reinforce the following safety information: contraindication of the use of Fentora in non-opioid-tolerant patients, including patients with migraines; when prescribing, do not convert patients on a microgram-per-microgram basis from Actiq to Fentora; when dispensing, do not substitute Fentora for other fentanyl products; and proper dosing was outlined.

In summary, there are presently two oral transmucosal fentanyl products marketed for the indication of the management of breakthrough pain cancer pain in opioid-tolerant patients. Due to the higher bioavailability of Fentora, Actiq and Fentora are not interchangeable on a microgram-per-microgram basis. And despite strong labeling language, a MedGuide, and a risk management program, there have been medication errors reported to the Agency that have resulted in adverse events, including death. This concludes my presentation.

ACTING CHAIR SORIANO: Thank you,

Dr. Fields. The panel now recognizes Lieutenant Commander Kendra Worthy.

DR. WORTHY: Good morning. My name is Kendra Worthy. I'm a Drug Utilization Specialist in the Division of Epidemiology in the Office of Surveillance and Epidemiology. This morning, I will be discussing outpatient drug utilization trends for Fentora and Actiq.

Outlining my talk this morning, I will be discussing sales distribution data that was provided by IMS Health, IMS National Sales Perspectives, retail and non-retail. We will be looking at retail prescription data, specifically trends within the opioid market; prescriber specialty data from various Verispan's Vector One National, otherwise known as VONA. Please note that VONA does not include data from mail-order pharmacies, outpatient clinics, long-term care facilities, or same-day surgery centers.

An age distribution of patient-level data from Verispan's total patient

tracker, as well as the concurrency analysis from Verispan's Vector One Concurrency, are also included. Physician survey data from Verispan's Physician Drug and Diagnosis Audit will also be discussed. Lastly, I will summarize with conclusions.

We will now take a look at sales distribution data from the year 2007 with a brief description of the database. The IMS Health Retail and Non-Retail Perspectives database measures the sale of a given product from the manufacturer to various settings. These databases measure sales volume information and unit sales from the manufacturer to various channels of distribution. The units measured in these databases are extended units, which are individual tablets, capsules, etcetera.

Retail Perspective measures chain independent, mass merchandisers, food stores with pharmacies, and mail-order pharmacies. The Non-Retail Perspective measures federal

facilities, non-federal hospitals, clinics, long-term care facilities, home healthcare, HMOs, miscellaneous channels such as prisons and universities.

The pie chart shows the number of Fentora tablets sold from the manufacturer to retail to non-retail pharmacies in the year 2007. Approximately 92 percent of sales were to retail channels of distribution. Therefore, this presentation will focus on retail data.

Moving on to prescription and patient-level data with a brief description of the databases. Verispan's Vector One National, otherwise known as VONA, is a national-level projected prescription and patient centric tracking service. They receive over 2 billion prescription claims per year, representing over 160 million unique patients. The number of dispensed prescriptions is obtained from a sample of approximately 59,000 pharmacies throughout the

United States, accounting for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide.

Retail pharmacies include national retail chains, mass merchandisers, pharmacy benefit managers, and their data systems and provider groups. Data on prescribing specialty and patient age and gender are available, as well as state-level data.

This graph shows a utilization trend of frequently-dispensed opioids for the past ten years. The hydrocodone products have dominated the opioid market. For the past ten years, hydrocodone, which is shown here in red, has been the number-one dispensed prescription product out of all prescription drug products. Among the opioids listed, oxycodone products, which are shown in bold, come in at a distant second to hydrocodone with approximately 42 million prescriptions dispensed in 2007.

This graph removes hydrocodone

from the previous slide and takes a closer look at the dispensing trends of the other opioid products since 1997. Fentanyl, which is represented by the gold line, and morphine, which is in green, have tied for third among opioid prescriptions dispensed in 2007 with approximately 5.5 million retail prescriptions. Approximately 4 million methadone prescriptions, which is represented in the light blue, and 1.6 million hydromorphone prescriptions in the dark blue were dispensed in the year 2007.

Fentanyl transdermal has replaced Duragesic as the leading fentanyl product dispensed from retail pharmacies. In 2007, approximately 4.5 million fentanyl transdermal prescriptions, which are shown in yellow, and 671,000 Duragesic prescriptions, which is shown in red, were dispensed. Removing these lines representing Duragesic and its generic and taking a closer look at the remaining fentanyl products, approximately 91,000

Fentora prescriptions were dispensed in the year 2007, and this is represented by these blue bars here.

Retail prescriptions for Actiq shown here as the pink bars peaked in 2005 with 357,000 prescriptions but has decreased approximately 77 percent since then to 66,000 prescriptions. There has been an approximate 500-percent increase in both Fentora and the oral transmucosal fentanyl between years 2006 and 2007. The generic Actiq oral transmucosal fentanyl, which is abbreviated OTFC, is represented by the green bar. Prescription totals, which is represented by this blue line here, have not increased with the addition of the generic oral transmucosal product or Fentora.

This graph shows the average retail cost per unit for Fentora, Actiq, and oral transmucosal fentanyl. In 2007, Actiq, which is again represented by the pink bar, had the highest cost per unit at approximately

$42, followed by the oral transmucosal fentanyl here in green at $26, and Fentora at $23. Actiq and oral transmucosal fentanyl are sold in packages of 30, and Fentora is sold in a package of 28. This cost data is relevant as there is a documented medication error that took place at the pharmacy level involving an insurance adjudication that will be discussed in an upcoming presentation by Dr. Arnwine.

This is a pie graph of dispensed retail prescriptions for Fentora stratified by prescribing physician specialty in 2007. The anesthesiology specialty prescribed the most prescriptions for Fentora with 31,000 prescriptions dispensed, representing 35 percent of Fentora prescriptions that were dispensed. This is followed by the physical medicine and rehabilitation specialty in 19,000 prescriptions at 21 percent. General practitioners, which include general practice, family medicine, and osteopathic physicians accounted for 8,000 prescriptions or nine

percent. The data is not shown but the oncology specialty ranked 14th in 2007, accounting for approximately one percent of Fentora retail prescriptions dispensed in 2007.

This graph is a breakdown of unique patients that fill the prescription for Actiq, Fentora, or oral transmucosal fentanyl stratified by age in year 2007. Approximately 15,900 patients filled a retail prescription for Actiq; 23,000 for Fentora; and 32,000 patients for oral transmucosal fentanyl citrate. Approximately 60 to 69 percent of patients that filled retail prescriptions for each of these three products were for patients aged 41 to 65 years old, which is represented in blue. Less than one percent of patients that filled retail prescriptions for each of the three products were for pediatric patients aged zero to 16 years.

This graph shows a percentage of Actiq prescriptions that were switched in the

next opioid prescription dispensed. I will focus on the two lines that are bolded here in the red and pink, which represent the oral transmucosal fentanyl and Fentora respectively.

During the fourth quarter of 2006, Actiq prescriptions that were switched were changed to the generic oral transmucosal fentanyl and 13 percent were switched to Fentora. By the fourth quarter of 2007, this number decreased to 14 percent for Actiq and 3 percent for Fentora.

We will now take a look at indications associated with drug use from year 2007 with a brief description of the database. Verispan's Physician Drug and Diagnosis Audit, which is also known as PDDA, is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the United States. The survey consists of data collected from approximately

3100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit, and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses a term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescriptions being generated. Rather, the term indicates that a given drug was mentioned during an office visit. Also, sample sizes can be small when general use for a product is low, which can produce unreliable estimates.

These graphs show the top diagnoses in 2007 associated with Actiq and Fentora during visits to office-based physicians, as previously described. The percentage of cancer-related indications is shown as the solid purple on both graphs. Nine cancer-related indications are shown in stripes. For both products, the majority of diagnoses are non-cancer related.

I will now discuss a concurrency analysis conducted using Verispan's Vector One Concurrency, otherwise known as VOCON. Data used in VOCON is derived from Verispan's Vector One database that was described earlier. VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using one of four scenarios. The VOCON module provides unprojected patient counts, and nationwide projections are not available.

An episode of concurrency is defined as a prescription in a base group,

which in this example would be Actiq or Fentora, that overlaps with a day's supply for a dispensed prescription in a concurrent group, which in this example is the entire pain market or product within the pain market. A day's supply is calculated by adding the number of therapy days to the time of prescription dispensing. For this analysis, a 30-day supply with a ten-percent grace period gave us a period of 36 days to examine if a retail prescription for a product within the pain market was filled concurrently with Actiq or Fentora. We also set the fill sequence report when a product from the pain market is filled before Actiq or Fentora.

