significant benefit to millions of people living with pain, and an important step in protecting public health.

I thank you.

DR. WATKINS: Our next presenter is Larry Golbom.

DR. GOLBOM: I am Larry Golbom. I'm a practicing pharmacist representing myself. I do a self-funded radio show called The Prescription Addiction Radio Show, breaking the silence for one hour a week in the Tampa Bay area of Florida. On a regular basis, I hear the damage and destruction Oxycodone is presently doing to individuals and families in our country.

I want to direct your attention to the overhead. It is the molecular structure of Oxycodone, the active ingredient of OxyContin next to the molecular structure of heroin. Oxycodone has been part of killing thousands of people and addicting thousands more.

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Oxycodone has brought devastation and heartache to an untold number of people and families. Oxycodone has helped kill way too many of our loved ones and children. In all due respect, I am in this room with some of the brightest minds in America, and these facts appear to have been ignored by the FDA.

Every narcotics police officer, every addiction specialist, and every addict knows that Oxycodone and heroin are interchangeable. How is it that every professional who interacts with the disease of addiction clearly knows that Oxycodone and heroin are interchangeable, and the FDA has for over 12 years ignored that fact?

I am very pleased to tell you that the American people are finally learning about the hoax of OxyContin, and today I am asking the Committee members to respond to it.

The side effects of heroin -- the side effects of heroin include possible euphoria, respiratory depression, constricted

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pupils, nausea, slow and shallow breathing, clammy skin, convulsions, coma, and possible death. The side effects of OxyContin -- the side effects of OxyContin include possible euphoria, respiratory depression, constricted pupils, nausea, slow and shallow breathing, clammy skin, convulsions, coma, and possible death.

When you look at the heroin molecule next to the Oxycodone molecule, I hope your decisions concerning OxyContin will be put in the proper perspective. In a moment, I will address the weaknesses of the actual formulation Purdue is presenting before you, but before I do I hope that this presentation will bring to light the convoluted logic of possibly putting more of this dangerous drug out onto our streets.

Oxycodone, the active ingredient of OxyContin, has reportedly killed more people than any other prescription drug, and I hope that today will be the beginning to

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dramatically curtail the use and indications of Oxycodone. Our forefathers had the good sense to ban heroin in 1924, and the medical use of heroin around the world is very limited.

When we discuss OxyContin, we are discussing the biggest medical hoax since heroin was introduced as a cough remedy over 100 years ago. The only difference is that OxyContin has been marketed and sold as a pain remedy, but its effects are no different than heroin. It remains -- it remains difficult to believe that an entire medical profession has been misled for so many years.

I do remain concerned about the information the Division of Anesthetics, Critical Care, and Addiction Drug Products Committee may be presenting to the Committee members. This is an August 12, 2003, memorandum from the Director of the Committee presenting information that can clearly be challenged using information we have available

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today.

I use this memorandum from almost five years ago to refer to the Director's opinion concerning the proper use of Oxycodone and the opiates for chronic pain therapy. Since 2003, I hope that the Director presents -- the Director present realizes that there is no proof that infers that tens of millions of people who are in chronic pain are in need of opiate therapy.

Earlier we heard Purdue mention 50 million. This young lady before me mentioned 76 million. There is no proof of those numbers.

In fact, the recent studies available indicate that the treatment of chronic pain with opiates for far too many people have had poor outcomes. OxyContin should be saved for the most tragic of medical situations. For thousands, the results of too many excessive and unnecessary prescriptions have resulted in death and addiction.

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OxyContin has been a part of way too many of those negative outcomes.

As a pharmacist, I see the sunken eyes and hopeless look from far too many people who have been mismanaged with opiate therapy. If I was a medical examiner or a coroner, I would be sharing with you the deaths and family members I have faced after people have taken OxyContin.

I hope the information coming from the Director of the Anesthetics Committee for this meeting has been updated since this memo was written in 2003. If it has not, the Anesthetics Committee has done a tremendous disservice to the Committee members here.

Also, the meeting background material -- it was just published Thursday or Friday, very late. This entire meeting is talking about the formulation that, at best, only addresses two to three percent of the final deaths. The reality is that it's estimated that 97 percent of the people who

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die from -- with OxyContin in their system took it whole.

So you are listening to addressing possibly two or three percent of this problem that we have right now.

Even if the FDA members decided to put all logic aside after today's comments, I believe there are some points that must be researched before the new OxyContin formulation is considered further. My letter sent to the Committee members dated April 17th covered these points.

And for review, "Have you been presented the standards for time-release Oxycodone products?" There are reports that people have died after taking one OxyContin. What standards does the FDA have that allows a formulation to be so dangerous? Who decides the appropriate testing procedures for the new products?

I encourage you to ask for the FDA guidelines on the new formulations. It is my

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assumption that there might not be any.

In due respect, only a foolish person would believe that any product containing Oxycodone could be tamper-resistant or abuse-resistant, whatever terminology you want to use. In 1995, the FDA was aware of being able to crush the present formulation, and the damage done since the introduction of OxyContin in 1995 is legendary. Somebody will figure out a way to inhale this product or extract the active ingredient. Only a naive person would believe otherwise.

Smoking is not mentioned in this article. After you dissolve it in water, drinking it with alcohol is not mentioned in these studies. More studies have to be done on this product.

This is a complex product with no proof that it can be duplicated a billion times over without any flaws. It's a polymer. This formulation you are discussing contains a chemical that is deadly. Have you

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thoroughly examined the manufacturing process that will ensure safety a billion times over?

This drug has clearly been fast-tracked by the FDA powers. Has long-term stability of the new formulation been assured? Did the testing for the new formulation follow FDA protocol? I have not been able to find any FDA protocol. If the protocol for the testing came from Purdue, then the test results must be questioned closely.

Finally, has the FDA verified and duplicated the tests Purdue has presented? This company has already been convicted in federal court for lying, and to believe the test results solely based on Purdue's word should question the Advisory Committee members' logic.

Have you asked the question if all of the laboratories and testing areas Purdue used at the time of the test were FDA approved or licensed by the FDA? If the proper licensing did not take place prior to the

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testing of the new formulation, the members of the FDA responsible for this meeting have wasted everybody's time.

If I have given you a number of reasons -- I hope I have given you a number of reasons to prevent more Oxycodone from getting out onto our streets today. But the most important reason I can give you, the most important reason, children do stupid things. Children do stupid things. Locking the medicine cabinet is only part of the solution.

Parents needs support from the FDA. The medical hoax of OxyContin, the FDA has remained silent on for too long, has to stop. I hope it is not one of your children or grandchildren who because of your decision after today gets hold of the new formulation of OxyContin.

I can promise you it will be a decision that you will regret for the rest of your life, and I pray -- I pray the FDA Advisory Committees do the right thing after

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today.

You know, I still have a minute left. I want to mention just one sentence concerning fentanyl tomorrow, the Fentora product. This is also a formulation that has proven deadly in the wrong hands.

For the FDA to be considering a sublingual fentanyl product for chronic pain is as equally ludicrous as the underregulated release of OxyContin 12 years ago.

Thank you for the courtesy.

DR. WATKINS: Thank you.

Our next speaker is Beatrice Setnik, please.

DR. SETNIK: Good afternoon. My name is Beatrice Setnik. I am a scientific consultant and Director of Scientific Business Development at DecisionLine Clinical Research Corporation in Toronto, Canada.

DecisionLine provides consulting services and conducts numerous clinical trials in the fields of abuse liability and tamper

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resistance. My presence here today is not supported by any sponsor.

The main concern that generally comes up with any types of controlled release formulations is the effect with alcohol, particularly with tampering. And more importantly so because alcohol is not a benign substance. It's not only used as a solvent, but it also has centrally acting effects. And a careful assessment of this interaction is critical.

The term "dose dumping" we have seen in various different applications to various different degrees as a term that is generally applied to accelerated drug release. Now, this has been historically termed and not always paired with something that is of clinical importance.

It has been based on in vitro dissolution data and pharmacokinetic data, which has been oftentimes limiting in the types of information on clinical relevance.

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The pharmacokinetic data that is often presented has -- does not predict with ease any types of safety implications, pharmacodynamic effects, what happens with somebody takes -- ingests alcohol with an opiate and gets into a car, and the efficacy issue is not explained.

What happens when somebody who is a legitimate patient consumes alcohol and may have not only safety implications but compromised efficacy over a controlled release substance that is supposed to be releasing over an extended period of time.

