FOOD AND DRUG ADMINISTRATION (FDA)

STANDARDS FOR FUTURE OPIOID ANALGESIC APPROVALS AND INCENTIVES FOR NEW THERAPEUTICS TO TREAT PAIN AND ADDICTION

PUBLIC HEARING

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P R O C E E D I N G S

OPENING REMARKS

DR. THROCKMORTON: Good morning everybody, and why don't we go ahead and get started? Welcome to the public meeting Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction. My name is Douglas Throckmorton. I'm the Deputy Center Director for Regulatory Programs at the Center for Drug Evaluation and Research, Food and Drug Administration. I will serve as the presiding official at this hearing. Before we get started, I'd like to give some background and review some of the Part 15 materials, procedures and then get going.

On June 21st, 2019, FDA issued a draft guidance on the application of FDA's benefit risk assessment framework to applications for the approval of opioid analgesic drugs entitled, Opioid Analgesic Drugs; Considerations for Benefit Risk Assessment Framework. As explained in the FDA's Federal Register notice announcing today's public meeting, while the existing benefit risk assessment has been and continues to be a comprehensive and effective mechanism for

evaluating all new drug approvals, including opioids. Given the current opioid crisis, it is critical that the FDA explore every possible option for effectively responding to opioid misuse and abuse.

For this reason, and in connection with FDA's commitment under the SUPPORT Act, this public hearing is intended to receive stakeholder input, not only on the benefit risk guidance, but also on the approval process for new opioids and on how FDA might best consider the existing armamentarium of therapies for pain among other factors in reviewing applications, renewal opioid analgesics.

FDA also seeks input on potential new pre-approval incentives in addition to existing incentives. We are aiming to foster the development of new therapeutics to treat pain and new treatments for addiction. Before I begin -- we begin I want to make a few administrative announcements. First, please silence all of your cell phones and other mobile devices as they may interfere with the audio in this room. Second, we ask that all attendees sign in, in the registration. Those who are outside, hopefully you

did that. Third, the restrooms are down the hall behind you and past the coffee area and down the hallway. Finally, copies of the presentations today are available on request. The contact information for making this request is available at the registration tables and will be on the monitors during our breaks.

I would now like to ask the FDA panelists to introduce themselves. I already have done that, so I'll look to have…

DR. THANH HAI: Good morning. I'm Mary Thanh Hai. I am the Acting Director in the Office of New Drugs at CDER.

DR. STEIN: Good morning. I'm Peter Stein. I'm Director at the Office of New Drugs in CDER.

MR. DAL PAN: Good morning. I'm Gerald Dal Pan. I'm the Director at the Office of Surveillance and Epidemiology in CDER.

DR. THROCKMORTON: There are two other individuals we hope will be arriving, and we'll have them introduce themselves when they do so. Thank you. For media at this point, there's Officer Sandy Walsh. Sandy -- put her hand up maybe. There you go. Thank

you. If any members of the media are here today, please sign in. If you have any questions or are interested in speaking with the FDA about this public meeting, please contact Ms. Walsh. The hearing is intended to give FDA the opportunity to listen to comments from the presenters, so the panelists and other FDA employees will not be available to make statements to the media. Although there are no rules of evidence for this public meeting, there are some general procedural rules. No participants may interrupt the presentations of another participant, and only FDA panel members will be allowed to ask questions of the presenters.

There will be an open public hearing at the comment period at the end of the day once all of the presenters are finished. Public hearings are public administrative proceedings and are subject to FDA's policy and procedures for media coverage. Representatives of the media are permitted subject to certain limitations to video, film or otherwise record FDA's public proceedings including the presentations of the speakers today. This hearing will also be

transcribed, and copies of the transcript can be ordered through the docket or accessed on our meeting website approximately 30 days after the public hearing.

Today we have 16 presentations, each of which are allotted 10 minutes. After each presentation, 3 minutes will be scheduled for the panel members to ask questions, if necessary. If a presenter finishes early or withdraws, or if the question from the panel do not take the fully allotted time, we intend to move directly to the next speaker. This means that the presenters may find themselves being called on to give their presentation before the time that's listed on the agenda. And although we may be adjusting the presenter's schedules as needed, we do hope to keep to our scheduled breaks. For the speakers, we have the timer lights to guide you, a green light -- green light will indicate when to speak and a red light when to stop. The timer will give you a 1minute yellow warning before the red light goes on.

If you do not conclude your remarks by the time of the end of the allotted time, we may ask you to do so or wrap your comments up quickly. If you did not

register to speak, but would like to present oral comments, you may do so during open public hearing which is currently scheduled to begin at 2:45. If interested, please sign up with the registration table outside the meeting room by 10:30 for an available 4-minute speaker slot.