The results of the concurrency analysis were as follows. In 2005, approximately 40 percent of Actiq patients were on concurrent therapy with a product from the pain market. In 2007, this percentage decreased to 26 percent. In 2007, approximately 59 percent of Fentora patients

were on concurrent therapy with a product from the pain market. In 2007, there was a higher prevalence of concurrent therapy with products from the pain market with Fentora than with Actiq. Fentanyl transdermal, hydrocodone with acetaminophen, and oxycodone immediate-release products were the most common concurrent products within the pain market.

Some limitations to the VOCON database are that VOCON does not capture data from inpatient hospitals, oncology clinics, same-day surgery centers, or mail-order pharmacies. Also, true opioid tolerance and non-tolerance cannot be determined within the confines of this analysis as a patient could begin opioid treatment as an inpatient or in a clinic and continue therapy as an outpatient.

In conclusion, approximately 92 percent of Fentora sales go to retail channels of distribution. There was approximately 500-percent increase in Fentora prescriptions from

14,620 prescriptions dispensed in 2006 to 90,751 dispensed in 2007. Total number of patients that filled a prescription for Actiq in year 2007 were close to 16,000, for Fentora 23,000, and the generic oral transmucosal fentanyl 32,000.

Approximately three percent of Actiq prescriptions were switched to Fentora during the last quarter of 2007. The sum of total prescriptions dispensed for Actiq, Fentora, and the oral transmucosal fentanyl citrate have not caused an increase in the trend of these products.

In the year 2007, Actiq had the highest cost per unit out of the three products. The anesthesiology specialty accounted for approximately 35 percent of Fentora prescriptions in 2007, followed by physical medicine and rehabilitation specialty with 21 percent. The oncology specialty ranked 14th in year 2007 with approximately one percent of prescriptions. The majority of

Fentora uses are associated with non-cancer indications and office-based practices. There is a higher prevalence of concurrent therapy with products in the pain market with Fentora than with Actiq.

This concludes my presentation. Thank you.

ACTING CHAIR SORIANO: Thank you, Lieutenant Commander Worthy. We will now take a short ten-minute break. I'd like to remind the panel members there should be no discussion of the topic during the breaks amongst yourselves or with any members of the audience. By my clock, it's ten minutes to ten, so we'll reconvene at 10:00. Thank you.

(Whereupon, the foregoing matter went off the record at 9:53 a.m. and went back on the record at 10:02 a.m.)

ACTING CHAIR SORIANO: The Chair now recognizes Dr. Chang for her presentation with the team of FDA.

DR. CHANG: Good morning. My name

is Joo Yung Chang. I'm a Safety Evaluator in the Division of Adverse Event Analysis II in the Office of Surveillance and Epidemiology, and I'll present post-marketing safety data for Fentora and Actiq.

I'll begin with the objectives of the presentation followed by an overview of the adverse event reporting system referred to as AERS. I'll review all adverse event reports with Fentora since drug approval, then serious adverse events with Actiq that were received by the Agency in 2007. These reports were reviewed to identify trends between Fentora and Actiq because it may provide insight into Fentora's potential for drug diversion, misuse, and overdose. Finally, a summary of the findings will be presented. The objectives are to identify unlabeled adverse events or other safety concerns, particularly with issues of drug diversion, misuse, and overdose, and to identify trends between Fentora and Actiq adverse events.

Before going into the AERS reviews, I'd like to provide a brief background to the spontaneous adverse event reporting. It's a voluntary system for consumers and healthcare professionals to report adverse events. Under the code of federal regulations, sponsors of an approved NDA product are required to report adverse events. These reports are sent to the Agency through the FDA MedWatch program and stored in the AERS database.

Spontaneous adverse event reporting is useful since it includes all U.S. marketed products. It's best to detect events not seen in clinical trials and is a good tool for events with a rare background rate and short latency.

There are some limitations, such as extensive under-reporting, the quality of the reports may be variable, there may be reporting biases based on notoriety, media attention a particular product is receiving,

or if it's a new drug. The actual numerator and denominator are not known, and so the quantification of risk assessment is subject to limitations and the causality of a drug event association is often in question.

The first review is on all adverse events associated with the use of Fentora. The AERS database was searched for all reports up to February 25th of 2008. Since fentanyl has multiple formulations, we used a brand name search to capture only Fentora cases. The search included all adverse events from both foreign and domestic sources with no other restrictions.

Forty-two cases were retrieved from the database, of which 23 were excluded from the case series, as shown on the slide. Cases involving a medication error but no adverse event were excluded. However, a more comprehensive and detailed review of medication errors will be discussed in the next presentation. Other reasons for

exclusion included the lack of patient information or if the events were not related to the drug. The remaining 19 cases were included in the case series.

This table shows the demographics and indications of the Fentora cases. Males and females were fairly evenly represented, and the median age was 43 years with a range of 16 to 73 years. It's notable that only one case reported an FDA-approved indication for Fentora use. Eleven cases reported the use of Fentora for management of non-cancer pain, and six cases were categorized as miscellaneous and included reports of suicidal attempt, abuse, intentional overdose, and accidental exposure, which are obviously not medical uses.

This table shows the median daily dose of 2,000 micrograms and a median time to onset of eight days. Each case was assessed for opioid tolerance, and it was determined that six cases were opioid tolerant based on

the criteria listed in the Fentora label. One case reported being non-tolerant, and in the remaining 12 cases there was insufficient information to determine the tolerance. However, in at least 11 of 19 cases, concomitant use of other opioids were mentioned in the reports.

This table shows the outcomes of the cases. There were five reports of death, one life-threatening event, one hospitalization. Three were considered medically significant, and nine did not specify an outcome. The year in which the report was received by the Agency is as expected since the data was collected only up to February of 2008. Thus, the number of reports for 2008 appear low. All were domestic cases despite the search criteria for U.S. and foreign reports.

There were five reports of death, three of which were due to Fentora. These cases involved the two cases of accidental

overdose and one case of suicide. The cause of death in the fourth case was due to the underlying cancer. In the fifth case, although the cause of death was unknown, it is interesting that the patient stole Fentora from a spouse and overdosed. He was taken to the emergency department where he was diagnosed with an acute MI but left against medical advice and returned home, where he later died. Overall, four out of five deaths involved an overdose of Fentora.

The adverse events were categorized according to specific organ classes. The unlabeled adverse events are underlined. In parentheses is the number of reported events and not necessarily the number of cases since cases may have reported more than one event. As you can see, most events are labeled. The only unlabeled event shown here is the acute MI which was described in the previous slide.

This is a continuation of the

adverse events by specific organ class. Again, the unlabeled adverse events are underlined, and you can see that most events are labeled. The unlabeled events shown here includes CVA, which there was not enough information to determine a relationship with Fentora. Dysarthria and dysuria, which were possibly related to the patient's underlying medical condition and other concomitant drug use. These cases are described in more detail in the background package.

Besides a heavy off-label use, there were reports of overdose, misuse, and suicide. The intentional overdose and misuse cases show that drug diversion is occurring despite a RiskMAP for Fentora to minimize these events.

In summary, there were 19 adverse event cases for Fentora in AERS. There was extensive off-label use for only about five-percent of the cases reported in FDA-approved indication. Thirty-two percent of the cases

were determined to be opioid tolerant, and over half of the adverse events reported involved medication errors. Medication errors will be covered in more detail in a later presentation.

Approximately one-third of the cases involved overdoses, 11-percent involved intentional misuse, and another 11-percent involved suicide attempts. There were five deaths, for of which involved overdoses. The unlabeled adverse events in this case series do not appear to be directly related to Fentora.

Next, I'll present a review of serious adverse events associated with the use of Actiq from cases that were reported in 2007. Serious, per regulatory definition, includes death, hospitalization, or prolongation of hospitalization, life-threatening, disability, congenital anomaly, and other medically-important events based upon appropriate medical judgment.

The purpose of reviewing Actiq is not to provide a direct comparison to Fentora but to identify possible trends. Actiq is the only other FDA-approved oral transmucosal fentanyl product on the market and has a narrow indication similar to Fentora, and they have similar safety concerns. By reviewing Actiq's adverse event profile, it may provide insight into Fentora's potential for drug diversion, misuse, and overdose, which are typical problems with opioids.

The AERS database was searched for cases that were received by the Agency from January 1st to December 31st of 2007. Since fentanyl has multiple formulations, we used a brand name search to capture only Actiq cases. Only cases coded as serious and U.S. reports were included. The year 2007 was selected for several reasons.