Now, historically, due to safety reasons, a lot of these studies in a clinical setting have been used with a Naltrexone cover. The use of the Naltrexone, obviously an antagonist, does block many of the critical questions. It not only manipulates the pharmacokinetics, but can often prevent you from getting critical data on safety and pharmacodynamics that can be important in

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determining clinical relevance of drug interactions.

There are ways of designing safe clinical trials, which need to be more prevalent nowadays. And the importance of the pharmacodynamic and safety are critical assessments in determining the relevance.

The issues with the in vitro data, although in vitro data does provide to you limited information about the physical and chemical properties, it tells you a story about solubility. But it's inexpensive, it's a fairly quick method, but it's not always correlated to clinical trial data.

And we have had recent case examples where in vitro dissolution data has come up with negative results in various different ethanol mediums, and different as outcomes in clinical trial data.

So it's very different information that is being put out by in vitro data, because in clinical studies you do not address

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-- you address issues such as first-pass metabolism and a variety of different effects when these drugs are put together with alcohol in an in vivo environment.

So clinical studies are an integral piece of determining that clinical relevance. And not only from a pharmacokinetic standpoint, but from a pharmacodynamic and safety perspective, to determine relevance.

Oftentimes -- and it has been mentioned quite a few times today -- is really the terminology in these types -- in describing these types of formulations, particularly with abuse deterrence and often the interchangeable "tamper resistance."

Tamper resistance really would be best described as formulations that have a controlled release caption that is not really easily accessible by the common methods that have been described today, and, of course, also by smoking, which is also an important

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route of administration, and/or may have tampered or physical chemical properties that may be less appealing for administration, such as a chemical aversion or an antagonist on board.

However, it's important to understand that these types of tamper-resistant formulations also have immediate release captions, which if taken intact may also have a degree of abuse associated with these types of formulation.

So, however, the true form of an abuse deterrent formulation really would be -- and it was mentioned earlier -- a manipulation of the pharmacokinetics, a decrease in the Cmax. But in order for this to be really truly affected, there has to be really an abuse deterrent factor with these types of formulations. So it's really comparing the two.

And this is really only assessed through very well-designed clinical trials,

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and then the epidemiological data to support an abuse deterrent claim.

So, in summary, the human studies and epidemiological safety data are really needed to address not only the issues of alcohol-drug interactions but also the abuse potential that these formulations will be -- and the claims that can be made as such.

The determination of clinical importance or relevance is -- really requires information that is beyond in vitro data and beyond pharmacokinetic data in human clinical trials. This really needs to address important safety and pharmacodynamic implications.

Dose dumping, because the degree of dose dumping can vary within formulations, really needs to be describing a situation where there is a clinically relevant effect occurring. And the criteria for the clinical importance really should be developed, and it needs to be developed for the drug classes, as

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there will probably be many more different types of abuse deterrent, controlled release formulations for drug classes outside of opiates. So this will be an important issue to address.

And the appropriate terminology and evidence that is required to make claims on labels needs to be really well defined, so that some -- going forward drug companies can continue to make these types of formulations, which are very important, and will have, then, the knowledge of what to -- they can be putting into labels in order to support any types of explicit claims.

And that's it. Thank you very much.

DR. WATKINS: Thank you. Our next speaker is Art Van Zee.

DR. VAN ZEE: Yes. My name is Dr. Art Van Zee. I am a general internist in a small coal mining town, St. Charles, Virginia. I have no financial disclosures.

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My interest in pain and addiction dates back eight to ten years when OxyContin came to the coal fields. It would be very hard to overstate the tragedy that has been OxyContin in our region, and then perhaps we were the canary in the coal mines as the OxyContin problem spread -- became a national one.

I am not anti-opioid. I use opioids generously and liberally in my patients with cancer, terminal pain. I treat patients with chronic non-cancer pain selectively for a subgroup of chronic pain patients. And then, for the last five years, I have used buprenorphine in treatment of opioid-addicted individuals.

I want to just add one little indicator to all of the indicators that has been discussed about the national prescription opioid problem, kind of go over efficacy and safety of OxyContin in relation to other available opioids, as I think that is very

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germane to the discussion, and then of review what I see as risk and benefits of an abuse-resistant OxyContin and what possible responses can be made to this.

These next three slides really come from Dr. Len Paulozzi's work at the CDC on unintentional drug overdose deaths. And it has been very clear over the last several years prescription opioid deaths rising fairly dramatically, now exceeding cocaine and heroin.

Again, another graphic demonstration of this same point.

And then, this slide really correlates the drug overdose deaths rate and the total sales of prescription opioid painkillers in the United States over the last several years. Clear correlation.

Now, all prescription opioids have been prescribed, much more available over the last decade, but clearly OxyContin has been a leader of that. And in this 2004 study, the

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OxyContin abuse problem had gone from a local and regional problem to be a national problem. And in at least this one study it had become the most prevalent drug of abuse at that time. so availability is the key with prescription drug abuse.

This is just some data from DEA on their production quotas and showing a rise -- significant rise in all prescription opioids -- fentanyl, 16-fold; oxycodone, 14-fold, over the 12 years it has been surveyed there.

Now, this is a little bit different depiction of the data you saw earlier today, which was mostly number of prescriptions. Now, this is ARCOS data on the millions of grams -- in millions of grams of the opioids out there. And I'm afraid if I used a pointer I'd probably put somebody's eye out there, so we'll have to go on the graph.

But you've had a dramatic increase in all of the opioids. Oxycodone, which is on the very top of your slide, was a 580 percent

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increase as opposed to morphine, which was a 150 percent increase in millions of grams.

This slide -- I want to thank Cathy Gallagher at the DEA and INS Health for allowing us to share this data. But this is the quantity of controlled substances in the supply chain, total dispensed prescriptions. And in 2007, it's about 190 million prescriptions of opioids available in the country.

This is the total dosage units in 2006/2007, and it's about 12.4 billion units of prescription opioids out there. A lot of availability. And, of course, that is reflected in this very familiar slide where most patients report -- or most people report the illicit pain reliever use as either from a doctor or a friend or relative.

So I think it is germane to look at OxyContin in comparison to efficacy and safety issues in regard to other available opioids, Oxycodone itself comparable in

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analgesia and addiction potential to morphine.

And then Dr. Curtis Wright was medical review officer of the OxyContin new drug application in 1995. His conclusion was that OxyContin was equivalent to QID immediate release Oxycodone. I would not allow a better claim.

He also concluded that -- you know, that OxyContin was just a BID alternative to conventional QID Oxycodone. Care should be taken to limit competitive promotion. This product has not been shown to have a significant advantage beyond reduction in frequency of dosing.

And in back pain and cancer pain, immediate release Oxycodone versus controlled release Oxycodone -- comparable efficacy and safety. Sustained release morphine and oxycodone are comparable in treating cancer pain.

And then, Dr. Chou and his colleagues at the University Virginia reviewed

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all of the opioid preparations and concluded that there was not sufficient evidence to indicate that one preparation was any better than any other, either in the long-activity class, sustained release, or between the long-acting and immediate release classes.

So what are the risks and benefits of an abuse-resistant OxyContin? Of course, the benefit we all want is some major deterrence for abuse, primary from altered route of use, reduced snorting, reduced injection. You know, whether this preparation proposed today does have the safety and efficacy to do that will be the Committee's decision, but that's, of course, what all of us want in this room.

What are some of the potential risks of an abuse-resistant Oxycontin, or at least from the looks of this preparation you would have to label it more a tamper reduction preparation. But certainly there would be the risk of iatrogenic addiction in chronic non-

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cancer pain patients when they take it exactly as prescribed.

And the irony of much of the debate about chronic non-cancer pain is we really don't know what the risk of addiction is when patients -- iatrogenic addiction taking opioids over long periods of time. We don't know if it's one percent, five percent, eight percent.

There is the increased risk of addiction when the preparation is chewed rather than swallowed, the risk of inadvertent overdose and death.

Patrick Stewart, a 24-year old man who died in California, pictured with his mother here, Barbara Van Rooyan, bright and promising future, college student, actually the grandson of a physician, one of the physician founders of U.C. Medical School at Davis, not a regular drug user, had taken one OxyContin and drunk a beer at a party and died from that. And I'm afraid this -- there are

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many bereaved families around the country that have been in a similar situation.