We also strongly encourage you to submit your comments to the docket by November 18th, 2019. Please see the Federal Register for details on how to consent [sic] that. This hearing is being webcast live. This is not an interactive meeting. Again, only the FDA panel members are allowed to ask the presenters questions. In closing, I want to thank everyone including our panelists and speakers for participating today, and I'll look forward to a productive meeting. Thanks.

Dr. Bonnie, I believe you are the first speaker.

COMMENTS ON BEHALF OF AUTHORS OF NASEM CONSENSUS REPORT ON PAIN MANAGEMENT AND THE OPIOID EPIDEMIC (2017)

MR. BONNIE: So, my name is Richard Bonnie,

and I am accompanied by my colleague, Margaret Foster Riley. We've participated, both of us, in a study that was conducted by the National Academies of Sciences, Engineering, and Medicine which will issue a -- release a consensus report on end management and the opioid epidemic in 2017. The study was requested in 2016 with a -- by the FDA with a broad charge including among other things helping the Agency develop and implement a framework for taking public health considerations into account and opioid regulation.

I can say on behalf of the committee as a whole with whom we consulted for this presentation that we are pleased that the Agency has taken a decisive step forward to embrace the public health framework outline in the committee's report by -- and by issuing a proposed guidance document regarding the Agency's expectations, the manufacturers regarding the data that are expected during the NDA process as recommended in the report.

This is the first step in what we all recognize will be a challenging and iterative process. I also meant to say earlier that in drafting our

comments here and submitting them, we were joined also by Dr. Aaron Kesselheim, professor in the Medical School at Harvard and also Patricia --

MS. ZETTLER: Zettler.

MR. BONNIE: -- Zettler, sorry, from Ohio State Law School, all of whom -- Aaron was a member of the committee, and Dr. Zettler was -- contributed as a consultant.

So essential advice that is given by the committee in the 2017 report was that the FDA consider a broad range of evidence and apply a -- what we called a comprehensive systems approach in its regulation of prescription opioids. I'll just mention it is entirely appropriate to use a comprehensive public health approach to refer to what the committee recommended in the report.

I did want to highlight that the reason that the systems approach was used also as a way of referring to what we recommended was that the Agency actually also asked us to think about how to develop a formal model once the broad public health considerations were being taken into account that would

enable us to quantify the range of possible effects of different types of regulatory actions that could be taken, not only by the Agency in its work, but also by the other governmental agencies that regulate in this field.

We applaud the Agency for developing a draft guidance with the recommendations of the committee's report in mind. The Agency's proposal to consider broad public health effects in its overall benefit-risk assessment of opioid analgesic drugs is an important first step in implementation of the committee's recommendations and will lead to significant benefits for the public health. FDA should move to finalize the public health approach which balances the individual needs for pain control with considerations for broad public health consequences of opioid use in a disorder.

This approach is obviously permitted by the existing statutory authority, and we were pleased to see that the Agency recently, in responding to the Public Citizen's request for a moratorium, indicated quite clearly that they agreed with the committee's assessment also that initiating this public health

broad view of public health considerations in the Agency's decision-making in this area is well within the existing Agency authority. I quote from Dr. Woodcock's letter, you probably note that the draft guidance and the public discussion of the draft guidance builds on and seeks to formalize FDA's historic practice of considering the larger public impact of our regulatory decisions regarding opioids.

So, we applaud the Agency again for having taken this initial step. The -- they all are, however, mentioned in the report additional actions after this initial step is taken that the Agency needs to address to accomplish the public -- comprehensive public health approach. This is not the time obviously to go to them in depth but let me just mention three very important further steps that need to be taken.

First, it's very important to collect a wide range of data that bear on the public health consequences of opioid use and of the effects of public health interventions that go beyond obviously the data that's typically connected in connection with approvals and clinical trials. Secondly, it's important to

strengthen post-approval oversight, including the REMS as the Agency itself has recognized in these matters will continue to be intensified as we go forward. And then thirdly, and very importantly, the committee recommended a full review of currently marketed and approved opioids in a comprehensive study.

First with regard to the data, the -- in each data, not just from well-designed clinical trials, but also from other sources that can help inform an assessment of opioids public health effects. This should include traditional sources, as well as less traditional sources including non-health data to understand the real-world impact of opioids in the various domains that are important for a public health analysis. The FDA should quickly establish guidelines for the collection and analysis of such data.