First, the burden of cases from approval to present was too large to complete an individual review given the limited time

and resources. Second, the year 2007 had the greatest number of reports. And, third, to select the most relevant and recent cases since the issue surrounding opioid overdose and misuse and the management of those issues with risk minimization plans have changed over the years.

This table shows the indication and opioid tolerance of the cases. Three cases reported an FDA-approved indication of cancer pain. This accounted for only approximately five percent of all cases. Thirty-one cases reported the use of Actiq for the management of non-cancer pain. Twenty-three cases were categorized as miscellaneous and included reports of suicide, suicidal attempt, intentional misuse, and accidental exposure, which are not medical uses.

Each case was also assessed for opioid tolerance. Sixteen cases were determined to be opioid tolerant based on the criteria that's listed in the Actiq label, and

four were non-tolerant. The tolerance could not be determined in the remaining cases due to insufficient information. However, in 28 of 61 cases, concomitant use of other opioids were mentioned in the reports.

This table shows the outcomes of the cases. Cases may have reported more than one outcome. Nine reported a death, six involved a life-threatening event, twenty-eight were hospitalized, two reported a disability, and twenty-five reported a medically-significant outcome.

There were nine reports of death. The cause of the deaths per the reports are as shown. Seven of nine reports involved an overdose of Actiq.

Of the remaining two reports, the first case reported a fetal death in a woman pregnant with twins. This case was confounded by the concomitant use of other medications, one of which was labeled as Pregnancy Category D. The surviving twin was born healthy with

the exception of requiring narcotic withdrawal treatment.

The second case involved the death of an opioid non-tolerant patient who had taken Actiq in the past but had been weaned off of opioids. He had restarted Actiq and possibly other opioids on his own and not under the direction of a physician.

Notable adverse events were categorized according to specific organ classes. Not all adverse events are listed here because of space limitations. The majority of adverse events are labeled. Among the unlabeled events, most occurred in the context of a drug overdose, and the remaining cases were not directly related to the use of Actiq. These cases are described in more detail in the background package.

Thirty-two cases involved a drug overdose or misuse. This accounts for 52-percent of all cases. They were further grouped by the manner of overdose.

Intentional misuse, which includes suicide, suicide attempt, and abuse accounted for half of the overdose cases. Accidental exposures in children accounted for a quarter of the overdose cases. Accidental overdose was reported in six cases, of which only one reported inadequate analgesia as a potential cause of accidental overdose. The manner of overdose could not be determined in two of the cases.

In summary, there were 61 serious adverse event reports of Actiq and errors reported in 2007. There was extensive off-label use for only five-percent of the cases reported in FDA-approved indication. Twenty-six percent of the cases were determined to be opioid tolerant. Over half of the cases involved overdose and misuse. Thirty percent of the cases involved a medication error. There were nine deaths, seven of which involved an overdose. The unlabeled adverse events in this case series occurred mostly in

the context of drug overdoses, and the remaining cases were not directly related to the use of Actiq.

In conclusion, it was difficult to make any direct comparisons of Fentora and Actiq because of the different search criteria and type of cases. However, there were some trends. There was extensive off-label use for both drugs. Twenty-six to thirty-two percent of the cases were determined to be opioid tolerant. Overdose and misuse represented 32 to 52 percent of all cases. Medication errors were reported in 53 percent of Fentora cases versus 30 percent for Actiq. There were reports of unlabeled adverse events for both drugs. However, they occurred mostly in the context of overdoses for Actiq, and no positive drug event associations were noted for Fentora.

This concludes my presentation. Thank you.

ACTING CHAIR SORIANO: Thank you,

Dr. Chang. The panel now recognizes Lieutenant Commander Arnwine.

DR. ARNWINE: Good morning. My name is Lieutenant Commander Kristina Arnwine, and I'm a Team Leader in the Division of Medication Error Prevention in the Office of Surveillance and Epidemiology.

Today I'm going to provide you an overview of medication errors associated with the use of Fentora. I will first review how we identify cases in the AERS database. Then I will discuss the results of this search, followed by a discussion of the specific types of errors identified. And, finally, I will summarize our findings.

Before we discuss the results of the error search, it is important to note that our search was conducted approximately one month following our colleagues in the Division of Adverse Event Analysis. Therefore, you may note some disparity in the number of cases retrieved from the errors database when

compared to those presented earlier.

The FDA Adverse Event Reporting System database was searched to identify any post-marketing reports of medication errors associated with Fentora. Errors were searched without using reference to any measure terms in order to retrieve all Fentora cases. Our search retrieved a total of 63 cases.

Of the 63 cases retrieved, 20 were excluded from further analysis because they did not involve a medication error. These cases involved intentional overdoses, adverse events that were not the result of a medication error, or did not contain enough information to determine if a medication error occurred. The remaining 43 cases were medication errors and were further analyzed for type and causality. The medication error cases that resulted in adverse events presented earlier by Dr. Chang are included in this analysis.

Thirty-five of the forty-three

reported medication errors occurred in patients being treated for an off-label use. The most common categories of off-label use included chronic and/or non-cancer pain, migraines, and back pain. Other reported off-label uses are presented on the slide.

Four medication error cases occurred in patients being treated for the approved indication of use, breakthrough cancer pain, and, in four cases, the indication was unspecified.

The 43 medication error cases were divided into the following nine types of error: wrong route of administration, improper patient selection, improper frequency of administration, microgram-per-microgram conversion between Actiq and Fentora, improper dose prescribed when converting from Actiq to Fentora, improper substitution, improper technique, accidental exposure, and accidental overdose. The three types of errors highlighted here in yellow represent confusion

between Actiq and Fentora, and, when grouped together, they represent the most numerous type of errors reported.

The first type of error identified was wrong route of administration. The majority of these cases involved patients using Fentora sublingually instead of buccally. We note that some of these patients used Fentora sublingually to avoid the ulceration they previously experienced when taking Fentora by the buccal route. One case resulted in lack of effect, one case resulted in tongue ulceration, and the remaining eight cases did not report any adverse events or no outcome was reported.

The second type of error reported was improper frequency of administration. Fentora should be taken with at least four hours in between doses, and it is not to be taken more than four times daily. Additionally, when treating a single breakthrough pain episode, patients are

supposed to wait at least 30 minutes before re-dosing. However, the majority of the improper frequency cases described Fentora being administered with less than four hours between doses or more than four times daily. One of these cases resulted in death of a patient because she took Fentora every 30 minutes for treatment of migraines. Other cases of improper frequency describe Fentora being prescribed on a regularly-scheduled interval, for example twice daily, rather than as needed. Overall, most cases resulted in non-serious adverse events.

The next type of error was improper patient selection. In seven of these cases, no other medication error was described other than off-label use. We note that off-label use, per se, is not considered a medication error. However, these cases were included in our analysis since one of the goals of the current Fentora risk minimization action plan is that Fentora should only be

used by opioid tolerant patients with cancer. These cases resulted in withdrawal, lack of affect, or no adverse event was reported. In the two remaining cases of improper patient selection, the patients were reported to not be on concomitant around-the-clock opioid therapy while taking Fentora. Fentora is only intended to be used in patients that are already taking opioids around the clock. One of these cases resulted in respiratory depression and hospitalization, and the other case did not report an adverse event.

A total of 12 cases involved confusion between Actiq and Fentora. However, these errors were broken down further into the following types: microgram-per-microgram conversion between Actiq and Fentora, improper dose prescribed when converting from Actiq to Fentora, and improper substitution. We remind you that Fentora and Actiq are not bioequivalent and, thus, are not interchangeable on a microgram-per-microgram

basis. Additionally, the Fentora professional insert contains specific instructions regarding converting patients from Actiq to Fentora. And, finally, the carton and insert labeling both contain warnings that Fentora and Actiq are not bioequivalent and should not be interchanged.

Despite these labeled warnings, six cases reported inappropriate conversion between Actiq and Fentora where the prescriber converted the patient to Fentora on the same microgram dose they were taking for Actiq. For example, Actiq 800 micrograms to Fentora 800 micrograms. Reported outcomes of these cases included lack of affect and application site burning and bleeding.

Four cases involved a prescriber converting the patient from Actiq to Fentora in a manner that differed from the instructions in the professional insert. For example, a patient taking Actiq 400 micrograms being converted to Fentora 200 micrograms when

they should have been converted to Fentora 100 micrograms. In these cases, it seemed the prescriber was aware that Actiq and Fentora are not bioequivalent. However, we don't know if they actually consulted the professional insert when converting the patient's dose. Reported outcomes of these cases include decreased blood sugar, application site ulcers and burning, or the error being caught before the prescription was dispensed.

