similar pathophysiologies. I think from an empiric, clinical, and a scientific standpoint, the absence of an indication for one and not the other is not sustainable.

However, it's fully acknowledged as a clinician and, if you will, as all physicians, officers of the public health if you will, that we have to not only balance these obligations to treat the patients that come to us in the best manner we can but also to assure the public health when we write any prescription, especially for controlled substances. So it's an essential principle of balance that has been the foundation of practice management and risk mitigation from which we've learned from the perspective of treating patients with opioids over the last numbers of years. And so, clearly, the responsibilities that we all have now to assure best practices for patients in need but also to safeguard the public health centers around the risk management and risk mitigation

plan.

So with that, I want to introduce Dr. Messina, who is going to further report on the efficacy trials, as well as introduce the RiskMAP. Thank you.

DR. MESSINA: Good morning. My name is John Messina. You've just heard from Dr. Fine that there's a need to effectively treat breakthrough pain patients with chronic pain regardless if it's related to cancer. We've conducted a clinical program to evaluate the efficacy of Fentora in the treatment of breakthrough pain in opioid-tolerant patients with non-cancer related pain.

The development of Fentora was heavily influenced by our experience with Actiq. We were aware that Actiq was being used in non-cancer related breakthrough pain. So with Fentora, we initiated clinical trials in patients with both cancer and non-cancer related breakthrough pain. This was done in order to demonstrate efficacy and safety in

both populations.

Fentora delivers fentanyl in an efficient manner via the oral mucosa. The characteristics of fentanyl allow it to cross the blood/brain barrier faster and thereby get to its site of action quicker than most other opioids. And because a large proportion of the dose of fentanyl is absorbed by the oral mucosa, the pharmacokinetic profile more closely matches the onset of the breakthrough pain episode.

Here we show how quickly patients report their maximum breakthrough pain intensity being reached from the time that it starts. The graph represents the percentage of breakthrough pains that reach maximum intensity within the indicated time. The majority of patients report that their maximum intensity is reached within 15 minutes of onset. This green line depicts the percent of the maximum concentrations of one of the most commonly used short-acting opioids to treat

breakthrough pain today, oxycodone. The orange line represents fentanyl concentrations with Fentora. And as you can see, the curve is shifted to the left with more medication becoming available earlier. This, taking with fentanyl's ability to cross into the central nervous system faster than most other opioids, allows its analgesic action to more closely match that of the breakthrough pain onset.

In our supplemental NDA application, data from four phase three studies were included. The pivotal study was designed in collaboration with FDA, and it assessed efficacy over a 12-week period. In addition, there was one open-label study with a duration of up to 18 months. All patients entering the trials were required to be opioid-tolerant, and this was defined as being on an around-the-clock opioid of at least 60 milligrams of oral morphine or equivalent. In addition, all patients were already treating breakthrough pain with opioids.

In all of these studies, patients began at the lowest dose of Fentora regardless of the around-the-clock opioid dose. Patients were subsequently titrated to a dose that was both effective and tolerated, up to a maximum dose of 800 micrograms. In the efficacy studies, a within patient design was utilized to compare the analgesic effects of Fentora to that of placebo. In this design, patients get randomized to a sequence of nine treatments, six with Fentora and three placebo. These were used to treat breakthrough pain episodes, and efficacy measures, such as pain intensity and pain relief, were utilized to assess the effects.

A total of 941 patients entered these trials, and their baseline characteristics are reflective of the intended population. The average age was approximately 50 years old, and the majority of patients were women. Chronic pain conditions and the frequencies of the different types that were

included are typical of this population of opioid-tolerant patients. The average pain of the breakthrough pain episodes prior to treatment was seven out of a ten on a numerical rating scale, indicating that for most patients the pain was severe in intensity.

One of the important findings from this clinical program has been our development in understanding of the characteristics of this population. Specifically, these patients have significant levels of co-morbidity, which impact many of the outcomes that we observed during the trials. It's worth noting the high rate of psychiatric and cardiovascular co-morbidity. Also, over 60 percent of the patients who entered these studies reported having more than one painful condition at study entry. And, on average, these patients were using five or more concomitant medications.

On average, the dose of the

around-the-clock opioid medication used at study entry was significantly higher than the minimum of 60 milligrams of oral morphine, as indicated in the protocols. And all patients entering the trials were using opioids to manage their breakthrough pain. Therefore, it's important to remember that Fentora was, in fact, replacing the opioid being used for breakthrough pain.

The next three slides I'll share with you are efficacy results from the pivotal study at the primary time point of interest, which was week 12. This slide shows the average difference in pain intensity scores from baseline at each time point measured for Fentora and placebo after 12 weeks. As you can see, separation is first observed at 15 minutes, and this difference increases through 60 minutes and is maintained throughout the two-hour observation period.

The primary outcome variable for the study was the sum of these pain intensity

differences through 60 minutes. The difference between treatments was statistically significant in favor of Fentora, and this pattern of effect you see was consistent at weeks four and eight in this pivotal study, as well as in the supportive studies that we've conducted.

We also evaluated the proportion of episodes in which a clinically important change occurred. This graph represents the proportion of episodes where at least a 33-percent reduction in pain intensity was achieved. And this is considered to represent at least a moderate level of improvement. Separation is observed as early as five minutes, and this increases with time.