With regard to REMS, FDA must take steps to improve post-approval monitoring of opioids. REMS is currently structured or not meeting public health needs for opioids. FDA should routinely provide public information about how well the REMS are achieving such goals. The Agency should consider convening a forum

that allows for public input to advise on appropriate modifications, and the Agency should immediately take steps to require any necessary modifications to the existing REMS including creative approaches such as academic detailing, educational interventions, post monitoring of messaging to healthcare providers and should use independent third parties rather than manufacturers to lead the REMS. A key advantage of initiating this process also is that it would enable the Agency to use actual real-world experiential data from drugs already in the market to help develop the framework by conducting oversight.

Oh, in fact I just blended my two slides here. Let me -- so this is what I actually was just referring to, the committee recommended importantly a -- an opioid -- what we call an opioid study implementation process to review currently marketed and approved prescription opioids to assess their safety and effectiveness based on the same standards that are applied to new drugs. The FDA -- the Drugs and Cosmetics Act, in our view, does not provide a legal basis for taking a different approach to assessing

benefits and risk for currently marketed products than it does for unapproved products. This process can be undertaken while assuring an adequate access for pain treatment options, and the cost should not increase as long as sufficient numbers of generic manufacturers continue to produce those opioid formulations that do remain on the market.

And again, as I have said out of order, a key advantage of initiating this process is that it would enable the Agency to use experiential data from drugs already on the market, helping develop the framework that needs to be developed for application of the comprehensive public health approach.

Then finally, in conclusion, the FDA's decision to consider opioids broader public health effects is a crucial step in the Agency's response to the opioid crisis. All these recommended actions, acquisition and analysis of new data, strengthening REMS and conducting a full review of all opioid drugs can be taken using FDA's existing statutory authorities. This is all part of a holistic approach to drug review that properly balances individual's need

for an adequate pain relief and public health requirements to combat opioid use disorder. Obviously, this is going to be a challenging process going forward, but obviously it is an urgent one, and we remain available to help the FDA in any way the basic bip [sic].

DR. THROCKMORTON: Down the table, to my panelists. Gerald, you'll have to raise your hand if you want to have, except (ph) based on that.

MR. DAL PAN: Dr. Bonnie…

SPEAKER: Mic.

MR. DAL PPAN: Dr. Bonnie, you had mentioned the use of less traditional sources of data. I can think of a lot of things that you might need. Can you give a few examples of things you might think are more important than other kinds of data sources?

MR. BONNIE: Well, in our comment letter, we did identify a number of these areas specifically that they thought would be indicative of the kind of data that we had in mind. And maybe rather than looking for it in the letter.

DR. THROCKMORTON: Okay. Great. Thank you

very much. Other questions? Pete -- Dr. Stein?

DR. STEIN: Thank you for the presentation. Can you say a few more words about the -- how you conceive that the OSI process, are you thinking about this as looking in groups of agents, or you're looking at this as individual agents? Are you looking -- and any comments about how you would prioritize or how you would select this, obviously it'd be a wide range of drugs that potentially could be included. How would you foresee that being organized just at a high level?

MS. RILEY: So, we didn't go into the detail of an individual versus the systems piece. I would say we started with a model deci (ph), but deci wouldn't necessarily control. What we're looking for is an effective review, and if you could group different classes with each other, that would be fine. What we're looking for is to understand the public health effects of the existing drugs as well. That's going to be very much tied to the data that is being collected at the same time because with all -- in fact all three parts of this are very closely aligned because you need the data, you need parts of the REMS pieces in order to

conduct that OSI review. We did not go into exactly the systematic way, where you would start, where you would end in having a group.

SPEAKER: Thank you.

DR. THROCKMORTON: Thank you, Dr. Bonnie. Next speaker is Dr. Michael Carome from Public Citizen's.

FDA'S RESPONSE TO THE NATIONAL ACADEMIES 2017 RECOMMENDATIONS FOR A NEW OPIOID REGULATORY FRAMEWORK: WOEFULLY INADEQUATE IN SUBSTANCE, DEVOID OF NECESSARY URGENCY

DR. CAROME: Good morning. I'm Dr. Michael Carome, Director of Public Citizen's Health Research Group. The following comments were prepared jointly with my colleague Dr. Sidney Wolfe. The only realistic interpretation of the first part of the title for this meeting, Standards for Future Opioid Analgesic Approvals, is that the FDA is very belatedly beginning the process of developing and seeking public input for such standards. That the title specifically refers for future opioid approval, not to a more expansive detailed opioid regulatory framework that already put

in place to evaluate currently approved and future new opioid analgesics is an admission of the dangerously preliminary progress the FDA has made thus far in developing such a framework.