I'm real concerned about the risk of a false sense of security about an "abuse-resistant" preparation fueling increased opioid prescribing, increased availability, and increased public health problems.

I am concerned about the risk of the manner in which this drug could be marketed and promoted. Purdue Pharma took a drug that was basically comparable in efficacy and safety to other available opioid preparations, and in the most aggressive and heavily financed opioid promotion campaign in the history of the industry made it a blockbuster drug.

I think this is very notable. In 1990, six years before the marketing of OxyContin, it was reported in a mainstream medical journal that Purdue's MS-Contin had been abused in the very same fashion OxyContin later to be abused, meaning being crushed and

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injected, and had in a major metropolitan area become the drug of choice, surpassing the perennial favorite, Dilaudid.

And, of course, this was shown in the new drug application that this was -- you know, 70 percent could be recovered.

So we had -- some of these slides were prepared before I saw what we had today, and I do think abuse resistant is in quotes, should be in quotes. It may be tamper reduction is more appropriate to what we've seen. I'm concerned about how much can still be extracted in the studies.

I'm concerned about the 60 and 80 milligrams not being covered with a tamper reduction. I'm concerned about the fact that we need to have much enhanced oversight over the marketing, and the biggest thing -- we need to replace, rather than supplement, the current preparation, and perhaps this can --

DR. WATKINS: Thank you.

Our next presentation is a group

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presentation by Ellen and Peter Jackson.

MR. JACKSON: My name is Pete Jackson. I have no financial disclosures.

I am a biologist with the U.S. Environmental Protection Agency in Chicago. My wife, who is here with me, and I reside in Arlington Heights, Illinois, where we have raised two children.

The picture you see on the screen is our wonderful daughter Emily. This picture was taken in 2006 when she was 18 years old. A few months later, three days before she was to begin college, Emily was dead from OxyContin. Tragically, when Emily accepted this drug from a trusted relative, she was not told that it was as dangerous as heroin.

She was blind-sided. It was her only encounter with this killer drug OxyContin. One pill swallowed whole. What other drug can kill you with one pill?

For those of you on the ALSD Advisory Committee, she should look familiar.

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I showed you this picture on March 29th of last year when I came to call on the FDA to schedule a special public meeting to explicitly address the national epidemic that OxyContin has created. I begged you in my daughter's name that day to address this issue.

FDA still has not responded to my request. So I am back here with my wife to remind you and the FDA that we are still waiting. In fact, many thousands of American families are still waiting.

The FDA's approval of OxyContin in 1995 began a dramatic increase in the production and sale of prescription opioids in this country, as Mr. Zee just mentioned. Statistics indicate that the increase in the prescription of opioids is behind the rising mortality trend with prescription drugs, which are now the second-largest cause of unintentional deaths in the U.S. behind motor vehicle crashes.

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From 1992 to 2003, new abuse of all prescription opioids among teens was up an astounding 542 percent. And by the way, any statistics I give you are fully referenced and documented in my written statement.

It would be naive to believe that OxyContin was not the catalyst for this trend. Ten percent of teens have abused OxyContin. In 2005, an estimated 22,400 people died in this country from drug overdoses -- a toll largely attributed to opioid analgesics, which now cause more deaths than heroin and cocaine combined.

Again, the Joint Committee must recognize the introduction of OxyContin coinciding with the increasing number of deaths.

In Florida alone, prescription opioids caused 1,972 deaths in 2006. This is more than twice the number of U.S. soldiers who died in Iraq that year; 496 of these deaths were due to Oxycodone as the primary

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cause of -- suspected cause of death. And Oxycodone, as you know, is the active ingredient in OxyContin.

Oxycodone is the single most commonly reported suspect drug in mortality reports to the FDA -- the number one prescription drug killer, by your own FDA statistics, and you're considering releasing more of the product that killed my daughter.

My daughter is one of those statistics, and I am asking you not to turn your back on her.

The existence of this well-documented explosion of prescription opioid drug abuse since the introduction of OxyContin is proof that the drug control policies in this country have been an utter failure. FDA has taken a hands-off approach to the problem.

Regarding OxyContin, despite a variety of drug education programs, despite a risk management plan implemented by Purdue, despite ineffective FDA warning letters and

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labeling changes, and, incredibly, despite Purdue Pharma's guilty plea to a felony charge of illegally misbranding OxyContin "in an effort to mislead and defraud physicians and consumers" -- those are the words of U.S. Attorney John Brownlee -- FDA allows Purdue to continue to market OxyContin for a wide variety of moderate pain indications.

With the blessing of the FDA, Oxycodone production levels are even higher than last year. OxyContin pills continue to flood our nation's medicine cabinets and school lockers, and people continue to die in increasing numbers.

Meanwhile, a number of prominent reviews and studies have cited a lack of evidence on the long-term efficacy and safety of opioid therapy for chronic non-cancer pain.

Will someone please explain to me why the FDA continues to ignore all of these deaths and those who suffer the adverse consequences of OxyContin being so widely

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distributed in our country, like aspirin? How many more people need to die before the FDA will do something to stop this epidemic?

FDA plays a crucial role in the solution to this problem. After all, it was FDA that approved this drug. FDA has the authority to withdraw the approval of a drug, restrict its distribution, or negotiate labeling changes, and passage of Public Law 110-85 last year significantly enhances the agency's authority to effectively regulate drug safety, including drugs that are already on the market.

The official purpose of today's meeting -- at least in my opinion it is secondary -- the primary issue should be: what do we do with the existing products that are on the market? But the official purpose of today's meeting is to consider a new drug application for OxyContin that is purportedly tamper-proof, or make that tamper-resistant.

The FDA needs to be very leery of

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approving a new formulation that, upon approval, would be heavily marketed as tamper-resistant by the same company that pleaded guilty to a felony charge of lying to doctors about the safety of the original formulation.

It defies logic and reason that Purdue -- convicted, corporate felon -- is still in business selling the same drug, given this legacy of death and deceit.

I have been thinking very hard about this since I submitted my written statement. And I am unable to reconcile FDA's review of this NDA with this company's felony conviction. I do not understand how the FDA, an agency of the Federal Government, can even entertain an application from a company convicted of a felony by that same government when the company is still on probation for its crime.

FDA must realize that OxyContin is not only a dangerous drug, the legacy of death of OxyContin is also attributable to the

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reprehensible and unethical marketing practices of Purdue Pharma. Purdue's conduct in making false representations about its drug to doctors is well documented. In light of the company's recent felony conviction for lying to doctors, I believe that the FDA should not approve the new drug application.

I also believe that the FDA must restrict all existing formulations of OxyContin to severe pain cases only.

Finally, the FDA needs to hold a special public meeting to address the much broader opioid problem.

You have yet another opportunity to reign in this killer drug and save many lives. In my daughter Emily's name, I ask that you advise the FDA to reject the NDA and properly restrict the existing formulations. If FDA cannot effectively regulate OxyContin in a manner consistent with its mission to ensure the safety of drugs for the U.S. market, then it should be removed from the

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market all together.

OxyContin is interchangeable with heroin, and is its chemical equivalent. It is time that our drug policies reflected these facts.

In closing, I would like to show you some pictures of young people who we have lost to OxyContin, including several who died since we were here last time to ask for your help.

(Whereupon, several pictures were shown.)

Thank you.

MS. JACKSON: My name is Ellen Jackson. I'm a licensed clinical social worker, and I work as a school social worker in Illinois. I'm also the parent of a child who died after taking one OxyContin pill after she had been drinking alcohol.

This was the first time she had ever taken the drug. She was not a drug addict, just an 18-1/2 year old kid who had

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just graduated from high school.

My daughter Emily suffered from anxiety disorder. This was diagnosed after she learned at age 15 that she had thyroid cancer which had spread to her lymph nodes. Emily spent the summer of her freshman, sophomore, and junior years of high school having surgeries to remove the cancer and the lymph nodes.

At her last visit to Mayo Clinic in May, before her high school graduation, it looked like Emily may have been cured. There was still a dark spot on her ultrasound, and she was due to go back to Mayo in November of 2006 for follow up.

We never found out if she beat her cancer because she died that August. I tell you her story because Emily was a victim of this drug OxyContin. Of course, she shouldn't have taken this drug, which was given to her by a trusted relative. I believe she took it because she thought it could relieve her

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anxiety.

Emily did a stupid thing. Eighteen-year olds do stupid things all the time. Most of them get to learn from their mistakes. Emily paid for her mistake with her life.