The last two cases involving confusion between Fentora and Actiq reported Fentora being substituted for Actiq at the pharmacy level. These cases appeared to have resulted from pharmacists not being aware that Fentora and Actiq are not interchangeable. We note that one of these cases involved a prompt on the computer screen in the pharmacy from the patient's insurance carrier which suggested the use of Fentora rather than Actiq. This suggestion from the insurance company may be a result of the lower price

point of Fentora when compared to both Actiq and the generic equivalent for Actiq, as presented earlier by Dr. Worthy. The other case involved the pharmacist improperly dispensing Fentora as a generic equivalent to Actiq. One of these cases reported an outcome of lightheadedness.

The remaining errors were categorized into the following three types: improper technique, accidental exposure, and accidental overdose. The first case was categorized as improper technique because the patient was instructed by their physician to split the Fentora tablet in half. The prescription read to take one-half a full 100 microgram tablet of Fentora twice daily. The outcome of the error was not included in the medication error report. However, the labeling of Fentora contains a warning that Fentora should not be split or chewed.

The next type of error identified was accidental exposure. This case stated

that a patient removed Fentora from its blister and placed it an unmarked container before administration. The Fentora was mistaken for aspirin by another family member and administered. This case resulted in treatment at the emergency room. The Fentora blister contains a warning instructing patients not to remove Fentora from its blister until immediately prior to use.

The final type of error identified was accidental overdose that resulted in a patient's death. The patient was reportedly taking Fentora for back pain. The circumstances of the overdose are unknown; therefore, we cannot determine what contributed to the overdose and resultant death.

In September of 2007, Dear Doctor letters and a public health advisory were disseminated warning against the type of errors I have presented. Twenty-two of the forty-three errors were reported after

publication and dissemination of these safety communications. However, we must note that many of these cases did not include an event date, so it is not possible to determine what effect these communications have on the errors identified.

In summary, we note that more than two-thirds of all errors cases involve a medication error with Fentora. The majority of errors occurred in off-label use. However, some of the error types seen in off-label use were also seen in on-label use. Confusion between Actiq and Fentora represent the largest number of errors reported, and, although these errors did not result in serious outcomes, confusion between Actiq and Fentora could lead to overdose resulting in serious adverse events due to the higher bioavailability of Fentora. This confusion is likely the result of a lack of knowledge and respect to the fact that these products are not interchangeable.

The information I have presented today leads us to question the effectiveness of the labeling and risk minimization action plan to communicate and ensure the proper use of Fentora. This concludes my presentation. Thank you.

ACTING CHAIR SORIANO: Thank you, Lieutenant Commander Arnwine. The panel now calls on Dr. Love.

DR. LOVE: Good morning. I'm Lori Love, and I'm a Medical Officer in the Controlled Substance Staff, and I will cover two topics this morning. The first will be a brief overview of the history of fentanyl and abuse, and then I will move on to discuss what we know about clinical data on abuse potential of Fentora in the non-cancer pain population.

The concerns about safety, including abuse, really derive from the history of fentanyl and abuse. Fentanyl was first synthesized in the late 1950s. It was introduced as an IV anesthetic in the mid-

1960s and has since become widely used as an anesthetic and an analgesic agent. Illicit use of pharmaceutical fentanyl was first identified in the mid 1970s in the medical community. All pharmaceutical preparations have been abused. The intravenous route is the most frequently used route today, but snorting, smoking, and sublingual routes are also used. And there are multiple street names, including apache, china girl, china white, etcetera.

The history of abuse indicates there's a high abuse potential as demonstrated by the illicit manufacture for abuse. There are currently more than 12 different fentanyl analogs in U.S. drug traffic that have been clandestinely manufactured. Recently, there were hundreds of deaths in several communities attributed to abuse with fentanyl-laced heroin. One of the precursors of fentanyl was designed as a List 1 chemical, and DEA is now in the process of designating a second

chemical as a Schedule II intermediate precursor in an attempt to control clandestine manufacture. Finally, we have seen abuse of all domestic and foreign pharmaceutical products, as shown by databases like DAWN and publications in the scientific literature.

The next few slides are different in your handout because I've reordered these and added a slide for clarification. We provided an updated handout at the desk outside. Because of the recognized high abuse potential, fentanyl is a Schedule II narcotic. Fentora has recognized differences in potency and bioavailability from other fentanyl products, and these differences are understood and can be exploited by the using population, as shown by the comments that I've extracted from the web site Bluelight by using the search term "Fentora." Bluelight is a bulletin board that allows individuals to post their experience and questions on drug use and pain management. There are a number of other

internet sites with similar information. No attempt was made to collect and systematically analyze all the information. I am not going to read all the comments that are provided here. I provide them for your information, and they are included to provide perspective on the challenges that we had in instituting safety measures, including those in risk management programs that would protect public health.

I am now going to move on to the Fentora clinical studies. Dr. Shibuya will be presenting the safety and efficacy data of the Fentora Phase III studies in non-cancer clinical trials later. I'm going to focus on abuse potential.

As a reminder, there are four major studies in the non-cancer pain indication. There were three double blind. The pivotal study is 3052, which was a 12-week study. 3041 and 3052 were for shorter durations, and then there was a long-term, up

to 18 month, open label study, 3040.

In all these trials, the patients were screened and required to meet similar protocol-specific criteria. As inclusion criteria, they had to be taking an around-the-clock opioid and were managing breakthrough pain using an opioid. Because of the concerns for abuse and misuse, the clinical trials conducted by the sponsor incorporated criteria to eliminate those considered to be at highest risk for abuse. These included recent history, within five years, or current evidence of alcohol or substance abuse; evidence by urine drug screen of an illicit substance or medication for which there was no legitimate medical use. In addition, for safety purposes, there was an exclusion of certain psychiatric conditions that would compromise patient safety if they participated in the study, but we also note that some of these patients could be in a high abuse group.

Because of concerns regarding

abuse and diversion, FDA asked the sponsor for additional information which was submitted in a report entitled "Review and Assessment of Risk for Abuse and Diversion." This report reviews events of abuse, addiction, and overdose that have been reported in the Fentora clinical studies of opioid tolerant patients in chronic non-cancer pain and breakthrough pain.

A number of publications in the literature have identified aberrant drug use behaviors within patients with non-cancer pain who are taking opioids. Table One lists the behaviors as identified by the sponsors from their review of the literature, and they were using this to provide evidence of behavior that may be precursors or signs of abuse. They considered high abuse behaviors or high risk behaviors as abuse dependence, overdose, or a urine drug screen that was positive for an illicit substance or a medication for which there was no legitimate medical explanation.

Overall, of the 941 patients in the safety analysis set, the sponsor reported that three percent of the patients exhibited high risk behavior. This included abuse, dependence, overdose, and a positive drug screen. Seventeen percent of the patients, or 156, had at least one aberrant drug use behavior, but the majority, or 85 percent, of these patients only had one behavior identified. In addition, they identified 13 percent other aberrant behaviors, which are further characterized here and include overuse of the study drug in 44 patients, or five percent; study drug thefts occurring in 35 patients, or four percent overall; and lost to follow-up in 33 patients, or four percent.

The sponsor concluded that the 17 percent incidence of adverse drug use behaviors in these clinical trials is lower than that reported in observational studies in this population from the published literature. They postulated that the differences were

likely due to the differences between clinical studies and clinical practice. The sponsor's evaluation of possible baseline predictors of these behaviors revealed that younger patients and those with a history of mania or psychosis were at higher risk for displaying one or more of the identified aberrant behaviors. This was not true for patients with a history of anxiety or mood disorders, which are prevalent conditions in chronic disease. And, finally, the sponsor stated that the risk of developing an aberrant behavior was not affected by the duration of treatment in the study.

During the clinical study, thefts of drug occurred from both patients and from individual study centers and were reported to the sponsor. As noted here, thefts occurred in 35 patients, or 4.2 percent overall, and these thefts only occurred in the long-term studies 3040 and 3052, and so using the number of patients in these studies, 831, there's a 4.2 percent rate. Most of the thefts were

reported to have been perpetrated by people without regular access to the study drug, and 20 of the thefts were reported to have occurred outside the patient's home. As noted earlier, the husband of one patient who reportedly took the patient's study drug was found dead of a possible Fentora overdose.