But we evaluated response rates for a 50-percent reduction in pain, as well. For example, this means that a patient who reports a pain intensity of eight would have it reduced to at least a four or less. This is considered to represent substantial level

of improvement. The pattern of response you see here is similar with an early separation from placebo and a difference that increases over time. These data demonstrate that the effects with Fentora are clinically relevant.

Patients were asked to indicate whether they preferred Fentora or their breakthrough pain medication they were using at entry in the pivotal study. Nearly 70 percent of patients indicated that they preferred Fentora; and, overwhelmingly, patients indicated that Fentora provided faster relief than the medication they were using previously.

To summarize, these data demonstrate that Fentora is an effective treatment for breakthrough pain within this population and the effects observed are clinically meaningful and sustained over a 12-week period. The patients studied are reflective of those who will be treated with Fentora within clinical practice.

Dr. Schmider will now discuss the safety data from these studies.

DR. SCHMIDER: Good morning. My name is Juergen Schmider. Post-marketing experience for fentanyl has accumulated for more than 40 years; and, therefore, we have a good understanding of the safety profile to expect from a fentanyl-containing formulation.

I will now provide you with a high-level overview of the relevant clinical safety and pharmacovigilance data for Fentora. I will cover the overall adverse event profile seen in the clinical trial program, the comparison between the safety profiles for cancer and non-cancer breakthrough pain populations, and the post hoc analysis of the occurrence of drug-related behavior.

The clinical trial experience with Fentora involved almost 1300 patients, of which 941 patients participated in trials for non-cancer related breakthrough pain. The related cumulative clinical trial patient

exposure to Fentora equals almost 230,000 patient treatment days.

The most common adverse events in the clinical trials for non-cancer breakthrough pain were typical of opioid analgesic drugs. There were two expected exceptions. One was related to the formulation-specific application site events, which are all grouped together on this line. The other was related to the trial population as reflected in the events of back pain and arthralgia.

A total of ten overdose cases were observed in the clinical trial program. Discernable causal factors included suicide attempt, substance abuse, and multiple dose strengths available during the titration period. None of these overdoses were fatal; and in some patients, the circumstances were not known. One non-study subject experienced a fatal overdose after diverting study medication from his wife, who was a study

participant.

We have addressed these reasons for overdose in the proposed package insert. Overdose is also one of the two risks specifically addressed in the proposed Fentora RiskMAP.

I will now compare the incidents of adverse in the cancer and non-cancer breakthrough pain populations. This comparison was also performed by the FDA and is contained in their briefing documents. The profiles of the frequently observed adverse events were largely similar in cancer and non-cancer breakthrough pain, with the exception of dizziness and constipation which had a higher incidence in the cancer trial participants.

We analyzed adverse events of special interests as defined by the FDA. In contrast to the FDA analysis, rights on this slide reflect all severities, not just moderate and severe. Any crossover events

subsequent to the same incident were counted only once for each pooled term. For example, we counted nine fractures that occurred in one patient as a result of a motor vehicle accident only once, while it appears that the FDA counted each of these separately, which may account for the discrepancy in the number of fractures that we observed between our two analyses.

The table on this slide is analogous to the table in the FDA briefing document. When taking into account differing study durations, it is apparent from our analysis that only withdrawal was more frequent in the non-cancer populations.

We believe that it is appropriate to use an all-severities analysis because a selective analysis limited to moderate to severe only introduces a bias. For example, this is one of the reasons why labels for most products do not differentiate by severity of adverse events. Although the safety profile

between the two trial populations is largely comparable. The events of interest were more frequent in the cancer population with the exception of withdrawal.

As part of the evaluation of Fentora, during the clinical trial program we evaluated abuse and diversion risks within clinical trials. During clinical studies, 21 patients were reported to have a drug abuse event. Eight patients had a reported event of drug abuse. Additionally, 13 of 568 patients who had an unscheduled urine drug screen on study tested positive for illicit substance or non-prescribed medication. Published reports for other clinical programs with opioid and chronic pain have revealed similar incidences of events of drug abuse.

The size and scope of the clinical database provided an opportunity to evaluate the occurrence and predictors of aberrant drug-related behaviors in a population of chronic pain patients treated with opioids.

It is widely supported in the medical literature that aberrant behaviors are signals for potential substance abuse and not surrogates for diagnosis of abuse or addiction.

We conducted a post hoc analysis of the clinical data to identify behaviors defined within the medical literature as being an aberrant. The intent of the analysis was to identify baseline characteristics associated with these behaviors to aid an appropriate patient selection. In this analysis, we evaluated events of substance abuse, overdose, and aberrant behaviors.

Aberrant behaviors were sorted into two main categories: those involving the use of study medication and those which did not. This table gives you an idea of the type of events that were looked at. The percentage of individual aberrant behaviors was relatively low, and 85 percent of patients with any aberrant behaviors had only one

behavior identified. To our knowledge, this has been the first attempt in assessing aberrant behaviors within a clinical trial setting.

We observed markedly fewer aberrant behaviors than are reported in the literature for similar populations within the clinical practice.

Next, we will review the post-marketing experience of Fentora with the currently approved indication of cancer-related breakthrough pain. About 80 percent of use occurred in non-cancer related breakthrough pain. The post-marketing data reflect mostly the patient population for which we seek approval. These post-marketing data are based on the cumulative observations over the 15 months from launch of the product to the end of last year. During this time frame, more than two million treatment days of exposure experienced were accumulated with Fentora in approximately 20,000 unique

patients.