This morning we heard numerous statistics about emergency department visits regarding those who had taken opiates and were treated. Where were the mortality statistics? How many others like my daughter have died?

It's my understanding that there's thousands of people who have died after taking OxyContin. Why doesn't FDA do something about this dangerous drug? Other drugs have been pulled from the market due to safety concerns, like Vioxx, drugs with nowhere near the mortality track record of OxyContin, yet FDA sits by year after year allowing OxyContin to stay on the market when it can cause many to -- cause death to many who take it.

FDA seems to care more about food

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that is toxic to pets than it does pills that kill people.

I ask that you look very seriously at OxyContin, which has caused so much pain to those who have lost loved ones who took it and died. This drug needs to be treated differently than all other drugs, because it can kill when only one pill is consumed.

If cigarette packages have warnings that say smoking can kill you, then OxyContin prescription bottles should have had the same warning on them. Smoking cigarettes can kill you, but only after you use them repeatedly for many years. OxyContin can kill you after you take it only one time.

I lost a beautiful child just beginning her adult life to this drug. I used the money saved for her college to bury her. I speak for all the other parents who have lost children to this dangerous drug. We will never see our children get married, have children, have a career, have a future. I

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will never get to have another Mother's Day with my daughter.

FDA, you need to take steps to make this drug safer. And until you can guarantee that one pill won't kill someone, you should be taking OxyContin off the market, not approving new formulations.

DR. WATKINS: Thank you.

CHAIR FARRAR: The open public hearing portion of this meeting is now concluded, and we will no longer take comment from the audience.

The Committee will now turn its attention to addressing the task at hand, the careful consideration of the data before the Committee as well as the public comments.

In moving forward, the next step is the Committee's opportunity to ask questions of the various presenters. And I believe, Dr. Haddox, you are moderating for the Purdue folk, and questions can also be asked of the FDA presentations as well.

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In a similar manner as before, please indicate your interest in speaking. We will try and write your name down and call you in the order in which you have indicated you want to speak. If we seem to miss you, I apologize up front, but just let us know and we'll try and indicate that.

Does that mean you want to speak? Okay. Dr. Burlington?

DR. BURLINGTON: Yes. I'd like to start with Dr. Haddox. Clearly, you are advocating that your product's tamper-resistant features, or some words to that effect, be included in the labeling. And could you go over for us what were your key considerations in reaching that conclusion? And also, how would you label the unreformulated 80 milligram tablet?

DR. HADDOX: We have given a lot of thought, as I mentioned earlier, about the language proposed -- that we proposed to the FDA, and we have -- I could bring that up

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again if we need to.

But I think it was pretty obvious what we were proposing, that we want to include information in the label about the 10 through 40 milligram that distinguishes it from the 60 and 80 milligram, so that physicians know the difference between those two formulations, and that they can make their -- having accurate medicine about -- accurate information about the medicine, can make appropriate prescribing decisions.

It's important to realize when you are caring for patients, as the prescribers here on the panel know, you are dealing with individuals, and it's a tenet of pain care that you individualize therapy in every single case.

And as a physician, I want to know what the advantages/disadvantages, pros and cons, of a particular formulation are. When I was in practice, I did that all the time -- comparing one anti-depressant to another anti-

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depressant, for instance, in a given individual to try and decide which was the best one for that person.

The other thing that you know is we have had a tremendous amount of misconceptions already. Confusion is reigning. Even though this drug has not even been subject to an approval decision yet by the FDA, there are people out there who are saying it's abuse-proof, which it's clearly not. There are people who are seeing it's abuse-resistant, which it may be, but we don't know that yet, and we won't know that until the end of the studies that we do.

What we can demonstrate is that to certain forms of tampering it does have more resistance than the original formulation, and we think health care professionals need to know that information.

DR. WATKINS: Dr. Soriano?

DR. SORIANO: Sul Soriano. This is a question for the sponsor as well as

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SAMHSA. I think this application is built on the premise that by decreasing the yield of the drug from this preparation will result in decreased abuse.

Now, is there any epidemiological data that show that indeed this approach actually has some public health benefits at all?

DR. HADDOX: Well, I don't think there are data now, which is why we proposed the epidemiological study as part of our RiskMAP, to find out what the effect of this formulation is once it is actually available and assuming that the 60 and 80 are also approved in the new formulation once the supply pipeline has sort of been transitioned over to where the only OxyContin available is in the OTR formulation, and then look at it systematically and see if it makes a difference.

This has not really been tried on a large scale, to my knowledge, in the past.

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There have been a few attempts here and there but nothing of this magnitude. So I don't think there are data, which is why we proposed a study, and it's part of the RiskMAP to find out.

I would welcome any comments from the SAMHSA folks, too, though.

DR. SORIANO: Well, if someone from SAMHSA can come up. But the other -- the follow up to that is that, certainly, if you break down two pills of 80 milligrams each, if you do the same thing to 100 pills of 10 milligrams each, you will still get the same amount of yield. So that's why I posed the question of whether or not there is any efficacy in this new formulation.

DR. HADDOX: Well, if there is -- I'll let Nick -- are you going to come up? I'll talk until you get up here.

PARTICIPANT: Just that we don't have the data to answer that question right now.

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DR. HADDOX: Okay. And if that question does get answered in a positive way, I think it will do with what Dr. Henningfield talked about, the response cost. What we don't know is what is a sufficient enough barrier, an impediment, to drive an individual away from abusing one formulation and doing something else instead of perhaps not abusing at all? That's an unanswered question.

In a laboratory setting, in a given individual, you can build in paradigms with increasing effort, so you can sort of get a behavioral economic study. But that's one individual. And even if you do a bunch of them, you'll find a big range, as he said, that the break point varies so much between people.

So we don't really know what that answer is, and that's why we want to do the study.

CHAIR FARRAR: Dr. Gardner?

DR. GARDNER: I have a question

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also for the sponsor. I haven't heard anything today about a clinical program for this formulation, and I wondered if clinical trials are scheduled or in progress or planned. And along with that, are children or youth to be included in clinical trials with this formulation?

And the second thing -- question while you're there, I wondered if you have a projection for how far behind the 60 to 80s are in the trajectory for the other strengths that we have seen today?

DR. HADDOX: Well, one of my clinical research colleagues can help me answer the first part. I will address the second part.

We will be ready to submit the SNDA, assuming the NDA for the 10 through 40 gets approved, within about 30 days of that approval. And then it will take the FDA -- I think the regulatory time is somewhere in the four-month range to approve it.

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We anticipate that the turnover in the marketplace will actually be relatively rapid, because once we get approval we will start filling all new orders with the OTR formulation, regardless of what strength it is for, assuming we have an approved formulation in that strength.

And the people who know that part of the business a lot better than I do tell me that's a matter of months, that it will sort of change out in the marketplace.

DR. GARDNER: Excuse me. Will you withdraw all of the existing non-tamper-proof product that is on the market now?

DR. HADDOX: We do not have a recall planned, because, apparently the -- again, this is the business part that I just confess, as a doctor, I don't really understand it that well.

But what my commercial colleagues tell me is that the suppliers are managing their inventory for commercial reasons on

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their end at a fairly low level, so that once we start filling new orders with the OTR it will change over in the marketplace fairly quickly, in a matter of months.

The concern about a recall program is, do we create artificial shortages for patients who need this medication? And, remember, you know, one of the concerns here is not so much what patients are doing with the medicine. It's what non-patients are doing with the medicine.

And as our research objectives, you know, were based on, the first thing is we don't want to cause new problems for patients if we can possibly avoid that.

Can someone help me about the clinical trials? I know we did bioequivalency trials. Obviously, that's the data we're submitting. Dr. Harris in our clinical research -- does he need to come to the microphone?

CHAIR FARRAR: Yes, please.

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DR. HADDOX: Okay.

DR. HARRIS: Yes, I can address that question. I'm Steve Harris, Head of Clinical Pharmacology with Purdue. And as far as the clinical work that we have conducted with the new formulation, we have completed and submitted the results of a series of bioequivalence trials, comparing the new formulation, OTR as we call it internally, to the initial formulation of OxyContin.

We have examined healthy subjects dosed with both formulations in cross-over fashion, in the fasting state, in a set of studies, as well as in the fed state in a set of studies. So we have established to the standards that are specified in FDA guidance documents for the comparison of formulations, that the formulations are what is termed "bioequivalent," which is a surrogate for therapeutic equivalence.