This meeting was announced simultaneously with the now closed public comment period for the Agency's June 2019 draft guidance for industry entitled "Opioid Analgesic Drugs; Considerations for Benefit Risk Assessment Framework." Overall, we found the draft guidance to be woefully inadequate because its cursory content is far more focused on non-specific generalized factors that the FDA itself will consider when reviewing a new drug application for an opioid rather than providing industry with guidance as to what specific benefit and risk information should be sought out and included in future NDAs for approval. The non-directive nature of the draft guidance was bluntly stated by the FDA in the document's background section, "This guidance describes the various factors that FDA will consider in evaluating the benefits and the risks of an opioid analgesic drug. FDA encourages applicants to provide information relevant to these factors."

As an example of the lack of specific directive guidance, the draft guidance noted that the FDA will consider the following questions among others in assessing the effectiveness and safety of an opioid analgesic drug, "Do any comparative efficacy data exists for the drug relative to approved opioid or non-opioid analgesic drugs. Does this analgesic drug offer any advantages relative to available approved analgesic drugs for each indication with regard to effectiveness or duration of response? Do any comparative safety data exist for the drug relative to approved opioid or non-opioid analgesic drugs? Does this analgesic drug offer any safety advantage or disadvantages relative to available approved analgesic drugs for each indication?"

Merely "Encouraging applicants to provide information relevant to these factors," is an unacceptable replacement for a more specific recommendation that clinical trials, testing new opioids should include not just comparator control groups, not just placebo-control groups, to get quickly answered -- quickly the answers to these questions.

Among the important details lacking from the guidance are recommendations that companies seeking approval for new opioids review the previous evidence for diversion of similar earlier marketed opioids and that the companies discussed in the NDAs what intervention they plan to implement to ensure that their new opioids would be diverted less often than similar predecessor drugs as recommended by the National Academies in the 2017 report which was commissioned by the FDA in 2016 to review the status of FDA opioid regulation and to suggest improvements in it.

It is noteworthy that seven of the nine questions for today's meetings also deal with comparator assessment of the effectiveness or safety of new opioids, issues that were specifically addressed in the recommendations and discussion made in the National Academies 2017 report. Ironically, on June 20th, 2019, the day before the FDA's June 2019 draft guidance was posted for public comment, the FDA withdrew an earlier 2014 draft guidance that dealt with the same comparator safety and efficacy issues, but in much more detail and a properly directive manner as reflected in the

following excerpt among others.

"As previously noted, efficacy trials for analgesics should be superiority trials. Even if a placebo-controlled design is used, sponsors are encouraged to include an active comparator in single dose, as well as multi-dose trials. An active comparator may provide useful information on the relative utility of the investigation of drug in that population, particularly when there's already an analgesic that's commonly used for the type of pain under evaluation."

Including such specific recommendations in the FDA guidance would be fully consistent with the type of new opioid regulatory framework envisioned by the National Academies' report. Given that National Academies' additional recommendation that the FDA develop a process for reviewing and complete a review of the safety and effectiveness of all currently approved opioids, recommendation 66, using the still to be developed opioid regulatory framework which will likely lead to some of these opioids making a move from the market, it is imperative that FDA expand its focus

beyond just standards for approval of future opioids.

In April of this year, because of the then more than 80-month FDA delay in any meaningful public response, the National Academies' 2017 recommendations, we filed a petition with the FDA to immediately impose a moratorium on approval of all NDAs for new opioids and new opioid formulations. The petition argued that the moratorium should not be lifted until the Agency has implemented the elements recommended by the National Academies for inclusion in the currently non-existing opioid regulatory framework.

The petition denied on September 6 would have provided the FDA and relevant advisory committees the necessary time to construct and implement the National Academies' framework. We agree with many of the comments submitted jointly by the chair, one member, and two consultants of the National Academies committee expressing their own views in response to the FDA's June 2019 draft guidance, including the following which I'd like to reiterate, "The draft guidance is an important first step in implementing the 2017 report's recommendations that will lead to benefits for public

health. But they remain critical actions for the Agency to take using existing authorities to help address the opioid crisis in a balanced way and fully implement the comprehensive systems approach recommended in the 2017 report."

Although the draft guidance begins to implement the recommendations of the National Academies committee's 2017 report, much remains unstated in the draft guidance. We encourage the Agency to integrate more recommendations from the 2017 report in its final guidance or additional guidance documents with the goal of using the full reach of the Agency's existing authority. The National Academies committee recommended that FDA conduct a full review of currently marketed and approved opioids which would treat similarly all prescription opioid analgesics, whether being considered for approval for the first time or already on the market. There is no sound medical reason for using a different approach for assessing the benefits and the risk of currently marketed opioids than the Agency uses for valid applications for future unapproved opioids. Likewise, the Agency's authority

under the Food, Drug and Cosmetic Act does not provide a basis for taking a different approach for assessing benefits and risks for currently marketed products and for unapproved products.