Despite significant protocol precautions to ensure safe delivery, handling, and storage of study drug in accordance with local and federal regulations, five study centers participating in study 3040 reported thefts of study drug which were reported to local authorities and to DEA. This accounted for over 4.3 grams of drugs stolen. I note there are 69 study centers in 3040, and using additional information provided by the sponsor this represents over 8,000 tablets, the majority of which were 600 and 800 microgram tablets.

We note that these were lost from locked cabinets in three thefts, including one

that showed evidence of forced entry, was lost in transit from a health facility distribution center to the pharmacy in one, and in one case the unused study drug had been returned by the patient and was subsequently missing during drug accountability review.

Our experiences with Fentora in Phase III trials with breakthrough pain in cancer is very different from that found in non-cancer breakthrough pain indications, as noted in the previous slides. Data from the sponsor indicate that thefts had occurred in two patients, one from the patient's home by the patient's daughter and another outside the house. There was one report of positive urine drug screen, and one patient was taking opioids from multiple sources.

Our review is still ongoing, but we have identified additional cases outside those initially provided by the sponsor, and these have mainly been in the categories of misuse of study drug, noncompliance, and

protocol violations, and we have asked the sponsor for additional information on these. The cases that we identified were not originally part of those identified by the sponsor and were mainly categorized as noncompliance and overuse or failure to return packaging. The sponsor has replied, and we agree that most instances of noncompliance do not automatically indicate drug use behavior or substance abuse, but instances where study drug is not returned as required does indicate a problem with drug accountability which could potentially signify abuse or diversion. This is especially important for Schedule II drug where accountability is a requirement of DEA registrants.

We are also concerned about the apparent lack of criteria on how investigators were trained to identify and report abuse, misuse, noncompliance, and diversion cases across the studies at study sites. These types of information are essential to

providing accurate information on assessing potential abuse and addiction occurring in these trials. Because this information is not available or perhaps was not gathered, the rates of abuse, diversion, and aberrant behavior in general are likely unreported in these clinical trials. Furthermore, we note that because most individuals who would have been at high risk of substance abuse were already excluded from participation in these phase trials, the rates of these behaviors are not representative of what would occur if Fentora were approved for expanded indication in the general population with chronic pain.

So, in summary, the risks of unintentional potentially fatal overdose, misuse, abuse, or diversion of fentanyl and of Fentora in particular are extremely high, as demonstrated by instances of overdose, misuse, abuse, and diversion in the clinical studies, and from signals in post-marketing data where off-label use differed from the currently-

approved indication. These clinical trials are not representative of potential risks of Fentora in the general population. This population was highly screened to eliminate high-risk patients and, further, detection of aberrant drug use is uncommon in controlled clinical trials and appears to be much more frequent in the non-cancer patients who use Fentora long term.

In conclusion, taking together, these findings suggest that expanded use of this product will raise serious safety concerns and will result in significant abuse and diversion that further impacts the public health and safety. Thank you.

ACTING CHAIR SORIANO: Thank you, Dr. Love. The panel now calls on Dr. Ball.

DR. BALL: Good morning. My name is Judy Ball, and I'm the Director of the Division of Facility Surveys in the Office of Applied Studies at SAMHSA. I'm going to be talking about some findings from the Drug

Abuse Warning Network, which is the only one of our surveys that can actually address questions about fentanyl products.

Today I will give you a brief overview of DAWN methods and, for those of you who were here yesterday, it will be a brief review. And then I want to talk about key findings from 2006 concerning the non-medical use of opiates and opioids as they appear in emergency department visits with comparisons from 2004 and 2005, and I'll be doing an analysis, showing an analysis of extended versus immediate-release fentanyl products. These are not estimates that have been published yet. They are in the process of getting ready for publication.

DAWN relies on a stratified probability sample of short-term general non-federal hospitals that operate 24-hour emergency departments. The DAWN sample is structured so that we have an over-sampling of hospitals in selected metropolitan areas,

which we refer to as over-sample areas. And then we complete the national sample by having a sample from the remainder of the country, so that is referred to as the remainder area. The sole purpose of the remainder area is to complete the national estimate. We can't actually do and we don't publish estimates for the remainder area itself. The national estimates are derived such that they account for the sample design for non-response of facilities and for partial non-response in responding facilities.

So the estimates I'll be presenting today are national estimates for the entire country. For 2004 and 2005, the over-sample of the areas that contributed to these estimates numbered 13. In 2006, we had 12 over-sample areas following the loss of New Orleans. And, again, in each of those years, the remainder area covers the remainder of the country.

The DAWN sample contains more than

500 hospitals. In each of the three years I'm going to discuss, we have had more than 200 hospitals participating, and these hospitals reported between 169,000 and 269,000 drug-related emergency department visits. The DAWN cases that are reported are any ED visit that is related to recent drug use, regardless of the reason for taking the drug.

These drug-related emergency department visits are collected. Information on them is collected based on a retrospective review of emergency department medical records. And in 2006, nearly 10 million charts were reviewed in order to find about 347,000 drug-related ED visits that we call DAWN cases, and the estimates are produced from a subset of those DAWN cases. In 2006, approximately 15 percent of ED charts were not reviewed and were unavailable for review.

Starting with all the drug-related ED visits that are submitted to DAWN, we can analyze these by breaking them first into

cases involving medical use of pharmaceuticals or non-medical use of either pharmaceuticals, illicit drugs, or alcohol. For non-medical use of pharmaceuticals, here's how we make the determination based on the information that's recorded in the patient's chart. Non-medical use includes patients who took more than the prescribed or recommended dose of their own prescriptions; an ED patient who took someone else's drug; a malicious poisoning; or if there's documented substance abuse. This excludes drug-related suicide attempts defined very narrowly, but it does include cases involving suicide ideation, plans, or gestures.

Now, this slide provides an overview of the estimates for 2004 to 2006. And let me draw your attention to the coding that I've used in this slide. When you see gray bars, that means no significant change across the years. When you see colored bars, it will be either a significant change from

2004 to 2006 or 2005 to 2006.

So the first group here, this is the total number of emergency department visits estimated for the country between 2004, 5, and 6, and it was a significant increase between 2004 and 2006. For the non-medical use cases, we also saw a significant increase from 2004 to 2006, and for the medical use cases we saw an increase over all three years. We believe that some of the increase that we saw from 2004 to 2005 in particular on the medical use cases were a learning phenomenon. These types of cases had never been captured by DAWN before, and there was some additional training and learning that was going on.

So now let me turn my attention to the national estimates for non-medical use involving the prescription opiates and opioids. This looks at estimates shown as confidence intervals. We have to remember that estimates are not exact numbers, and estimates based on sample data always have

that so-called margin of error associated with them. To emphasize this, many of the estimates that I'm going to be showing will look like this in terms of a confidence interval. The green bar represents the entire interval with the point estimate denoted by the red box in the center. The length of the confidence interval shows the margin of error around the estimate, and what this means is in repeated sampling we would expect the estimate to fall within this interval 95 percent of the time.

DAWN estimates, in terms of non-medical use emergency department visits, that there were about 16,000 of them in the United States involving fentanyl products in 2006. This estimate ranges from about 7,000 visits to about 25,000 visits. Lower numbers often have wider confidence intervals. The estimate for fentanyl is not significantly different than the estimate shown here for morphine products. The two confidence intervals

overlap. But both fentanyl and morphine shown here occur less frequently in non-medical use visits than either hydrocodone or oxycodone products.

This chart shows estimates and confidence intervals for three other opiates and opioids, which I provide for some context. Sometimes emergency department medical records don't specify the opiate or opioid that is involved in the visit, and this chart shows that the number of emergency department visits for unspecified opiates is similar to the number that we saw for the hydrocodone and oxycodone products on the prior slide. It's this confidence interval right here. But we can't determine exactly what this means. Typically, this is a report that says positive for opiates from a tox screen, and we know no more and can glean no more from the medical chart.

Another issue arises for patients receiving buprenorphine or methadone treatment

for opiate addiction. When such a patient presents to the ED, the chart may not clearly distinguish whether that drug is actually related to the visit. It may be an incidental finding, and this makes it very difficult to interpret the numbers for methadone in particular, which are shown here.

Now let me move on to the fentanyl estimates that I've broken down by release type. In order to do this, we took all the terms that are related to fentanyl products in the DAWN drug vocabulary and classified them by whether they indicated extended release product, an immediate release product, or an unknown release type. DAWN drug data can be reported by brand or trade name. It can be reported by generic name. It can be reported by ingredient, and sometimes the drug terms that are reported are non-specific. It depends on what is in the medical record.