We have also conducted studies across the range -- the full range of the new

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formulation dosage strengths to show that they are what is called "dose proportional," so that the exposure that results from a 20 milligram new formulation product is twice that from a 10 milligram formulation product. And we examined that across the full range of doses.

CHAIR FARRAR: So just to make sure, the answer was no, you are not planning any more clinical research.

(Laughter.)

DR. HARRIS: Oh, I didn't -- was that -- yes, that's true. The submission is based on the bioequivalence studies.

CHAIR FARRAR: Dr. Bickel?

DR. BICKEL: I have a couple of questions for the sponsors. I was wondering what the rationale for maintaining the physical appearance of the new product -- you said you wanted to make sure that the physicians were able to discriminate the old product from the new product. Wouldn't it be

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helpful if others could discriminate it as well?

DR. HADDOX: Well, the -- you know, as a prescriber, a former prescriber, I think it's very important to -- when I had patients who got changed to a new formulation, if it didn't look very much like the old one, that was a problem for them. They had a lot of questions. They caused -- it caused a lot of unnecessary anxiety.

The physicians and the patients who are taking this medicine know what these tablets look like, and our goal was to sort of emulate that, to the degree possible. But as you saw from the slides, these are a little chunkier tablets, little fatter tablets, so there will be some questions I think. But the goal was to try to -- since the idea is a replacement strategy, is to make this look like OxyContin.

DR. BICKEL: The other question I have is about the availability of the lower

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doses with this new formulation, while maintaining the higher doses, even for some period of time, without that formulation. If we take a strictly behavioral economic view, the higher dose tablets, then, would have a lower unit price. They would be cheaper. They wouldn't take any effort to manipulate in order to produce the drug.

I would expect, all things being equal, that there would be a shift away from the lower concentration and to the higher concentration for that period of time that the higher concentration is not formulated in this new way.

Any comments?

DR. HADDOX: Well, I think that's one plausible outcome during the transition period. Remember that 83 percent of the prescriptions for the current formulations -- all of them, generics included -- are in that 10 to 40 milligram tablet range. So we'd be replacing a substantial portion of those.

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But you're right. If the 60 and 80 milligrams still have vulnerability, then that may become a more enhanced target for the very reasons you cite. That's why we spend so much time with educating physicians about how to address proper patient management, how to identify abuse, how to prevent diversion, how to interpret urine drug tests, and why we have the other elements of the risk management program.

DR. BICKEL: One last question. Although I appreciate your epidemiology study, we saw, you know, such a wonderful array of data, and I was wondering if it may be possible to think about a more multi-modal assessment of the impact of this medication than merely looking at the outpatient treatment programs, given that, you know, we saw from the presentation earlier a lot of different ways of looking at the impact of this medication, looking to see whether it has a favorable outcome, and it could be looked at

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in several different dimensions that are not equivalent to each other.

So I guess the real question I'm asking is, you know, why that one? Why not others? Why not a more multi-modal approach?

DR. HADDOX: Well, actually, we agree with you. And what I focused on during the presentation was the long-term epidemiologic study, because FDA's position has been that they would not allow an abuse-resistant, as opposed to a tamper-resistant claim, until it was proven on that basis. And that's why I focused on that.

In fact, we will continue to monitor the databases, as you've heard here today mentioned -- TEDS, the Monitoring the Future, the National Survey on Drug Use and Health, DAWN, both the medical examiner and the emergency department components.

The RADARS system, we will continue to monitor that, because that will also include Oxycodone controlled release

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products. In addition, there are two other assays or assessments that we have planned. One is using a vendor to -- who frequents these drug abuse chat sites that we talked about, and there is a fairly active community of people who create what we refer to as Internet chatter about drugs and drugs of abuse and how they are abused.

We think that may have us some early indications, based on the content of those chatters, about this particular formulation compared to the original formulation or other comparators in the marketplace.

In addition, we also plan, using those drug abuse sites as portals, to push out a pre/post survey of people who are admitted drug abusers who are willing to take a survey on their behaviors. And we plan to do that as well, so we are planning a multi-modal approach. Hopefully, what we will see is all of these will sort of converge in the same

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direction, but we will see what the data tell us.

CHAIR FARRAR: We're interested in an ongoing conversation here, but the number of people that have asked to speak here is very large. So if folks could keep their questions short and concise and the answers as well, it might help us move along. But I don't want to cut off conversation.

Dr. Wolfe.

DR. WOLFE: In your slide 45 which is physically manipulated followed by extended extraction time at room temperature, we've just heard from your pharmacologist that you have worked it so there's a proportion amount of drug available in proportion to what the dose is supposed to be. But just the upper part of this slide, if you can get it up there, that would be fine.

There's a quite predictable and narrow range of how much is released from the old formulation, 91 to 107 percent, 96 to 101,

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and so forth. But then when you get to the new formulation, as you pointed out, this is different as a function of whether it's the 10 mg or 80 mg, but the ranges are enormous, 32 percent up to 78 percent, 22 percent up to 66 percent. So they are one and a half to threefold variations in the percent of the drug that's released as presumably a function of different sized pills.

I mean, how is this possible given that you claim you got this technology down? Why is this happening? Is it happening because it's not a good sampling or what? And these are variations, which for me have a huge public health worry because at the abuser level if you think that it's only going to half available, you may use a certain amount. But if it turns out that 100 percent is available, you may wind up killing yourself. So could you just answer the question why there are these huge ranges with the new formulation milled and then extended

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extraction time at room temperature?

DR. HADDOX: Is this the slide to which you're referring, sir?

DR. WOLFE: It is and we're talking about really the first line in the slide on the upper part, new formulation 32 to 78 -- Why is that going on?

DR. HADDOX: Okay. I'll let Dr. Mannion who is the pharmaceutical expert address that.

DR. MANNION: First, let me start by reiterating that there are no standardized methods for doing these tests and the way in which the tablets are treated in preparation for doing these tests is we first treat the tablets in a mechanical mill and that mechanical mill has a slightly different effect on every strand. It's not so much a matter of the individual strands, but more the way that the test is done.

Sorry. I'm losing my voice here. I've been talking too much. So the

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variability is not necessarily -- is partly the result of the test being done in a way which there's no real standard way and this is not the same as testing, for example, a pharmaceutical product as a release test where you would expect to get a consistent number each time.

Thank you.

I could also say that part of the reason why you get great consistency for the current OxyContin product is because the numbers are pretty much a case of all the drug coming out for most of these tests. As you can see, when you do the same test on formulations when you do tests where the product doesn't release its entire contents, for example, those on the bottom row, you tend to get similar variability in the current OxyContin product.

DR. WOLFE: So what you're saying is that the kind of a variability you have depending on whether you press for three or

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five seconds or a minute on the coffee grinder, but that was done to try and simulate the circumstances in which they're abused.

So my question and problem is still at the abuser level which is you're trying to reduce abuse unlike your claim that you had reduced it back when you had put this drug on the market is how is abuse going to be reduced if you have these huge variations in your no standardized protocol and, certainly at the drug abuser level, there is also no standardized protocol.

DR. MANNION: Let me clarify a few misconceptions. Firstly, I think you made a slip of the tongue. Sorry, Dr. Wolfe. You mentioned something that was confidential.

DR. WOLFE: What did I mention?

DR. MANNION: You mentioned the method of milling.

DR. WOLFE: You said a grinder there. You said that yourself.

DR. MANNION: No, sorry. Well,

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I'll go back and answer your question. Your question was how does this formulation reduce in part time for resistence and I think you're looking at the data -- You need to look at the data across multiple levels.

Firstly, you have to look at these two rows in their entirety. You have to look and think the top row has been milled. The bottom row has been crushed. The amount of pretreatment in order to even get to this stage is significantly greater than the amount of pretreatment to get to here. A potential abuser has to go through an extra step even to get to this stage where they can start to see that variability.

Now when they do a standardized test, the test is not done in a variable way. The test is done in a way where the tablets are exposed to an equal amount of stress. But clearly when you're looking at small numbers of tablets and tests which are not industry standard tests, you can get some variability

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in the results of those tests. But I think it's important to take into consideration. But even to get there, the tablets have been manipulated in ways --

DR. WOLFE: How small is the number of tablets?

DR. MANNION: For each of these, we were looking at a -- Now I need to go into some clarification of the data that you see in here. The data here are arranged from 10 mg to 80 mg.

DR. WOLFE: Right.