The post-marketing profile of the most frequently voluntarily reported adverse events is as expected with fentanyl. Again, we noted the exception of formulation-specific application site events, which are grouped together here again.

Two cases of diversion and two cases of non-medical use were reported. In both cases of diversion, the partner of a patient diverted Fentora and experienced a fatal overdose. In the one case of non-medical use reported as drug dependence, the patient sought treatment for abuse. The other case is an American association of poison control center report of drug abuse.

Diversion, abuse, and misuse are known properties of Schedule II opioid analgesics. This makes risk management plans for this class of compounds unique. Not only do they have to deal with the risk that occurs in the patient population, but they also have

to mitigate the risks in non-patients.

During the 15 months of post-marketing period, we only received one report of accidental exposure in which the subject recovered. This occurred in a 73-year-old woman with dementia who mistook her daughter's medication for aspirin. Her daughter had taken the medication out of the original blister package and replaced into an unlabeled container. Now, in contrast to Actiq where accidental pediatric exposure is a major concern, no report of accidentally-exposed children for Fentora has been received.

One of the areas of concern with Fentora is use in opioid non-tolerant individuals. Information about non-tolerant use is difficult to obtain. One approach is to apply an algorithm to prescription data to identify patients Fentora uses with concurrent use of other pain medication. Another approach is to use post-marketing experience where information about concomitant medication

is obtained directly from the patient.

Through December of 2007, Cephalon received almost 2,000 post-marketing reports for Fentora. In one-quarter of the reports, the opioid treatment status was not provided. In the reports where appropriate information was provided, 14 percent were in individuals receiving less than 60 milligrams per day morphine equivalent.

Rates of opioid non-tolerant use derived from IMS prescription data using an algorithm agreed upon with the Office of Surveillance and Epidemiology, or OSE, are higher with 23-percent non-tolerant use. The rates obtained from Verispan prescription data using the same OSE-agreed algorithm are similar. Rates from the concurrency analysis conducted by OSE using Verispan prescription data but a different algorithm, the VOCON analysis, resulted in a projection of non-tolerant use of 41 percent.

Regardless of the actual extent,

any opioid non-tolerant use is of great concern to us as it can lead to overdose. Therefore, we specifically address this concern in our RiskMAP.

Another common cause of overdose is medication errors. During the post-marketing observation period, we received 26 reports of medication errors. Eight of these were caused by dose conversion errors when switching patients to Actiq to Fentora. Half of the administration route errors were associated with using Fentora sublingual rather than buccal. We now have data indicating that the sublingual route of administration is bioequivalent.

Three medication errors were associated with too frequent use of Fentora. All of these root causes, particularly the dose conversion errors as well as the frequency of use, are specifically addressed in the RiskMAP, which has been significantly enhanced in response to these post-marketing

observations.

The most significant potential consequence of overdose is death. There were a total of six events in patients, five post-marketing fatalities and one life-threatening event. Two of the fatalities were related to progression of cancer and are not listed in this table.

Of the four remaining events, three events occurred in patients where Fentora was prescribed for headache or migraine, a population that is largely considered opioid non-tolerant. Little information is available on the root cause for the last patient in this table. Her death was interpreted as a combination of fentanyl toxicity and atherosclerotic disease upon autopsy. These cases occurred within a relatively narrow time frame during the summer of last year. We were very concerned about these cases and immediately engaged in a dialogue with the FDA and initiated a rapid

response, as well as long-term interventions.

Analyzing these reports of medication errors and deaths for their root causes, we identified prescribing errors, a lack of awareness about the appropriate patient selections, and the lack of awareness about the dosage and administration instructions for the use of Fentora as primary causes for these events. These root causes correspond to the following points of intervention: prescribing, dispensing, and patient use.

The immediate intervention was a Dear Healthcare Professional letter that we sent emphasizing the remedial actions to avoid such events. We made significant changes to the package insert to strengthen the language around appropriate patient selection, dosage and administration, and others, as well as analogous changes to the medication guide. We also made corresponding changes to the medication carton.

We started a pilot program involving NotifyRx, a computer-based messaging system that provides screen pop-up messages to the pharmacists at the time of dispensing. We added the safety activation card to the patient kit. In addition, all promotional and education materials were updated accordingly and the field force and speakers trained.

Let me highlight the specific changes we made to the package insert. Changes to the black box warning included improper patient selection and dosing, substitution of other fentanyl products that may result in fatal overdose. The contraindication was expanded to headache and migraine, and a warning was added not to convert Actiq doses to Fentora on a microgram-per-microgram basis.

Other changes to the label occurred in the sections for indication and usage, contraindications, warnings, precautions, information for patients and

caregivers, and dosage and administration. For example, in the dosage and administration section, we reinforced the critical guidance that patients should not take more than two doses of Fentora per breakthrough pain episode and wait at least four hours before treating the next episode of breakthrough pain.

Overall, the observed post-marketing safety and tolerability is consistent with the safety and tolerability observed in the clinical trial program and with a profile of a fentanyl-containing formulation. As I indicated previously, it is mostly reflective of a non-cancer breakthrough pain population.