To look at extended versus immediate release fentanyl product, we

classified each of the terms with help from our colleagues at the FDA. Duragesic, of course, is in the extended release column, and the three terms shown here for Duragesic and fentanyl patch account for most of the extended release reports. The alternate terms here that indicate different dosages, these actually capture very little data in DAWN.

The immediate release formulations are primarily Actiq and Fentora but also include, may include the multi-ingredient formulations. And you can see the breakdown here among the immediate release products, about 89 percent of the reports were Actiq and about 11 percent Fentora.

Sometimes, though, the drug reported to DAWN is simply fentanyl, and the unknown release type, about 95 percent of that was reported to DAWN simply as fentanyl. We can't say whether this is immediate or extended release.

So here for 2004 are the non-

medical use emergency department visit estimates for fentanyl products by release type. As you can see, the estimate for the extended type is greater than for the unknown type. The extended here about 9,000 visits ranging from 5 to 13,000, while the unknown release type ranges from 0.1 to 1.7 thousand visits.

You can see also here in the center of this chart that I have a blank. We don't have enough data in DAWN from 2004 to product an estimate for immediate release fentanyl products. And, of course, we've already heard that Fentora was introduced later to the marketplace.

Here are the similar estimates for 2005. We see quite the same pattern. Again, we can't produce an estimate for immediate release products. And we see a similar pattern in 2006, although the confidence interval for the extended release product here has certainly widened.

Now, this slide puts together all three of the years to look at the drug-related visits, all drug-related visits involving fentanyl products, not just the non-medical use. Again, the gray bars indicate that there's no significant difference across the years, and that's the case for the extended release products. And the color bars indicate that there were significant changes. And we saw that the unknown release type increased significantly in all three years. I don't know if this is a function of generics coming on the market and being picked up as an unknown release type rather than by brand name.

We can also look at DAWN at the medical use visits, and for medical use, which we might expect would more closely follow the prescription data, we see that, extended release types, the number of emergency department visits increased significantly between 2004 and 2006. The change from 2005

to 2006 was not significantly different, however.

And, finally, here are the non-medical use emergency department visits, and we did not see a significant increase in extended release type. We did see an increase from 2004 to 2006 on unknown release type. And, again, no immediate release estimates were possible.

This chart puts together the non-medical use and the medical use on the same slide side-by-side, and you can see that there's relatively little difference between the two sides in terms of the relative proportions of the extended release versus the unknown release types.

What happens to patients when they leave the emergency department may provide some clues about the problem that brought them there. And this chart shows that the majority of the visits involving both extended and unknown release type fentanyl products were

treated and released. That's the blue part of the bar here. About a third of the extended release group is admitted to an inpatient unit. That's the red part here. And about 40 percent of the unknown release type were admitted to inpatient units, which usually indicates that the patient was somewhat more severely ill.

Now, typically, non-medical use emergency department visits involve multiple drugs. When we look at this for the fentanyl products, we see a slightly different pattern, however. For the extended release products, the split between single drug visits and multi-drug visits is about even, and that's somewhat unusual. The single drug/multi-drug split, however, for the unknown release types is more typical with the single drug visits being less than a third and nearly three-quarters being multiple drug visits.

Now, being unable to provide you any estimates for the immediate release

fentanyl products, I decided to dig a little deeper and to go to DAWN Live to see what we might be able to learn from the raw data as they had been submitted. DAWN Live is a web-based system for querying the DAWN database in real time. The data are submitted electronically. As soon as the data hit the database, they're available for querying through the DAWN Live system. DAWN Live is a delivery mechanism for de-identified data because identifiable data in DAWN are protected. But because DAWN Live presents de-identified data, we can have authorized users both in the DAWN hospitals, member hospitals have access to their own information as well as comparison information for other hospitals; the FDA; federal, state, and local public health agencies; and even pharmaceutical firms can use DAWN Live to monitor these drugs.

So last week, I queried DAWN Live for all the drug-related emergency department visits for 2007 and 2008 to date involving any

fentanyl product, and I started with 2007 because of the introduction of Fentora in 2006. This query showed that nearly 1900 reports of extended release fentanyl had been submitted to DAWN in this period: the entire calendar year 2007 and up to April 30th, 2008. About 648 reports I had to classify as the unknown release type, and we had 21 reports during this time period for the immediate release type of fentanyl products. Of those, 11 involved Actiq, eight involved Fentora, and two Sublimaze.

And then I looked at the types of visits for Fentora in particular, and I used Actiq here as a comparison to give a sense of how the data may vary. So on the left here is the bar for the Fentora reports, the eight reports. On the left -- did I say the, I don't know my left from my right. This is the right, that's the left. The Actiq reports are on the left. What we see from Fentora is that three out of the eight reports involved visits

we would have classified as non-medical use. Half of the eight reports were involved in medical uses. This means an adverse event associated with a drug taking as prescribed or recommended. And one of the eight reports was a visit involving suicide attempt.

Using Actiq as the comparator, 8 out of the 11 Actiq reports were non-medical use visits. One of the 11 were medical use visits, and 2 of the 11 were classified in seeking detox visits. These tend to be hospitals that have the door to their substance abuse treatment unit or their detox unit requires the patient to go through the emergency departments, where we usually pick up the seeking detox cases.

Finally, I looked at the disposition for the Actiq and the Fentora visits, and for Fentora we saw that three of the eight visits resulted in the patient being discharged home and five out of the eight visits the patient was admitted to the

inpatient unit. Whether that admission was solely due to the drug or to some underlying condition we can't determine. For Actiq, seven of the eleven visits had patients discharged home, three were admitted to inpatient units, and one left against medical advice.

Now, I caution you that these are small numbers, and we don't like to take small numbers to draw broad conclusions from them. But I can tell you that the reports that we have seen of immediate-release type fentanyl are too infrequent to support national estimates at this time. And those small numbers continue to be confirmed in 2007, 2008, up to last week, April 30th. We did see one report from Fentora in 2006, which was not included in this analysis, and then eight reports in 2007 and 8. We see similar numbers of medical and non-medical use visits for Fentora and possibly more inpatient admissions than for the comparator drug Actiq.

A few important limitations to note. First is that DAWN depends on the content of emergency department medical records, and so for DAWN to capture a drug-related emergency department visit the link between the visit and the drug must be recorded in the chart. And for a new drug, sometimes new linkages have to be discovered before they can be documented and appear in charts and, therefore, can be picked up with DAWN. Emergency department and medical records don't give us information on dose levels or source of drugs, whether the drug came from an illicit source for example. We can make that determination sometime for the medical versus non-medical use, but oftentimes it's not available.

Sometimes, emergency department medical records don't give us the specific drug that was involved, and non-specific drug reports impede our ability to account for all the visits of any particular drug. For

fentanyl, the rise in the unknown release type is certainly problematic in this analysis.

I should mention that DAWN has another component, a medical examiner component, that looks at mortality data, and one of the reasons I'm not showing mortality data today is because this issue of drugs being identified by trade name or brand name is even a bigger problem in the medical examiner data. And the data lag is also much longer, so we get less current information out of the medical examiner component of DAWN.

And, finally, I just want to note that with more than 200 hospitals reporting each year and millions of charts being reviewed, DAWN is able to capture these very rare events, and surveillance of a new drug can begin as soon as the drug has been approved. Sometimes we actually catch drugs before they've been approved. But, nonetheless, we have to be cautious in interpreting small numbers. Thank you.

ACTING CHAIR SORIANO: Thank you, Dr. Ball. The panel now calls on Dr. Shibuya for his report.

DR. SHIBUYA: Good morning. My name is Rob Shibuya, and I'm a Medical Officer in the Division of Anesthesia, Analgesia, and Rheumatology Products. I'm responsible for the clinical review of efficacy and safety for this product.

I want to state that our review is ongoing and our findings at this point should be considered preliminary. My presentation will cover implications of the new indication, were it to be approved, then a very brief review of the data supporting efficacy, a review of the key safety findings from clinical trials, then our preliminary findings regarding safety and efficacy.

I'll read the currently approved and the proposed indications verbatim. The current indication reads in part "management of breakthrough pain in patients with cancer

who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain." The proposed indication reads in part "management of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying persistent pain."

This particular phrase here in the current approved application is underlined in the package insert because opioid tolerance is critical for the safe use of Fentora. The key differences then are the deletion of the requirement for the patients to have cancer and the specific requirement for opioid tolerance.