DR. MANNION: So that's seven different strands. Then each test is repeated twice. So effectively, the -- is 14 for each of these rows.

DR. WOLFE: Okay.

CHAIR FARRAR: I think in the interest of -- there are lots of other questions that we need to move on.

Dr. Maxwell.

DR. MAXWELL: Yes, sir. I have a

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few questions about the epidemiological study. Your handout refers -- One handout refers to and you referred to as a long-term study. I'm a little concerned that four quarters pre and four quarters post is long-term. It doesn't meet the criteria I don't think.

However, some other questions very quickly and we could just yes and no but some of my concerns, you're going to use 68 methadone programs. You'll get very different results with the methadone programs and long-established heroin markets versus new methadone programs in areas where OxyContin is the major reason for these programs.

The methodology, are you going to take just any patient that walks in? Will these only be brand new patients? Will these be repeat patients? Will these be patients who have been in treatment eight years and you just happen to ask them?

I'm getting very concerned about risk surveillance and do the methodologies,

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will they meet the criteria of a peer-reviewed journal article? How are you going to choose these patients that are going -- And given the questions about coloring and formulation new or old drugs?

DR. HADDOX: Yes. Okay. A lot of questions. Let me see if I can sort of boil it down. First off, the RADARS Study Opioid Treatment Program has 68 sites distributed around the country and we know from the 15,000 admissions or so we've tracked to date that a significant number of them are abusing OxyContin as well as other prescription opioids. So I think that addresses one of your points.

The second point I think about the new formulation looking like the old formulation, was that one of your questions?

DR. MAXWELL: Yes.

DR. HADDOX: We will asking that particular question. We have done some pilot data to show that the people are actually

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reasonably good at picking out what they say they're taking and actually picking out a photograph of what they're abusing in this particular program.

Secondly, we are going to analyze the OxyContin data together. So if there is, let's say, I'll just pick a number, 10 percent of the people abusing the old formulation and 90 percent are abusing the new formulation or visa versa, we're just going to consider that as one number at each site. So we're going to compare the pre/post value at each site as well as at the aggregate.

The issue about the long-term, if we had a graphic that it's the four quarters prior to approval of the first, the 10-40, the NDA that's being considered today and then four quarters after the availability of all strengths in OTR and time for the supply pipeline to have filled up with the new formulation. We won't wait until every last tablet of the original formulation is

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exhausted in the marketplace. But we think as I said this is a matter of months not years. So we have some period of time between approval of 10-40 actual marketability in the retail sector, then approval of 60-80, availability of that, time to sort of flush out the supply pipeline and then those four quarters. So it's not four quarters and then four quarters right on top of it. It is going to be stretched out probably over a few years to actually do this properly.

Did that get all your questions?

DR. MAXWELL: One more question. Let me go back again. Just the concern about your response earlier that you want the pill to look about the same so that there's not a question. Clearly, DAWN won't be able to pick it up if the patients are coming in and they were taking a pink pill.

DR. HADDOX: Right.

DR. MAXWELL: So, I mean, either/or, which is it?

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DR. HADDOX: In the methadone program, we're going to put all that together so it won't -- I mean, we're going to ask them to distinguish, if they know, between if it's a new formulation or an old formulation. But we're going to sum that data. So we're going to look at the use of OxyContin in the past month to get high in the four quarters prior and those four quarters, some number of a determinant quarters later. So, if anything, if there is a original formulation still out there, it will sort of dilute the positive aspect of the results.

The other question you asked, I think, was how do we pick the enrollee. It's offered to every new admission and it's this one page questionnaire and those that complete it, complete it. So it is possible that we, in fact, have picked up some people who are coming back. But we should not be picking up people or RADARS shouldn't be picking up people who are in ongoing treatment. These

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are only new admissions.

CHAIR FARRAR: Dr. Day.

DR. HADDOX: And the other question is we have published some information on this. The RADARS system has published some data and Dr. Rosenbloom has it. So we think it is publishable. Okay.

DR. DAY: This question is for the sponsor. So much of what we're doing today is deciding the first question and that is do the data convince us that the new formulation will decrease the chances of abuse, misuse and diversion. So I want to make sure we understand where the numbers came from.

In the laboratory, there are various manual means. There are hammer strikes and spoon crushings and so on. Were the laboratory testers blind with respect to which formulation they were testing at a given point in time, whether it was the original or the new formulation?

DR. HADDOX: No. It would be very

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difficult to blind it particularly with spoons because you functionally cannot fracture the --

DR. DAY: I'm saying once you put the pill on the spoon or you put the pill on the table and you take the hammer. There is a way with the -- At least, one of the tablets that you showed us says OC or OP. You could put it, say, face down so a person might know as easily. I'm just wondering whether the tester was blinded with respect to which formulation.

DR. HADDOX: No.

DR. DAY: No. And then the second question is did they have a fixed amount of time to apply whatever method they were using or they just did it until they --

DR. HADDOX: Let me ask Dr. Mannion whose is the expert on the tamper protocol to address that.

DR. DAY: I mean, that would include like the number of hammer strikes. I

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mean, was there a fixed protocol that was applied to all of the tests?

DR. MANNION: Let me go back and address the question that David just responded to with regard to blinding. It would actually be very difficult to maintain that blinding for any significant length of time just because of the dramatic differences they're seeing when the tests are carried out.

Now let's go back again to your question about standardization. The tests can be divided into two different categories here. I showed images of hammer strikes and the spoons tests. The hammer strikes and the spoons test aren't part of the standardization testing protocol. So these are really just empirical tests that we did to determine whether we had achieved the right physical properties of the product. Did it have the plastic type makeup that we were trying to see?

Now you come onto the second type

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of tests which are the tests which are part of the protocol and those tests were standardized. Those tests are carried out for a fixed time period. They are carried out in a fixed volume. They are carried out for a fixed time at a fixed temperature. So the tests in the standardized protocol are as they sound. They are standardized tests.

The tests in terms of like the hammer strike and the spoons are not standardized tests and if you remember, I just showed visuals. So it just shows that the hammer flattens the tablet. The spoons crush the current formulation. It is able to break the new formulation. But then take those samples and test them in any way.

DR. DAY: At slide 37, it does say that the percent of the product released following manual crushing.

DR. MANNION: Okay. I have addressed that.

CHAIR FARRAR: I think question

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has actually been answered.

Dr. Cortinovis.

DR. CORTINOVIS: We've heard from the epidemiologist today that the intravenous route is a recognized method of abuse of OxyContin. This is directed to the sponsor. You have presented us with data today saying that the new proposed agent, the new formulation, is not likely to be utilized via the IV route because using current street preparatory methods the material turns into a gel that's readily difficult or is not readily easy to inject. I've worked on a professional basis with intravenous drug users and they are very creative.

What I'd like to know is have tried injecting this gelatinous substance into animals. Have you tried just squirting this gel into a beaker of human blood? If so, if you've done any animal studies, is this gelatinous material pharmacologically active? If you've tried putting it into a beaker of

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human blood, does this rapidly or readily dissolve the substance?

DR. HADDOX: Richard, do you want to address that?

(Off the record discussion.)

DR. MANNION: We haven't done any such tests.

DR. HADDOX: The concern that we're trying to address here is this sort of rapid, impulsive point of acquisition type of abuse and while I don't doubt that there could be with multiple stage extraction methods a way someone could extract the oxycodone with or without some of the occipients, we think that the fact that you can't aspire this through a 16 gauge needle is going to dissuade a significant fraction of those people who would try to inject.

CHAIR FARRAR: Dr. Nelson.

DR. CORTINOVIS: May I have just one follow-up on that? Trying to -- The way you presented the information to us trying to

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inject through a 16 gauge needle on a TB syringe is far more difficult than trying to aspire the same stuff through a 16 gauge needle in, say, a five or 10 cc syringe or the syringe itself.

CHAIR FARRAR: But my understanding is the testing was not done.

DR. HADDOX: Yes, the animal testing was not.

CHAIR FARRAR: Dr. Nelson.

DR. NELSON: Yes. I realize we're talking simply now about abuse potential. We're not talking about all the other factors associated with inappropriate drug use, inadvertent and otherwise kind of -- not for this type of abuse potential.

But I guess my question comes down to the fact that a lot of what you're proposing with your epidemiologic study and the blog surfing and these other types of work are really post marketing surveillance studies which I think for the most part have proven to

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be fairly poor in many other past endeavors. I think that they typically take a long time. They don't provide the data you'd like them to provide.