The risk of overdose, which includes the concerns arising from medication errors, inappropriate prescribing, and deaths are specifically addressed in the RiskMAP.

We propose to mitigate the risks associated with Fentora with our RiskMAP. The FDA defines risk management as an iterative

process of assessing a products benefit/risk balance, developing and implementing tools to minimize its risk while preserving the benefits, and evaluating tool effectiveness and reassessing the benefit/risk balance. This includes making adjustments, as appropriate, to the risk minimization tools to further improve the benefit risk balance. Particular emphasis is placed on the expectation that a RiskMAP presents an iterative process of implementation, evaluation, reassessment, and adjustment of tools to minimize the risks while preserving the benefits.

The RiskMAP goals should address the risks to be mitigated and reflect an ideal outcome that cannot be achieved but should be aspired to. It is important to recognize that a RiskMAP cannot completely eliminate risks, but it is implemented to minimize risks while preserving the patient benefits.

We confirmed two primary risks

that need to be mitigated: the risk of abuse and diversion and the risk of overdose. To each of the risks, respective goals are associated that reflect the ideal outcome that all RiskMAPs objectives aspire. For the risk of abuse and diversion, the goals are that abuse should not occur and that diversion should not occur. For the risk of overdose, the associated goals are that Fentora should only be used by opioid-tolerant individuals, that unintended or accidental exposure should not occur, and that the dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use Fentora.

To address these risks, we incorporated innovative as well as established tools to create what we believe is a truly robust RiskMAP for an opioid analgesic drug. This slide is just to provide you with a high-level overview of all the tools proposed in the Fentora RiskMAP and to illustrate the

number of tools.

The tools presented on the previous slide were selected to systematically address these points of intervention, as well as the primary audiences for the key risk messages: the prescriber, the pharmacist, and the patient. We will now present the details of our proposed RiskMAP. Dr. Messina will address the strategies and tools to mitigate the risk of abuse and diversion, and then I will be back to present the strategies and tools we designed to mitigate the risk of overdose. Dr. Messina?

DR. MESSINA: Unlike other medications with risk-minimization plans, opioids are unique in that part of the risk that must be mitigated is not in the intended population. Specifically, because of the abuse liability associated with opioids, the risk of diversion and subsequent abuse must be managed. Over the past 15 years, the amount of opioid medications being prescribed in the

U.S. has been rising. The combination opioid analgesics, specifically hydrocodone and oxycodone, represent the majority of the prescriptions over this time period.

Unfortunately, there has also been an increase in the abuse of these medications during that time period. This graph displays the results from the national household survey regarding the non-medical use of pain relievers. The two age categories for which the non-medical use of pain relievers have been increasing are 12 to 17 and 18 to 25 years of age. These data are reflective of the rising concern over prescription opioid abuse.

The most recent publically-available DAWN data shows similar rising rates of abuse over a similar time period with the most commonly prescribed opioids being the most frequently mentioned. These data are reflective of the number of prescriptions written for each of these opioids, suggesting

that availability impacts the level of abuse.

RADARS is a system developed to capture events and calculate rates of misuse, abuse, and diversion of prescription opioids and stimulants, and it provides coverage for approximately 90 percent of the U.S. population with information coming from every state. The information in RADARS originates from four sources: poison centers, law enforcement, key informants which are drug treatment centers, and opioid treatment programs. There are two ways in which RADARS provides rates, and that is one per 100,000 population, as well as using unique recipients of dispensed drug as a denominator.

Surveillance from RADARS for rates of abuse and diversion per 100,000 population has consistently shown that hydrocodone and oxycodone have the highest rates of prescription opioid abuse across time, and this is within all four components of the system. Fentanyl is among the opioids with

the lowest rates, and these data are consistent with DAWN in showing that the two most frequently prescribed opioids also have the highest rates of abuse. When taking into account unique recipients of drug, we see some changes in the relative rates among the different opioids. However, the rates for fentanyl products are consistently low.

Fentora was launched at the end of 2006. 2007 represents the first full year of commercialization for Fentora. And the rates per 100,000 were low for fentanyl and, as depicted by the orange arrow, they were much lower for Fentora across all four components of the system. The reason we only show rates per 100,000 is that there are two few prescriptions of Fentora to allow for a valid calculation using unique recipients of drug, but it's something we will continue to follow.

We've identified a number of key strategies to meet the stated goal that abuse and diversion should not occur with Fentora.

Controlling the availability and growth of Fentora are important components of the strategy, which will be achieved by limiting the physicians visited by Cephalon sales representatives and thereby controlling prescribing.

We will also provide healthcare professionals with information, and we support educational efforts aimed at preventing abuse and diversion. In addition, we will continue to employ a number of surveillance systems which will allow us to closely monitor these risks so we may determine where and when an intervention is needed.

In the FDA briefing document, there's an estimate that approximately 18 million Americans would be candidates for Fentora. Our estimate is approximately 2 million. In order to obtain this estimate, we reviewed published literature, as well as market research information, and we've categorized patients into four main buckets

that represent the overwhelming proportion of chronic painful conditions. Based on this analysis, we estimate that there are approximately 2.7 million adults treated with opioids, and approximately 75 percent of those would have breakthrough pain. This results in an estimated population of approximately 2 million, which is significantly less than 18 million.