So what are the predictable results of the change to the indication? I'm going to limit my discussion to the removal of the restriction to cancer patients. The proposed modification to the requirement that patients not be opioid tolerant will not be

permitted since, as I noted before, that is one of the keys to safe use of the product. Naturally, this list here is not all inclusive. There are undoubtedly unintended consequences of changing the indication for Fentora that are not foreseen at this time.

That being said, here are the most predictable implications of the proposed change. From the perspective of predicted benefits, we would predict that insurers would become obligated or responsible for coverage for the new indication. Therefore, more patients would have access to Fentora. From the perspective of predicted risks of broadening the indication, we would predict that there would be a larger, less expert prescriber base. The applicant would be able to increase their promotion, which we would predict would lead to wider prescribing and larger amounts of drug being available for misuse, abuse, and diversion.

The applicant did not provide an

estimate of the magnitude of increased use in their application. Therefore, we conducted a very rough estimate based upon the number of patients who would be theoretically eligible for therapy with Fentora. Those are patients with moderate to severe chronic pain and breakthrough pain using various sources. As shown here, using this method of estimation, there are approximately eight times the number of patients without cancer as patients with cancer who could be eligible for treatment with Fentora.

So from our estimate, there's the potential for a substantial increase in the amount of Fentora and fentanyl in the community, which we believe is of significant concern from a public health perspective. We further note that in the setting of misuse there's evidence that fentanyl may be more dangerous than other opioids. Let us examine this slide from Dr. Cathy Dormitzer's presentation from yesterday's advisory

committee, which has been formatted slightly differently here. She had the bars grouped differently.

In this slide, Dr. Dormitzer has plotted emergency department visits from the DAWN database normalized for the number of prescriptions of either hydrocodone-containing, oxycodone-containing, or fentanyl products over the years 2004 to 2006. As you can see, fentanyl shown in yellow has the highest rate of ED visits per 10,000 prescriptions when compared to oxycodone and hydrocodone, and this has been very consistent for the three years of data shown.

With that background, I'll briefly discuss efficacy. First, let me start by saying that our review is not complete. However, to date, we are in substantial agreement with the applicant regarding the efficacy findings. The applicant submitted three studies to support the new indication, 3052, 3041, and 3042. Study 3052 was a 12-

week study in patients with non-cancer breakthrough pain of any etiology. Studies 3041 and 3042 were short-term placebo-controlled studies in patients with neuropathic and low back pain respectively.

The applicant has reviewed the study design and results, and details are in the briefing document. In the interest in brevity, I will only show this one slide, the primary efficacy analysis for study 3052. The study met its objective with a difference in average SPID, summed pain intensity difference, of 3.1.

Again, we have not completed our review of studies 3041 and 3042. These were short supportive studies conducted in opioid tolerant patients with either neuropathic or chronic low back pain. Per the applicant, both studies showed a statistically significant treatment effect favoring Fentora.

So to conclude regarding efficacy, preliminarily Fentora appears to provide

analgesia for breakthrough pain superior to placebo over 12 weeks of therapy. We note that no comparative data were collected, be that comparisons between the cancer and non-cancer populations or between other available breakthrough pain therapies.

I'm moving to safety now. First of all, I must state that the assessment of safety for oral transmucosal fentanyl citrate products is not straightforward. The reasons for this include the fact that the studies are using single doses of rapid-onset fentanyl on a background of around-the-clock opioid and that fentanyl has no pathognomonic adverse events via this route of administration. Knowing the exact time of dosing and the onset of the adverse event will help us assess causality. However, that level of detail is generally not available.

Next, these studies do not have a true control group. In the placebo-controlled portions of studies, usually patients were

dosed with active and placebo in the same day. Last, in cancer populations, there is significant co-morbidity affecting the quantity and quality of adverse events observed.

For reformulated opioids, the usual approach to safety data collection is the solicitation of adverse events and vital signs assessment at each visit, and lab exams, physical exams, and oral cavity exams were appropriate at specified visits. Because of concerns regarding abuse, misuse, and diversion, the applicant retrospectively analyzed data collected during clinical development that included information captured in the narratives that could indicate abuse and addiction. We were unable to locate specific criteria that allows for the identification of abuse, misuse, noncompliance, and diversion cases across the studies in study sites.

In meetings with us, the applicant

was told that an appropriate database size was 1200 patients total, of which more than 900 should be non-cancer. Greater than 450 patients were to have been treated for over six months and over 300 for over one year. The key efficacy studies had insufficient exposure, so the applicant conducted study 3040 in open label study in patients without cancer and breakthrough pain. Study 3040 enrolled a total of 730 patients with a mean duration of exposure of 292 days. This slide I'll briefly cover just shows that the exposures exceeded those recommended by the division.

The applicant collected data and presented it in a conventional manner, meaning that deaths, serious adverse events, and adverse events leading to discontinuation were discussed in detail, and other data were tabulated. Since there was no clear placebo control, no comparator data were presented by the applicant. While the Agency agrees that

a comparison to placebo is not appropriate, we believe that, with caveats, there is an appropriate comparator group: the patients enrolled in the cancer and breakthrough pain clinical trials.

This slide summarizes the similarities between the cancer and non-cancer clinical trial populations. The shared characteristics include the fact that all of these patients were opioid tolerant adults with breakthrough pain. All of the clinical trials were of similar design, and adverse event capture was identical. There was also an identical dosing paradigm used across trials, as well as the dosing range was identical. Last, we note that the clinical trial data naturally meet data quality standards for NDA submission.

The main dissimilarity is the fact that cancer patients would be expected to be more ill. Therefore, they would be expected to experience more adverse events.

We examined the two populations in two ways. To put the safety findings into context, it was necessary to examine differences in demographics and the concomitant medications. Next, we compared adverse events in both groups. We did not examine non-specific adverse events commonly observed in clinical trials, such as nasal pharyngitis and headache; nor did we consider adverse events related to an advanced malignancy and related therapies, such as anemia, fatigue, and weight loss, to be relevant.

What could be fairly compared between the two groups were adverse events related to abuse, misuse, addiction, over-sedation, and the consequences thereof. We examined adverse events that let the regulatory definition of serious, meaning death, life-threatening, or requiring hospitalization as is defined down here, and those that did not. We also looked at common

opioid-related and formulation-related adverse events.

This slide summarizes the demographic information. I draw your attention to the sample sizes. There are approximately two and a half more times the number of non-cancer patients as there were cancer patients. Predictably, also, the cancer patients were older. The other demographic data were reasonably balanced.

In light of the nature of some of the adverse events of interest, we were interested in the concomitant medication use that causes CNS depression. We asked the applicant to conduct the analysis summarized here. We defined concomitant medication use as use for more than 50 percent of time on trial. This analysis shows that cancer patients were on higher doses of opioid, showing here the means. However, the non-cancer patients were more likely to be on every class of CNS depressant. The difference

was most striking for the class of muscle relaxants shown here, such as carisoprodol.

I searched the Adverse Event database for events that were considered serious and related in some way to abuse, misuse, over-sedation, and the consequences thereof, and I reviewed each case report form and the narrative. As this slide shows, a total of 11 patients falling into these categories were identified in the cancer database. They experience SAEs that appeared to be related to misuse of the drug. There were no deaths, so these adverse events were life-threatening or required hospitalization. There were no such cases in the cancer population.

I examined the cancer and non-cancer databases for non-serious events that were identified by the investigator as moderate or severe in intensity and again related to addiction, CNS depression, or similar. I conducted this analysis by

examining the most up-to-date adverse event database for each study and searching the verbatim adverse event term by hand. In counting cases where pertinent information was available, I took that information into account. I eliminated duplicate events occurring in the same patients, and I normalized for exposure by dividing by the total sample size.

This table shows that cancer patients had higher rates of the terms shown in yellow. The terms for which the non-cancer population had a higher incidence are shown down here in white. Many of the terms in the table were experienced by a single patient, actually in particular the last row down here. I note that each of the terms in that last row were experienced, though, by discrete patients. These were worrisome terms from a risk management perspective and included things such as addictive behavior, physical trauma, and substance abuse, which are rarely

seen in clinical trials.

This is a slightly different analysis. In this analysis, I did not delete duplicate events, and I normalized by dividing by time on trial as shown here. I'm sorry. Actually, the time on trial I think was shown in a different slide. In this analysis, almost every common opioid-related adverse event term was more common in the cancer patients, as you can see here shown in yellow. The vast majority were more common in the cancer population. However, again, the events that portend risk management issues are more prevalent in the non-cancer population. This comparison of the common either opioid or formulation-related adverse events, regardless of intensity, shows insignificant differences between the two groups.