So I kind of have two questions. One question is given this work that you're going to be doing that's going to take several years and the blog surfing, are there benchmarks or endpoints and are there fixes? When are you going to say this is a success and much more pointedly, when are you going to say this is a failure and we have to do something about it?

And I'll just ask my other question. In other words, you're going to see on the blog somebody says, "Hey, you can mix this and that together and, boy, this is great stuff." Are you going to then say, "You know, we were wrong and we're going to pull this stuff off the market because it's totally abusable." In other words, is there a point at which there's going to be something that

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gets done based on all of this work that you're doing with the methadone clinics and the other clinics? What's going to be the fix that's put in place once you recognize the problem and what's the problem going to be? What's going to be the benchmark to say there is, in fact, a problem?

I'll let you answer that, but my other question is since post marketing surveillances, I think it's what we do, but it's probably not really the best way to handle a problem like this which I think we could probably predict is going to turn out to be a problem. I mean, street pharmacologists are very smart and they will clearly figure out a way to get around this problem. Is there perhaps a role for very good pre-marketing work, more than what you're done already but, for example, focus groups. Instead of waiting for the blogs to tell you what's going on, find a bunch of these people out there who are the street pharmacologists

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and ask them how they'd manipulate this in order to get this to work and then fix it before it gets out there or don't put it out there. I'll let you answer.

DR. HADDOX: Okay. Well, the second question first I guess. We have not planned any focus groups. There have been other academic groups who have done similar things with formulations that share some of the features and they have suggested that, in fact, this may dissuade some fraction of abusers. So without having to repeat that, there are people who have done exactly what you've said, brought in groups of addicts who say, "Yes, I abuse this, this and this in the following methods" and let them play around for a while with something and see what they think.

DR. NELSON: But what do you do about it when they find out, so if you brought in this -- the people in the focus group?

DR. HADDOX: The main -- I think

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we need to remember that this is a drug primarily for patients, not to stop abusers. I mean, we hope it will dissuade abusers. But we're trying to make sure patients get what they need and the primary goal in the research was to make sure this was bioequivalent to OxyContin for patients. And so if, you know, OxyContin has been safe and effective, used appropriately for years now, the FDA has kept it on the market, I see no reason why that's going to change any time soon. It is a definite problem with the nonmedical use of OxyContin as with all the other opioids as well as the other medicines people often abuse with those, licit and illicit.

So to get back to your question about the internet surfing, it turns out that there is a growing body of evidence in this area, that, in fact, this is a fairly good, sentinel tool. So we may not have to wait that long to find something out. But the key here is, I think, implicit in the way you

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phrase your question, and if I misunderstood you please correct me, but I think you were addressing this issue of whether the tamper resistant qualities which we have demonstrated will actually translate into abuse resistance and we don't know that. Nobody does.

And that's why FDA has appropriately said do a long-term study and let's see if this actually works. That's the way to find out in terms of dissuading abusers. So no matter what the internet says unless there's something horrific that none of us saw coming, we have to play out the study and see what it actually tells us in the abusing population.

DR. NELSON: I understand that except I guess my question is we've recognized that this is going to be a potential problem and maybe we could be more proactive about it and rather than try to do a two-year follow-up study, if we found the problem ahead of time, maybe that would eliminate. We may wind up at

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the same point ultimately in two years and at which it said that this is not a viable alternative because it's still very abusable and I assume that bioequivalence is not here nor there at this meeting, I think, because we're not really deciding -- I think we're really talking about whether or not this is a tamper resistant, the term we're using.

CHAIR FARRAR: Yes, I think we can't solve this problem now. I think the company has been clear that they're not planning to do any of that. So you can make that as part of your recommendation.

Before we move on, we're at the time of the break and there are lots of questions still to be had and lots of discussion. I would like to ask the panel whether it would be okay to skip the break. If you have clear needs, then please go. It may actually make it quicker since there won't be long lines.

But let's move on. Dr. Lesar.

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DR. LESAR: I actually have a question that's related to the AB rating for a product like this. Assuming there will be a generic compound that has similar bioequivalence, will this be given exclusivity based on the purported imparting of "tamper proof" or "tamper resistant" characteristics to this product?

DR. HADDOX: I'm not sure I'm the best person to answer the AB rating question. Can one of my other colleagues address that for us?

(Off the record comment.)

DR. HADDOX: The FDA, I guess. Okay. Our regulatory guy says the FDA will answer that question. I don't really know what the answer is.

DR. ROSEBRAUGH: Neither do we.

(Laughter.)

CHAIR FARRAR: I would remind the panel that --

DR. ROSEBRAUGH: It's a concern.

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It's something that we'll talk to the lawyers about, but I can't give you an answer right now.

CHAIR FARRAR: Dr. Sang.

DR. SANG: So I appreciate the extensive bioavailability/bioequivalence/PK work that you've done. But just going back to the clinical research question, I wonder given the context why you haven't considered performing liking studies in select populations. They're quick to perform. They would help us understand some of the more clinical questions and the potential for, you know, really the potential that we're all concerned about actually.

And then as a corollary, since there are some PK parameters that we think may co-vary with likeability such as Cmax and Tmax, is there as much variability in your studies with Cmax and Tmax as there is with percent of the drug released with the OTR formulation as -- I mean, this really makes me

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wonder why you haven't presented some of the other PK data.

DR. HADDOX: Well, the PK data was done in the bioequivalency studies to assert that this is bioequivalent to OxyContin and therefore it meets AUC and Tmax bioequivalence regulatory criteria with appropriate competence intervals and so forth.

As far as the other question that you asked about liking studies, Steve, could you address that? We've had the discussion about it. There are a number of issues that we've gone over and I think Steve can talk about that.

DR. HARRIS: Yes. The issue of liking, I think, as I mentioned earlier, we've demonstrated bioequivalence and to us that means that the pharmacokinetic profiles of the new formulation and the old formulation for the same strengths meet the statistical and regulatory and therefore clinical definition of presumed therapeutic equivalence. So I'm

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not sure we would predict that in the liking study of the intact dosage forms that the two formulations would even be distinguishable.

The focus of the charge to the formulators for the new formulation was to make the controlled, released mechanism more durable, more resistant, to physical and chemical attempts to defeat it and so it would be only in the manipulated dosage form where I would anticipate seeing a difference if you were to do an in vivo study.

DR. SANG: Well, perhaps in different populations, you'll have the opportunity -- you would potentially have the opportunity to see how else the drug could be manipulated and perhaps then you could see how there may be differences in "likeability" given some of the innovative techniques that could arise from something like this.

DR. HARRIS: Yes. I guess those would address other methods of tampering and we'll have to see. That's obviously something

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we'll be looking at closely.

CHAIR FARRAR: Dr. Zuppa.

DR. ZUPPA: Just with -- I'm sorry. Just with regards to the bioequivalence studies, I just would -- if you could comment on the number of pediatric patients that were in that trial.

DR. HARRIS: The studies are all done in healthy adult volunteers. So it's 18 to 45 or 50. We've not done any studies in the pediatric population with the new formulation. That's not indicated for that formulation.

DR. HADDOX: It's also not indicated for the original formulation.

DR. HARRIS: Yes.

DR. HADDOX: That's why one element of the risk map is to monitor exposure to people under the age of 18, whether that's intentional or unintentional. That was in response to a specific request from FDA because we have not done pediatric studies on

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OxyContin. We are doing, I think, some of oxycodone now. Is that correct?

DR. HARRIS: Yes.

DR. HADDOX: But we are not -- We have not done them on OxyContin, the original formulation. We don't have an indication for childhood use.

CHAIR FARRAR: Okay, and Dr. Yesenko.

DR. YESENKO: This question is for the sponsor. My first question -- these are quick questions. The first question is when does the patent for OxyContin end.

DR. HADDOX: One of our attorneys maybe can help us with that. I'm getting a --

PARTICIPANT: 2013.

DR. HADDOX: Thank you. 2013 is the answer.

DR. YESENKO: The next question is the new formulation is less -- has the ability to less likely be abused. Some would say it's tamper resistant. Then what information

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should be included in the packaging or the labeling?

And then the last question is the formulated 10 and 40 will be on the market sooner than the 60 and 80. Will the original OxyContin still be on the market until the reformulated OTR is introduced?