In 2007, there were 204 million prescriptions for opioids filled in the United States. All fentanyl products, including Actiq and its generic equivalents of oral transmucosal fentanyl citrate, represented 0.2 percent of those prescriptions, or 332,000. Of these products, Fentora represented 27 percent of the prescriptions, and these Fentora prescriptions were written by approximately 6,000 prescribers. It's clear that Fentora represents only a fraction of the opioids that were prescribed.

We've re-evaluated our launch plan

and our launch strategy, and we'll commit within our RiskMAP to do the following. At launch, face-to-face detailing by sales representatives will be limited to those physicians who have prescribed Fentora, approximately 6,000. After 12 months, we will assess the safety and surveillance information, review that information with FDA and, if the safety data allow, we will propose to expand our face-to-face detailing to an additional 6,000 prescribers. Additional stepwise expansions up to a maximum of 30,000 prescribers will occur, provided safety data permit.

In addition to controlling growth, we've developed a number of tools that are designed to mitigate the risk of abuse and diversion. This illustrates a variety of tools being proposed, and they fall into four main categories: labeling, print communication, in-person communication, as well as computer-based initiatives. And I

will just focus on a few key items.

We will be utilizing radio frequency identification in order to track shipments of medications by tagging cases and pallets of Fentora. This allows us to identify where in the chain of custody Fentora was last received with increased speed and accuracy. Carton-level tagging is scheduled to be implemented next year. Another tool to prevent diversion is tamper-resistant prescription pads, which we provide to physicians to prevent the photocopying and chemical alteration of prescriptions, which are known methods of diversion.

Emerging Solutions in Pain is an independent continuing medical education program specifically developed to address critical issues in pain management. Cephalon provides funding for this program but provides no input into the content. Through scientific data, validated tools, and the expertise of leading pain addiction experts, such as Dr.

Heit who is with us today, this program emphasizes a favorable interaction with regulatory and law enforcement agencies, as well as effective assessment, monitoring, and documentation strategies to optimize the outcome for patients, as well as minimize risks.

The ESP web site is continually updated by experts with new information and guidance for the appropriate management of pain patients requiring opioids. It is projected that over 100,000 user sessions will occur in 2008. Beyond this virtual present, ESP provides education opportunities at national medical meetings by the program experts themselves. ESP also contains a toolkit designed for clinicians to implement within their practice. The tools focus on appropriate patient selection, identification of aberrant or drug-seeking behaviors, screening tests, and techniques to monitor patients once opioids are prescribed.

Speaker programs centered around specific products are not unusual for pharmaceutical companies. What differentiates our approach is that we have collaborated with leading experts in the field of pain and addiction medicine to develop an un-branded educational slide kit that focuses on appropriate patient selection for opioid treatment, treatment plans, and proper documentation, all in an effort to optimize treatment while complying with laws and regulations. Speakers are trained by these experts to present this information at the sponsored speaker programs.

We've partnered with key national organizations that support initiatives to educate the public and healthcare professionals about prescription opioids and the risk of abuse and diversion. These partnerships help us address the risk of abuse outside the intended population through credible organizations that people in the

community trust. For example, the Partnership for a Drug Free America has created a fact sheet about teen abuse for prescription pain medicines. The fact sheet will be featured on the group's web site as resources for parents. And the National Pain Foundation initiated media outreach to encourage the public to safeguard their medications at home in order to minimize abuse.

Our RiskMAP also contains methods for us to monitor and intervene when necessary. We conduct both realtime reviews of DAWN Live! data and quarterly reviews of the RADARS data. We also review prescribing data on a regular basis and evaluate changes in the pattern of rates of prescribing. Additionally, we conduct comprehensive monitoring of media outlets for potential signals of Fentora diversion or abuse. Any findings from our surveillance system undergoes regular internal and external review.

Internally, we have the Fentora Safety Group, which is charged with reviewing the surveillance information on a regular basis and, if needed, will request an independent investigation through an independent third party. The Corporate Safety Board provides an oversight for the Fentora Safety Group.

External review occurs through our RiskMAP Advisory Committee, which is chaired by Dr. Sidney Schnoll who is with us today. This advisory committee meets every six months to review surveillance data but can be convened on an ad hoc basis. In addition, updates are provided to FDA on a quarterly basis.

If any illegal activity is discovered, the appropriate authorities will be informed. In cases of abuse, our first approach will be to provide community-based education or specific education to physicians and pharmacists within the local area.

We recognize the concern that abuse will increase with increased use, given the data surrounding prescription opioid abuse within the United States. We can effectively mitigate these risks through a strategy that includes controlling the growth of Fentora and providing appropriate tools that minimize diversion and educate prescribers on risk containment for opioid misuse, abuse, and addiction.

Dr. Schmider will now discuss our strategies and tools to address the risk of overdose.

DR. SCHMIDER: Thank you, Dr. Messina. You've already seen the slide on increasing non-medical use of opioids. Analogous to this rise in non-medical use, this graph, published by Paulozzi in Pharmacoepidemiology and Drug Safety in 2006, displays a consistent increase in unintentional drug poisoning mortality rates by drug category in the United States. These

data indicate the need to mitigate the risk of overdose particularly with opioids. Accordingly, it is a risk we will mitigate in our proposed RiskMAP.

The goals associated with the risk of overdose are that Fentora should only be used by opioid-tolerant individuals, that unintended or accidental exposure should not occur, and that the dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use Fentora.