We encourage the Agency both to move forward to finalize the draft guidance and to work to implement the numerous other recommendations in the 2017 report to embed considerations of these broader public health effects throughout FDA's regulatory framework for opioids. In announcing today's meeting, the FDA posed various questions about requiring a new opioids analgesics demonstrate a comparative advantage over existing analgesics, and about the authorities the FDA would need to impose such a requirement. We, the committee, believe that the recommendations in the National Academies committee's 2017 report would achieve much the same goals sought by a comparative advantage approach would apply to both existing market and novel drugs and have the benefit of being grounded in the Agency's existing authority. "Working to implement these recommendations therefore would be a way for the FDA to improve its efforts to address the

opioid crisis now without waiting for congressional action."

In conclusion, had the FDA acted with the urgency demanded by the ongoing opioid crisis and begun the important public process of developing a desperately needed improved opioid regulatory framework, soon after we received the detail, carefully considered National Academies recommendations 2 years ago, it is likely that the process of creating this framework would have been completed by now rather than just beginning. The FDA now must make the development and implementation of such a framework its number one priority. Thank you very much.

DR. THROCKMORTON: Thank you. Questions from the panel? Thank you, sir. Our next speaker is Ms. Kristin McGarity, National Council on Independent Living.

FDA OPIOID DRUG LABELS: A DISABILITY RIGHTS PERSPECTIVE

MS. McGARITY: Good morning. My name is Kristin McGarity. I have been volunteering with the NCIL Chronic Pain and Opioids Task Force. I should say

by way of disclosure I'm not paid by NCIL or anyone else to do this. I paid my way here, and I'm not aligned with any company or pharmaceutical company. In fact, my dad was one of the founders of Center for Progressive Reform and good folks at Public Citizen's know him well.

I'm doing this because it needs doing. So, to go through quickly, NCIL is the nation's longest running organization run by and for people with disabilities. It is our perspective that people with lived experience in this subject have largely been left out of conversation. And we're going to answer question 1 about benefit-risk assessment starting with history. Years of deceptive marketing leading to widespread harm, how do we prevent that? Someone suggests FDA should change the way it works to limit the duration of prescriptions for opioid analgesics. These kinds of limits have disproportionate impact on people with disabilities, especially the most serious and complex. Some would suggest FDA should limit the indications for opioid analgesics to cancer and end of life. Problem with this is chronic non-cancer pain is

a huge category. It includes catastrophic damage and genetic conditions where even the most conservative guidelines suggest long-term opioid therapy may be indicated.

They will change downstream effects on people in that population. Twenty-million Americans have high impact or disabling pain. The few studies we have that go long term suggest somewhere around at least 5 to 25 percent of patients do benefit from long-term opioid care. And it doesn't -- may not sound like much until you remember that often these are the patients who don't benefit from anything else, and it's not that small a group. Major changes have downstream effects on the practical logistics for people's lives. Starting with insurance, if you look to a lot of insurance formularies, they all say opioid medications are covered for FDA label indications only.

We -- on our membership, we're kind of an end-of-line treatment-wise. The only things left to try are things where the risk-benefit profile is worse. Experimental medications, medical devices, surgeries. The last thing we want to do is push people in

directions that are riskier. Multimodal pain therapy works really well for a lot of people if they can access it in the first place, if they can get there. Newer formulations have distinct practical advantages that shouldn't be denied to people just because their conditions are long-term.

And in the current environment, in this tangle of new guidelines and laws and metrics, we are in a situation where doctors can actually get better quality ratings by handing all their patients one last script saying I don't do pain meds anymore, good luck, and the quality metrics don't measure what complements to those patients. Yet another barrier in prescribing makes that problem worse. Palliative care, my state just passed a law defining palliative care as not requiring a terminal diagnosis. Any kind of palliative exemption at the federal level creates a 50-state patchwork of different definitions, but good palliative care keeps people out of institutions long-term and that's what NCIL is about.

Downstream effects, it's important to remember that opioid medication has other benefits besides pain

relief. Often this is in very rare conditions that their neurological benefits, functional benefits, immunosuppression and this is something we see a lot. Now, I want to be very clear who I'm talking about here. This is a specific subset of patients who were severely incapacitated before starting opioid medication in the first place. This is a group of patients who were offered long-term of opioid therapy as a last-ditch hope of maybe getting some function back. It worked. There are people in this group who've gone for decades on the same dose as working as teachers, lawyers, engineers, doctors, and what often happens is an attempt to do a really slow taper with all the available supports and all the available alternative therapies, the original disability comes back. It's not true to say that all deterioration would taper is attributable to hyperalgesia; attributable to dependence complications. It can also be an underlying condition, it doesn't heal. But the medication really was effectively palliating.