DR. HADDOX: Okay. Well, let me answer that question because that takes a little more than a slide. There -- Right now, even though there are no generic companies that are shipping generic OxyContin because of the court resolution you saw FDA present earlier, there are still warehouses and perhaps retail outlets that have stocks of the generic OxyContin in various strengths. So that's going to be out there for some indeterminate period of time. I don't know exactly how long. I've heard estimates of maybe a year before that is totally drained out of the marketplace. So there's that that will be there regardless of what happens with

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the approval of the 10-40 OTR.

If the 10-40 OTR are approved, then there will be a transition period of several months where both of those are out there. So you would have 10 in the original and then 10 in the OTR formulation right through the 40. Then if the 60-80 get approved, then we would have another transition period.

What I'm told by people who understand the actual commercial supply chain much better than I do is that this is a matter of months during each of these transition periods with the wild card being the generics because we don't know if some of the wholesalers bought up large stocks of the generics when they heard we'd settled with one company, for instances, to keep their acquisition costs down. So we don't know what's sitting out there in warehouses. I can't give you a good prediction on how long it will take for the generics to sort of

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dwindle out.

In regards to the question about the language, this is what we have proposed in our NDA. This is part of it. There's another sentence or two that's in your background, but this is sort of the relevant piece here that would apply only to the 10-40 mg to distinguish in the package insert or the full prescribing information from the 60-80 which would not initially have these features.

CHAIR FARRAR: Dr. Passik.

DR. PASSIK: We've heard a number of people comment about the concerns about a false sense of security if this comes on the market as the only tamper resistant opioid out there at that point and then a lot of the conversation has been sort of as if pain patients and abusers are distinct populations and, of course, they aren't completely distinct. And so I'm particularly concerned about the higher risk group, the patients that have a history of substance abuse.

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Now there may have been prescribers who have moved away from OxyContin in their high risk patients because they know something about the use, the abuse, of it and abuse potential who may now say to themselves, "Maybe I should come back to it because it's the only tamper resistant opioid out there."

So what I'd like you to comment on if you could is what specifically planned in terms of educational efforts to avoid a false sense of security so that the thought is that, you know, anyone can be treated with this, even a high risk patient.

DR. HADDOX: In my remarks, I made a reference a couple times to the fact that we need clear, concise, accurate language in the FPI because that forms the basis of our communication to the healthcare community. You know, the academics can say what they feel the data show but we are limited by what the FDA allows us to say and that's one of the reasons we're here today to talk about what is

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that box that we can operate within because it will be very important for the reasons you cite and a few others that we can -- what we can tell the prescribing, dispensing community and the other ancillary healthcare professionals who are involved in patients who are taking these medications.

I think it's critical that we be able to tell them (a) this is no guarantee of abuse resistance, we won't say that, we won't know that, obviously, it can't be studied until the drug is available, (b) that it does have these tamper quality and (c) we've analyzed this much like MIC levels in antibiotic package inserts where they say these are the MICs in laboratory settings, but we don't really know if this translates to clinical practice.

We want to be very, very precise, very clear, so that we don't miscommunicate and yet we can address the miscommunication or misconceptions that are happening as we sit

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here today before FDA has even made a decision on the approval. So I think it's critical that we get some language that gives us that box that FDA has said, "Okay. This is what you can say." Yes, I think that's the answer.

CHAIR FARRAR: Dr. Kweder.

DR. KWEDER: Yes. Thank you. I have a follow-up on that. On the slide there you have the point that you just made. It's in the second sub-bullet including "precise information in the FPI is better than providing no information." If you go back to slide 27, I just want to be clear that this is an example of what you would call precise, a precise version of what your data showed. Is that --

DR. HADDOX: This is what we submitted in our NDA. We think this is an accurate representation of what the data showed. But, of course, you get to make the final call on that.

DR. KWEDER: Okay. Thank you. I

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just wanted -- just for clarification. Thank you.

CHAIR FARRAR: Dr. Fleming.

DR. FLEMING: I think Dr. Nelson a bit earlier hit the nail on the head when he was talking about the challenges and limitations of post marketing evaluation of benefit/risk. It's already incredibly difficult to do so for safety, but we are looking at in essence both benefit and risk being assessed post marketing and it's a bit reminiscent of Subpart H where there has certainly been a checkered history there where it's been extremely difficult to get the validation trials done in a timely way and achieving proper regulatory changes when the validation trials are negative is also extremely difficult.

I would actually like to follow up on the issue relating to the false sense of security and how that impacts the proper scientific design of the epi study. But if my

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time is limited, I'd want to start with what I think is an even more important key question. Our materials pointed out in 1986 the WHO recognized the significant unmet need in nociceptive chronic cancer pain and they defined three steps, aspirin and ibuprofen type agents, codeine type agents and opioids, and Dr. Trunzo in her presentation talking about admissions to substance abuse treatment centers for abuse of opioid analgesics showed a striking over representation there of oxycodone users providing substantial evidence of a relative excess in serious safety risks for OxyContin even relative to other opioids.

So my question, possibly a two-part question, is are you currently or will you plan to limit competitive promotion of this reformulation specifically restricting to the setting of severe chronic pain and, if not, in view of the excess in serious safety risks, what's the scientific clinical data on benefit to risk that would justify broader

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promotion?

DR. HADDOX: Well, I think your first question actually asked if we intend to change the indication. Did I hear you correctly?

DR. FLEMING: That is part of what I'm asking. So the specific question is in view of what is available on benefit to risk including clear evidence of excess safety risks would you specifically restrict your promotion to the setting of severe chronic pain and, if not, what's that scientific data that would indicate from a benefit to risk perspective that broader promotion is appropriate.

DR. HADDOX: Okay. I think I can address that. Step one is, of course, that the FDA determines the indication based on the evidence we've presented to them. Step two is that our indication is really three parts. It's not just moderate to severe pain. It's moderate to severe pain in patients where a

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continuous, around-the-clock, analgesic is needed for an extended period of time and I can tell you from personal experience and I think the literature would support that if your pain is moderate but it is around the clock requiring continuous analgesia for an extended period of time that is a significant impact on quality of life.

DR. FLEMING: We're not debating whether pain meds are needed. We're talking about whether the evidence is sufficient to justify your marketing this product in a broader sense than simply the setting of severe chronic pain, for example, when other opioids may not be adequate.

DR. HADDOX: Well, I -- I mean, I don't think there would be any different marketing than what we're doing right now. We market it for that indication that FDA has approved.

DR. FLEMING: And in view of the evidence such as what Dr. Trunzo has put

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forward that does show an over representation in oxycodone-related serious risks, what's the justification from a benefit perspective that would say your intervention has a comparable benefit to risk of other alternatives?

DR. HADDOX: Well, that's a complex question because it's really getting at who are those people who are showing up in TEDS. Are those patients for whom the drug was appropriately prescribed and monitored? Or are those non patients? I don't know the answer to that. I'm not sure if TEDS actually knows the answer to that, although I think she made some reference to that that it was probably more non-medical use.

The other issue is that while there is evidence that oxycodone-containing products stand out there are lots of oxycodone-containing products as the DAWN data showed that are being non medically used that are not OxyContin or, in fact, are not even in that long-acting oxycodone class. And lastly,

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the data from that and from other data in the literature suggest these people are often non medically using multiple substances which clearly increases the --

DR. FLEMING: Could I try one last time?

DR. HADDOX: Yes.

DR. FLEMING: Is there scientific evidence you can put forward from a benefit to risk perspective that would argue that your product should be a choice over, for example, other opioids when someone has a severe unmet need?

DR. HADDOX: I think that physicians are in the best position to make an individual prescribing decision for that patient that's sitting in front of them right there at the time.

CHAIR FARRAR: I think the answer and non answer is there.

DR. HADDOX: Yes.

CHAIR FARRAR: Dr. Nussmeier.

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DR. NUSSMEIER: Yes. This is a fairly simple question. If the tamper-resistant OTR formulation is approved and your plan is to get the supply line transferred over as soon as possible, why would it be necessary to leave the 80 mg original formulation on the market even temporarily?

DR. HADDOX: The reason for that has to do with a couple of things. One is that there are people who take the 80 mg who are in a payment situation where just adding multiples of smaller tablets will not work. We've actually done that analysis and there's a substantial number of people who have an artificial limit on the number of tablets they can actually have dispensed at any given period, usually a 30-day period, by their payer and so to just say, "Let's just take the 80s off the market and let's just give them twice as many 40s if they need that," that is a solution that would negatively impact a significant number of patients according to

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