Here are the key safety messages and dosing instructions that are all geared towards mitigating the risk of overdose. All of these messages are carried through all of the RiskMAP tools. The major themes are appropriate patient selection and dosing instructions. Our proposed RiskMAP is based on the FDA guidance for RiskMAP development. Accordingly, our RiskMAP includes strategies based upon targeted education and outreach,

reminder systems, and performance-linked access systems.

Here are the tools falling into the category of targeted education and outreach further categorized by the type of communication: print communications, in-person communications, computer-based initiatives, and continuing education and distance learning initiatives. Each of these categories of tools reaches different audiences at different points of intervention by utilizing these different communication techniques.

Some of the tools were specifically developed by Cephalon. The majority of the other tools listed here are standard practice. What all of these tools have in common is that they educate the audience about the key safety messages and dosing instructions.

The next category of risk management tools recommended by FDA is reminder systems. At the point of

prescribing, the pharmacist is offered specific checklists and stamps as additional reminders of the key safety messages. Also, specific safety letters will be sent to prescribers if Cephalon learns of inappropriate patient selection and/or dosing to reinforce the dosing in patient selection instructions. NotifyRx and the safety activation card are pilot programs that I will discuss on the next slides.

NotifyRx is a messaging system that we are currently piloting to more effectively communicate the safety messages. This is being implemented in 40,700 pharmacies across the United States. Through this system, electronic messages can be delivered in context and in time to the right target, specifically to the pharmacists during the prescription-filling process at the pharmacy terminal.

And here is how the process works: when a patient reaches the pharmacy with a

prescription, the pharmacist initiates the reimbursement process with the payer. In this case, however, the transaction is routed through the access verification system of the Relay Health Network. The pharmacist receives the hard stop with the safety messages related to Fentora and a random override code to acknowledge reading of the message. After entering the code, the transaction can be completed normally.

The safety activation card also referenced as the debit card in the briefing document is a pilot program that delivers key safety messages to the patient. We are the first to pilot this tool as a safety intervention. After calling an 800 number, the patient will listen to the safety messages for Fentora and is subsequently registered in the database.

Based on feedback from our external advisors, which appears to be consistent with the FDA's view expressed in

their briefing document, we realized that these interventions alone are not adequate to address the risk of overdose. Therefore, we propose a novel approach that combines the technology of both an electronic access verification system and a registration database to create a performance link access system that will address the risk of overdose and, at the same time, enable appropriate patient access to Fentora. We call this novel approach COVERS, a controlled voice enrollment registration system. This registration system provides the access control of a traditional registry, but it eliminates much of the cumbersome processes that typically reduce patient access.

COVERS leverages the latest technologies to reduce the burden on registry participants, thereby assuring ready access to patients in need. It combines a similar technology as utilized with NotifyRx with an access verification system providing a hard

stop and the patient and physician registration database similar to that provided through the safety activation card.

The key innovation is linking the business rules utilized by the access verification system with a registration database. The patient goes to the pharmacy to get a prescription filled but only when the access verification system confirms that both patient and prescriber have registered can the transaction be completed. If the access verification system does not confirm registration, there is a hard stop.

We are currently exploring multiple options with a goal to cover as many pharmacies as possible. Distribution will be limited to those pharmacies participating. We are also exploring solutions to cover cash transactions.

Now let me show you how COVERS works in principle while we are currently still working on the details. I have here two

primary scenarios that will demonstrate the functionality of COVERS. This is how a normal transaction works. Prescribers call a 1-800 number, listen, and attest to their understanding of the safety messages and register using a unique registration number. The prescriber issues a prescription to the patient together with the safety activation card. The patients call that 1-800 number, listen, and attest to their understanding of the safety messages and enter the unique number of their safety activation card. The patient can now visit the pharmacist to have the prescription filled.

The pharmacist initiates the reimbursement through the computer terminal. The access verification system checks in the registration database to confirm that both the patient and the prescriber have registered. And if both have, the pharmacist receives a pop-up message prompting for confirmation that the patient is opioid-tolerant. After

entering a random override code, the transaction can be completed.

COVERS not only controls access, it also acts as a surveillance tool by tracking the amount of Fentora distributed to a pharmacy; and knowing how many prescriptions were approved we will know if any pharmacies fill prescriptions without confirming that the physician and patient are registered. By tracking approved and denied prescriptions, we can identify pharmacies that are filling prescriptions inappropriately. We will have the ability to take corrective action ranging from further education to the specific pharmacy from eliminating a pharmacy from our distribution network.

Now here is what happens if either the patient or prescriber had failed to register. When the pharmacist attempts to dispense the prescription, the prescription is denied and the pharmacist is instructed to encourage the patient or prescriber to

register.

Moving onto the evaluation of the effectiveness of the overdose mitigation tools. We have our own pharmacovigilance system, survey data obtained with our target audiences, patients, prescribers, and pharmacists, and review of prescription data such as IMS prescription data to monitor opioid non-tolerant prescribing, among other things.

A number of interventions are available to address signals of overdose or inappropriate prescribing ranging from Dear Healthcare Professional letters to removing a physician from our registry. For example, if we receive through our pharmacovigilance system reports of overdose as a result of inappropriate prescribing, we can specifically address the physician through the Cephalon field force and letters. Should these interventions not show improvement in the respective physician's prescribing patterns,

we will remove the physician from our registry.