So, point being if we are including broader consequences of diversion and misuse, we also need to

include the broader consequences of those people potentially not being able to participate in society and the contributions they would have made. So that brings us to -- and I'm not just talking about economic consequences by the way. In fact, it's wrong to evaluate people by their economic impact, but even the best multimodal integrated pain care, it should be paid for by insurance, it should be available everywhere, it should be first line.

It has a partial success rate, and it has a failure rate, and those are real people with real lives who can do well on a long-term palliative program. That brings us to the question are opioids safe and effective for chronic pain? It's the long question because the answer is always going to be it depends. Often though, they're not, but the evidence we have suggests the minority of patients do benefit long term, and because some of those conditions are so importantly understood and not -- they're all clearly defined, risk-benefit analysis can't be based on condition by condition, it's got to be individual per-patient level zoomed in. Obviously, we want to see a lot more

research, not just on pain in general, but on each of these specific conditions.

It's going to be very difficult for studies to predict which patients are the ones who benefit. The people who do benefit long term don't tend to sign up for studies, and there are some real ethical concerns with a disabling condition putting people in a control group for years. So, we do know from previous FDA research that science does not support strict limits by any patient, by cancer versus non-cancer. The things that cancer does to bodies, other conditions can do too. Science does not support strict limits by duration. Information on day 89 is still information on day 91. And every clinical guideline acknowledges for some patients benefit outweighs risk. But as prescribing has dropped nationally, a lot of that was just knocking down dosage on those people. Do we really need more of that? Or, could there be a better way?

Have you ever been to a drug company website just to look something up, and months later their ads for opioid drugs still follow you around the Internet?

You change the label, they can still do that. You haven't solved the deceptive marketing problem. You still have advertising that can push people toward drugs they don't need. But, what if Congress could regulate the marketing of controlled substances directly without going through the FDA label process they can effectively tie doctor's hands?

Substance use disorder can be a disability. For some people with other disabilities, the exact same substance may be the best risk-benefit balance we currently have. Enabling people with disabilities to work, parent, participate in society, and achieve quality of life is itself a public health benefit. We zoom all the way back out, the goal should be everybody on medication, the goal should be everybody off the medication. That right there, that should be the goal. The chairs of our task force are available at this contact information and I will attempt to answer any questions that I can, if there are any.

DR. THROCKMORTON: Thank you very much. Questions from the panel? Thank you. Thanks a lot. Next speaker -- next speaker is Mr. Anthony LaGreca

from Fed-Up.

FED-UP'S OPINION ON OPIOID ANALGESIC DRUGS

MR. LaGRECA: Good morning, members of the committee. My name is Tony LaGreca. I am the CEO of Bissell Commercial vacuums based in Plymouth, Mass. I serve of the advocacy committee of the Fed-Up coalition of organizations on the frontline of the opioid crisis. Five years ago, my son Matthew died of an acute overdose of methadone prescribed to him by a pain specialist. Two years later his partner also died of an acute overdose of methadone.

Thank you for holding this hearing. Your interest in seeking public input on applying the risk-benefit analysis for new opioid approvals is appreciated. I'm also grateful that in the Federal Register announcing this meeting. You welcome input on the other relevant issues as well. The other relevant issues that I will discuss is the application of a new risk-benefit analysis for removal of existing products.

Recommendation that FDA should consider removing existing products utilizing a new risk benefit analysis was contained in this report from the National

Academy of Sciences. A report tthat was commissioned by Dr. Robert Califf when he was Commissioner of the FDA. This is a picture of my son when he was young. Here is a brief excerpt from the NAS report on removal of existing products. The framework outlined in this section was designed for new opioid products and formulations. It can be applied with equal force to opioids already on the market.

Plus, in recommendation 6-6 the committee recommends that the FDA conduct a full review of currently marketed approved opioids. Such a review could be carried out by an expert panel that will systematically examine the current range of approved brand name and generic opioids to determine which of these drugs remain effective and safe, which might need revised labels, formulations and post market requirements and which should be withdrawn from the market entirely.

I am pleased that the FDA is holding this meeting and asking good questions about approving new opioids. With more strict regulations on approval of new products, while helpful, would likely have only a

slight impact on the opioid crisis, whereas removal of the most dangerous opioids would have a significant impact for -- impact.

For example, if ultra-high dosage opioid analgesics were removed from the market, many lives could be saved. It's too late for my son who lost his life to an ultra-high dosage of methadone prescribed for pain, but it's too late to spare other families from experiencing the nightmare.