I'll read our preliminary safety conclusions. The first is the non-cancer population has an excess incidence of serious adverse events related to overdose, abuse,

misuse, and those consistent with excessive CNS depression compared to analogous safety data from patients with cancer. And I just noticed this morning that I didn't write this the most clearly, so I'll read it slightly differently. Depending on the analysis conducted, the cancer population tends to have an increased incidence of non-serious opioid-related adverse events, such as sedation and dizziness, compared to the non-cancer population. However, the non-cancer database contains rare concerning reports related to addiction, substance abuse, etcetera, not observed in patients with cancer.

The higher rates of concomitant CNS depressant use in the non-cancer population may make medication errors more likely. And the last conclusion is the common opioid-related adverse event profile is similar between the two populations.

So at this point in our review, it appears that the product continues to show

efficacy over 12 weeks in the non-cancer population. Restated again, compared to the cancer population, the product shows evidence of excess abuse-related serious adverse events in the non-cancer population, which is concerning to us from the perspective of the public health. I think that concludes my presentation.

ACTING CHAIR SORIANO: Thank you, Dr. Shibuya. The panel now invites Ms. Best to present her report.

MS. BEST: Good morning. My name is Jeanine Best, and I'm a Senior Drug Risk Management Analyst in the Division of Risk Management in the Office of Surveillance and Epidemiology. My presentation will cover current Fentora risk management and is based on approved materials and information that has been submitted to FDA for review. The sponsor presented new risk management proposals this morning that are new to FDA, as well as to the committee.

Today, I will present brief background information on Fentora and an overview of the current approved Fentora risk minimization action plan, or RiskMAP, and its post-marketing or post-approval experience. I will then present additional risk mitigation strategy options for the committee's consideration and present our overall conclusions for risk mitigation strategies for Fentora.

Fentora was approved with a limited indication where the benefits relative to the risks were shown to be acceptable; a medication guide for patients; and a risk minimization action plan, or RiskMAP. Per the March 2005 Guidance for Industry: Development and Use of Risk Minimization Action Plans, FDA has recommended RiskMAPS for Schedule II extended-release or high-concentration opioids because these products have important benefits in alleviating pain, but they also have a significant risk of overdose, abuse, and

addiction.

The following slides describe the current approved Fentora RiskMAP. The risks of Fentora, including use by opioid non-tolerant individuals, abuse, misuse, and diversion, and unintended or accidental exposure were translated into these three RiskMAP goals: one, Fentora should be used only by opioid tolerant patients with cancer; abuse, misuse, and diversion of Fentora should not occur; and unintended or accidental exposure to Fentora should not occur. All goals have objectives to encourage appropriate patient selection and appropriate product use in order to minimize medication errors due to concerns unique with the Fentora formulation.

Labeling and education are the key strategies intended to minimize the serious risks with Fentora. Additional RiskMAP elements include surveillance, evaluation, and intervention activities. Fentora labeling includes a package insert for healthcare

professionals, a medication guide for patients, and carton labeling for pharmacists and patients. The package insert has a boxed warning that emphasizes Fentora key safety information including use only in opioid tolerant patients with breakthrough cancer pain, no use for acute pain, dosing and administration instructions, conversion instructions, no substitution for other fentanyl products, and abuse and misuse warnings. The medication guide contains the key safety information for patients in consumer friendly language.

The carton label contains a four-point reminder checklist for pharmacists to use before dispensing Fentora with the following instructions: patients must be opioid tolerant, no product substitution, counsel patients on product use, and instruct patients to read the medication guide. The label also includes warnings for patients and a prompt for patients to read the enclosed

medication guide.

The RiskMAP education plan is directed to prescribers, patients, and pharmacists. Labeling is the cornerstone of the education plan for Fentora. There is also an independent CME program for physicians about general opioid use, and there are general product educational and promotional tools, which are not all RiskMAP specific.

Routine surveillance activities include spontaneous and expedited reporting of adverse events. Expedited reporting is done per regulation, along with requested reporting of additional events. In addition, active surveillance for monitoring abuse, misuse, and diversion is done using the Research Abuse, Diversion, and Addiction Related Surveillance System, RADARS; the Toxic Exposure Surveillance System, TESS; and the Drug Abuse Warning Network, DAWN.

The sponsor performs periodic analysis to evaluate the effectiveness of the

key elements of the RiskMAP. Evaluation consists of quarterly evaluation of surveillance and monitoring activities, surveys to evaluate knowledge, attitudes, and behavior gained from education efforts, and assessing use in opioid non-tolerant patients by looking at patient longitudinal drug utilization data.

The following slides present the Fentora RiskMAP post-marketing or post-approval experience. This drug utilization information is reported in the sponsor's quarterly RiskMAP reports. Reported data is from approval in September 2006 through calendar year 2007. No data from 2008 has been submitted at this time for review. Note that non-opioid tolerant use has been steadily increasing since drug launch, and non-cancer use has been high and steady since initial marketing of the product.

There have been spontaneous and expedited reports of abuse, misuse, and

diversion for Fentora, and the RADARS signal detection systems have shown concerning rates but not definite signals for abuse, misuse, or diversion. And this was reported in the sponsor's fourth quarterly RiskMAP report.

Surveys are supposed to be utilized to assess the effectiveness of the RiskMAP education efforts, yet no results have been submitted to date to assess prescribers' and pharmacists' understanding of the key safety information for Fentora. Survey results have been submitted for patients with 624 patients completing the survey to date. The sponsor reports that most patients are aware of the key safety information, but more than 33 percent of patients are unaware of the need for safe storage to prevent theft and diversion, and approximately 25 percent of patients are unaware of the need to keep Fentora in its original blister package until use. We, however, are unable to draw any conclusions from the results of this survey

because the survey questions do not address all the key safety concerns.

Post-approval actions were taken in September 2007 following three reports of death in Fentora patients. The sponsor issued Dear Doctor and Dear Healthcare Professional letters, and FDA issued a public health advisory. In addition, all labeling components, including the package insert, medication guide, and carton label were revised in February 2008 to enhance the key safety information. The Dear Healthcare Professional letters and public health advisories do not appear to have had any effect on prescribing practices as noted by the increase in use of Fentora in opioid non-tolerant patients and the continued high level of non-indicated Fentora drug utilization reported in the recent fifth quarterly RiskMAP report.

The sponsor also submitted RiskMAP revisions that are currently under review. Of

note, additional material submitted as RiskMAP tools are mainly limited to promotional materials, such as the patient debit card, otherwise described as a safety activation card this morning. The sponsor describes a telephone counseling program where if a patient calls to listen to a counseling message, they activate a debit card and receive a reduction in their co-pay for Fentora.

The following slides present a summary of the RiskMAP experience and are comments on the RiskMAP experience. There has been increasing use of Fentora in opioid non-tolerant patients. These are patients who are at greater risk for life-threatening adverse events, and a high utilization in non-cancer indications. There have been reports of medication errors at all levels, prescriber, patient, and pharmacist, with inappropriate patient selection and improper product use accounting for two-thirds of the reports in

the Adverse Event Reporting System.

The additional drug communications issued in September 2007 do not appear to have had any effect on medication errors to date, and the revised labeling has not been out for a long enough period of time to determine any effect. In addition, we have received inadequate information to determine if healthcare professionals and patients have an understanding about the safe use of Fentora.

Based on the information we have received, the current risk minimization tools do not appear to achieve the RiskMAP goals. Expanding the indication will most likely amplify and exacerbate the post-marketing trending we have seen regarding opioid non-tolerant use, all medication errors, and abuse, misuse, and diversion.

Given our concerns with the current Fentora RiskMAP, I will present additional risk mitigation options in the form of prescribing requirements, dispensing

requirements, and additional safe use requirements for consideration as part of the committee's discussion today. Some of the options can be considered individually or considered together as part of a comprehensive risk mitigation plan. When considering these options, consider their feasibility, and also keep in mind that requirements such as these are generally reserved for products with serious risks in order to target a population and conditions of use most likely to confer benefit while minimizing risk.

One option is that we put requirements around Fentora prescribing. Prescribing requirements may include mandatory enrollment of all prescribers in order to prescribe Fentora, along with mandatory training or certification and/or acknowledgment of safe prescribing elements. Safe prescribing elements could include knowledge of appropriate or indicated use; screening for abuse, misuse, and diversion;