Our proposed RiskMAP is innovative and, to our knowledge, the strongest for any opioid analgesic. It includes comprehensive tools to prevent abuse and diversion, as well as to monitor and intervene for emerging signals, as presented by Dr. Messina. A physician and patient registration system, COVERS, that will provide the advantages of a registry while maintaining appropriate access to patients. With our proposed RiskMAP, the main risks associated with Fentora can be kept at a minimum.

I thank you for your attention, and Dr. Russell will now conclude our presentation.

DR. RUSSELL: Thank you, Dr. Schmider. My name is Lesley Russell, and I'm the Chief Medical Officer at Cephalon. I would like to take a few minutes to summarize the large amount of information you have read

and heard today and to emphasize our commitment to ensure that making Fentora available to patients who need it can be balanced by protecting patients and non-patients from its risks.

First, let me address an underlying concern regarding the current extent of off-label use of Fentora and the potential risk this poses. Fentora is not a highly-prescribed drug. To date, only 5,900 physicians have prescribed Fentora, and only 20,000 patients have received a prescription for the drug. We acknowledge that the majority of these 20,000 patients do not appear to have a diagnosis of cancer.

What does this tell us? It is clear that despite a restricted indication to breakthrough pain in cancer, the risk management plans for both Actiq and Fentora have not been successful in limiting the use of either of these drugs to cancer patients. Why is this? You have heard from Dr. Fine

that breakthrough pain, which can be debilitating, occurs in non-cancer patients treated with around-the-clock opioids just like it does in cancer patients. And like many pain care specialists, he treats the patients' pain and appropriately prescribes Fentora to patients who he believes will benefit from the drug. He does not discriminate whether the patient is a cancer patient or not.

The presentation by Dr. Fine illustrates the fact that there is a need for an effective treatment for breakthrough pain and that it does not make medical sense to restrict the indication to only those patients who have cancer. Dr. Messina presented data from the clinical program which demonstrates in adequate and well-controlled designs which were designed in collaboration with FDA that Fentora is an effective treatment for non-cancer breakthrough pain. Based on our analyses, there was little difference in the

safety profile between the cancer and non-cancer patient and that the side effects were largely those associated with many opioids.

So it is fair to say that Fentora is an effective drug for the treatment of breakthrough pain and that non-cancer patients will benefit from the product. Now let us address the risks.

The risk is not whether a patient on around-the-clock opioids with breakthrough pain has cancer or not. The risk for patients with Fentora is overdose, which may be fatal, and the use in opioid naive patients where this risk is exacerbated. You heard from Dr. Schmider that there have been fatalities and life-threatening events associated with Fentora. Three of these occurred in patients who are not opioid-tolerant and had been prescribed Fentora for the treatment of migraine headaches. This is clearly not an appropriate use of Fentora, and we are committed to preventing our drug being used in

opioid non-tolerant patients.

We are currently piloting interventions to address this risk, namely NotifyRx and the patient safety activation card. However, these interventions alone may not be adequate to address this risk. Therefore, as you heard from Dr. Schmider, we are proposing a novel approach to combine these two tools to create what is effectively a patient, physician, and pharmacy registration system with hard stops in place at the pharmacy level to prevent dispensing of Fentora if either the patient or the physician has not registered indicating that important messages have been listened to and attested to be followed. Ensuring the patient is opioid-tolerant before being dispensed Fentora is the key goal of this system.

Now let's turn to the public health risk of abuse and diversion. We clearly recognize the risk of abuse and diversion with Fentora. In view of this, the

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second goal of the RiskMAP is to mitigate the risk of abuse and diversion, and you have heard from Dr. Messina about how we intend to minimize this risk.

First and foremost, we commit to a controlled launch of Fentora with its expanded indication. Specifically, we commit to only detail Fentora to 6,000 physicians who have prescribed it to date whilst continuing to monitor the risk of abuse and diversion and safety for a period of 12 months. If at that time, no issues are identified, we will, in consultation with FDA, expand the detailing to an additional 6,000 patients and repeat the exercise.

We will not expand the detailing of Fentora to beyond a maximum of 30,000 physicians. The vast majority of the patients who are appropriate candidates for Fentora are seen by these 30,000 physicians, and there is simply no reason to expand the promotion of Fentora beyond this core group of treating

physicians.

In addition, as described by Dr. Messina, we will continue to partner with the FDA, the medical community, patient groups, nursing organizations, and the public to provide information regarding appropriate patient selection and safe use of Fentora.

Lastly, as an executive officer of the company, I want to state that it makes no business sense to immediately begin to broadly distribute Fentora only to see an increase in fatalities due to inappropriate prescribing and an increase in abuse and diversion. But there are patients who need this drug. Our data provide for the first time randomized clinical evidence to support the use of Fentora in this difficult clinical scenario. We want to partner with you to create an environment where the risks can be minimized whilst allowing appropriate patients legitimate access to Fentora. Thank you for your attention.

ACTING CHAIR SORIANO: Thank you, Dr. Russell and Floyd and members of your team for your presentation. Now we will hear a presentation from the FDA team. I'd like to introduce Dr. Fields from the FDA.