I'd like to show you my pictures of my son at different ages. I want you to see he is just a normal child like every other kid. Graduating from college. You can see he has broad shoulders. And you could see there with those forearms. My son addiction began after a football injury in college. He was sent to a local hospital where his first prescription was 100 tablets of 10 milligram oxycodone, 3 to 4 day -- 3 to 4 a day as needed. Now the race was in and out of rehab for the rest of his life. I filled that prescription. I had no idea what an opioid was at the time I filled it. Once after a 30-day rehab he left the facility and got into a bad car accident. Many broken bones

occurred. By the time I saw him in the hospital he was prescribed 80 milligrams a day of OxyContin, which is equal to 120 milligrams of morphine.

On top of this he was also prescribed a short-acting oxycodone to be taken as needed for so-called breakthrough pain. My son was prescribed extremely high doses of opioids by doctors who did not realize they were harming him. This is why high dosage opioids should come off the market, the existence of ultra-high dosage pills such as prescribers at the FDA considers the dose to be safe and effective.

Worst problem here is that tapering off high-dose opioids can be an excruciating experience. And there are few programs in place to wean patients off. He was on these doses for months with no plan in place to ever come off. The medical community does not want to hear about how addictive these drugs are. We all know that with these high dosages one dose they get cut off. Trying to find a place for weaning patients off is near impossible. This is one reason high doses are very dangerous. The medical establishment is not well-equipped for helping patients taper off them. A year

after my son died, it became a beratement facilitator for parents who watch children with substance use disorder, starting with prescription opioids.

Unfortunately, I spoke to hundreds of these parents over the past 4 years. Two patterns were quite prevalent. First an accident, injury or dental work introduced opioids to the child. This drug even at low levels within the body of certain people takes control of their brain. Nothing matters anymore but feeding this evil drug to the brain. Patient doesn't abuse it; the drug abuses the patient.

Important thing also is opioids is just a mask for pain. There were no use in recovery of injuries or ailments. The patients who shut off abruptly to prevent being dope sick they go out and get heroine and die when they get too much, or a patch with fentanyl. Others buy counterfeit pills, and some of these are also laced with fentanyl, and death occurs. This is not the majority, and that is why I'm here.

Many of the parents I've been with, their adult child went to sleep after taking pills for a long time and didn't wake up. No needle, no drama, just

going to sleep, and their breathing stopped, and their heart also stopped. Then they were found cold in their bed. This is the silent killer.

Adults between ages 45 and 60 or older don't get cut off from the doctors as a rule. They keep getting opioid prescriptions from their doctors. The buildup in their system shuts down the brain and death occurs. The higher the dosage, the faster this will happen. The number of deaths recorded actually is way high. Many autopsies are not even performed.

As I've gone around the country, I found that many places where people dying in their sleep over 50, never anything. So, when you see these numbers like 400,000 since 1999 or something, that's way low, it's way higher than that. So, my son and his girlfriend both died in their sleep with a buildup of ultra-high methadone pills in their body shutting down the brain.

Tens of thousands of Americans have died the same way. The number of opioid deaths is way higher than that as recorded in the government. I believe you cannot increase doses under any circumstance unless the patient is terminal. Long-term use will bring an

unhappy ending.

Our country is suffering from an opioid epidemic. The word epidemic in the dictionary means a fast-speeding disease. I believe the pharmaceutical industry has caused this epidemic, and the FDA could have stopped it. You had the information way back in 1999 and knew how dangerous these pills were. A disease that comes in place in a plastic bottle from your local pharmacy.

Last year it was reported that there were 244 million prescriptions in the U.S. for various forms of opioids. So, if you look at the graph of the CDC, it's quite obvious, the more prescriptions, the more overdose deaths. It's plain and simple. It's been going on for the last 15 years, and you don't have to be a rocket scientist to figure that out.

If the FDA wants to have an impact on this crisis, it needs to fix past mistakes and remove products from the market that should never have been approved.

My son who I love very much has been taken from me. Thousands of other parents in America are in

the same club without their child that they loved. My two great grandchildren, Adam and Madeline, will never know their grandparents. And even worse, their grandparents will never know them. I came here on my own expense. My goal was to explain the dangers of high dose opioids and to urge the FDA to seek removal of them. Let's stop this madness.

And here is where my son resides now. I get to go there 3 or 4 times a week, and that is where thousands of other young people have died. In this country right now, life expectancy has been cut by many years all because of the opioid epidemic. And the FDA can change that. You guys can fix it. You guys can change the way it is prescribed, and I don't disagree with the woman who spoke before me, yes, there are certain groups of people.

But we should not be giving opioids to 20-year-old for getting their wisdom teeth out or getting their broken toe and putting it in. It's like we might as well just be giving them a loaded gun. As you all know, it's the same as heroine. So, let's stop the madness.

DR. THROCKMORTON: Thank you…

MR. LaGRECA: -- good look at that picture. That's what all -- that's what over 400,000 sets of parents are looking at every year, every day. Any questions?