DR. FIELDS: Good morning. My name is Ellen Fields, and I am an Acting Clinical Team Leader in the Division of Anesthesia, Analgesia, and Rheumatology Products. Today I am going to present the regulatory history of the oral transmucosal fentanyl products, including important labeling changes that have occurred. I will also present a comparison of the pharmacokinetic characteristics of Actiq and Fentora that are relevant to the safe conversion of one product to the other.

There have been three approved oral transmucosal fentanyl products: Oralet, Actiq, and Fentora, only two of which remain on the market. Oralet was approved in 1993 for the pre-operative sedation in children.

It was intended for use only in a hospital setting. The formulation consisted of a raspberry-flavored lozenge on a stick, a lollipop, that was intended to be acceptable to children. It was available as 100, 200, and 400 microgram dosage units. Oralet was withdrawn from the market in 2001 because pediatric patients could not tolerate the adverse events of nausea and vomiting that resulted from its use.

Actiq was approved in 1998 for a narrow indication: the treatment of breakthrough pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer pain. The formulation was the same as Oralet but included higher dosage strengths up to 1600 microgram. Actiq was intended for use in both inpatient and outpatient settings.

There were a number of important safety issues that came to light during the

approval process for Actiq. Actiq's approval represented a unique circumstance where the population at greatest risk for adverse events, opioid-naive patients and children, was not the population that would benefit from the drug's approval. Along with the risks common to all high-potency opioids, including misuse, abuse, and diversion, an important risk stood out: the accidental or intentional ingestion of the product by children who have mistaken the lollipop formulation for candy. A single 200 microgram dosage unit contains fentanyl in an amount that can be fatal to a child. These issues were the subject of an advisory committee meeting in September of 1997. The committee voted that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health.

Actiq was approved in 1998 under Subpart H, approval with restriction to assure

safe use. The NDA was approved with restriction for use to the treatment of breakthrough pain associated with malignancy in opioid-tolerant cancer patients, also limiting pharmaceutical marketing detailing to oncology and pain medicine specialists and with the final printed labeling and risk management program as a condition of approval.

The regulations under which this product was approved also provide for accelerated withdrawal of the product if the sponsor does not adhere to the agreed-upon marketing restrictions. A risk management program was created to mitigate misuse, abuse, and diversion, and accidental exposure by children.

The original Actiq label had a box warning that contained the following information: the indication that the product must not be used in opioid non-tolerant patients; that it should be prescribed only by oncologists and pain specialists; that it must

be kept out of the reach of children; and that it must be disposed of properly. Additional information included contraindications for the management of acute or postoperative pain and use in opioid non-tolerant persons.

There have been several labeling changes for Actiq since the time of approval. Those with significance include the addition of a statement advising diabetic patients that Actiq contains two grams of sugar per unit. Statements added to the label based on post-marketing experience regarding the association of Actiq with dental caries, tooth loss, and gum line erosion; a formulation change to sugar-free, which was never marketed; conversion of the patient leaflet to a MedGuide; and the addition of pharmacokinetic data for patients 5 to 15 years of age based on a study carried out in the pediatric population.

Fentora was approved in September of 2006 for the same indication as Actiq. The

formulation is an effervescent buccal tablet with dosage units ranging from 100 to 800 micrograms. It was intended for use in both inpatient and outpatient settings, and the risk management plan and MedGuide were part of the approval. The risk management experience will be presented in detail later this morning.

The originally-approved label had a box warning that was similar to that of Actiq with the addition of the statement that, due to the higher bioavailability of fentanyl in Fentora, conversion from other fentanyl products should not be done on a microgram-per-microgram basis.

At this point, I'm going to compare the pharmacokinetic attributes of Fentora and Actiq. Both Fentora and Actiq deliver fentanyl through the oral mucosa, which prevents considerable first pass metabolism by the intestinal mucosa and the liver via the CYP-450 3A4 route. The results

from a comparative study show that the rate, Cmax, and extent, AUC, of fentanyl absorption from Fentora were considerably different from Actiq. The absolute bioavailability of fentanyl from Actiq in this study was 47 percent with 31 percent of the dose being absorbed via the oral mucosa and 16 percent via the GI tract. The absolute bioavailability of Fentora was approximately 65 percent with 50 percent of the dose being absorbed via the oral mucosa and the remaining 15 percent via the GI tract. Comparing Fentora and Actiq, Fentora delivered approximately 18 percent more fentanyl via the oral mucosa than Actiq.

The initial dosing recommendations for patients on Actiq converting to Fentora are included in the Fentora label. Because of the differences in bioavailability and intersubject variability, you will note that the conversation is very conservative.

Despite extensive labeling, within

the first year of Fentora's approval, there were prescribing errors associated with adverse events, including death. Errors included off-label prescribing to non-opioid-tolerant patients, patients being prescribed the wrong dose of Fentora, patients took too many Fentora doses, and healthcare professionals substituted Fentora for another fentanyl-containing product that is not equivalent to Fentora. These medical errors will be presented in detail in a presentation later this morning.

In September of 2007, a public health advisory was issued for Fentora. The issues addressed in the advisory included off-label prescribing to non-opioid-tolerant patients, misunderstanding of dosing instructions by both prescribers and patients, and inappropriate substitution of Fentora for Actiq by pharmacists and prescribers.

The Fentora label and MedGuide were revised on February 7th, 2008 in order to