DR. THROCKMORTON: Questions for the parent? Thank you, sir, very much.

BENEFIT-RISK ASSESSMENT OF OPIOIDS:

OXYMORPHONE AS A CASE STUDY

DR. THROCKMORTON: Next speaker is Dr. Janetta Iwanicki from Denver Health and Hospital Authority.

DR. IWANICKI: Good morning. Thank you for the opportunity to speak here today. My name is Janetta Iwanicki, and I'm a scientific director of the RADARS System at Denver Health and Hospital Authority in Denver, Colorado. I'm also a physician and practice emergency medicine and medical toxicology.

Just briefly a bit about the RADARS System. The RADARS System is the property of Denver Health and Hospital Authority, which is a political subdivision of the State of Colorado. RADARS System provides post-marketing surveillance and research regarding many

prescription opioids and other drugs, and many manufacturers are subscribers to our data.

Our role is to provide the information needed and often required of manufacturers to fulfill DFA requests. In order to do this, we rigorously manage our competing interests. Denver Health and Hospital Authority of the governmental subdivision of the State of Colorado is a good home for independent program precisely because of its government nature.

Our employees, including me, receive a salary and are not allowed to have consulting or other relationships with any subscriber or government agency. For example, if someone wants our data or my advice on a topic, they must contact Denver Health, and those funds do not come to me.

In general, our data is independent and provides a unique view of what happens with prescription drugs after they are on the market. And subscribers, when they receive our data, whether being government agencies or pharmaceutical companies, do not have access to the raw data itself, may only use this data for regulatory purposes.

So, a point of consideration in the draft opioid benefit-risk guidance that I'd like to address today. In the benefit-risk guidance there is a section on public health considerations for abuse-deterrent formulations. And the guidance notes that potential unintended consequences of drugs such as abuse-deterrent formulations may be consider.

And in particular, one thing that's noted here is that potential tampering methods that could result in harmful effects such as injection-related harms should be considered when the approval of the drug is under review.

Now this is important, because as we think about what the next steps may be in benefit-risk assessment for opioids, trying to understand where drugs such as abuse-deterrent formulations may play a role is really crucial. However, one of the biggest challenges is trying to understand what those actual risks may be and trying to predict them ahead of time is particularly challenging. And this is where, oftentimes, post-marketing surveillance can be absolutely essential to really understand what may be

happening with these drugs in the real world.

So just briefly, I'd like to talk a little bit about a case study that I think is particularly relevant at this point. So, one of the things that's mentioned in the guidance is the concept of a small versus a large volume extraction of the drug. I like to talk a little bit about what that means before we get into our case study.

Small-volume extraction is when a pill intended for oral use is dissolved in something small, less than 10 milliliters, to be injected by someone. Oftentimes water, saline or alcohol are used for this process. And extraction, generally speaking, is followed by testing with different sizes of the needle to assess syringeability in the setting of Phase 1 studies prior to an DFA meeting.

Large-volume extraction is typically 30 to 100 milliliters. And this, if you can think about that volume, this is the size of a small medicine cup or larger. It's really not feasible for an injection. Generally speaking, injection users are using small insulin syringes or perhaps something slightly larger

than that. Injecting 30 to 100 milliliters would be a huge volume.

This can be done with either simple or advanced solvents. And particularly this is relevant for the concepts of dose pumping in oral administration. So, by dissolving a pill into a volume and drinking it one can sometimes overcome abuse-deterrent features. However again, it's difficult to inject.

So, case study I'll be talking about today is that of Opana ER. Opana ER is an extended release oxymorphone that was reformulated to deter intranasal administration. It was approved in 2011 without an abuse-deterrent label claim. And the biggest issue that was observed after it -- this new formulation was on the market were unintended consequences associated with intravenous administration.

In particular thrombotic thrombocytopenic purpura-like illness was noted and needle-sharing behaviors along with HIV and Hepatitis C transmission was very high. A few things about Opana ER that were a little bit unique, and we'll talk a little bit more

about momentarily. But I think reasonably the data after this drug was on the market led to its removal at the request of the FDA in 2017.

So, looking a bit of RADARS data associated with Opana ER, this was presented to the FDA. What we see is that before the reformulation from 2010 through the end of 2011 a relatively large quantity, 34 percent of cases, involved inhalation or intranasal use of this drug. However, after reformulation we did see a decrease in intranasal use, down to 21 percent.

Unfortunately, this was accompanied by an increase in injection, up to 29 percent. This shift was not -- has not been seen with other abuse-deterrent formulations such as OxyContin. And this really highlights how crucial post-marketing data can be in trying to understand where that risk-benefit ratio may lie for a killer drug.

So, what you see here is data from poison centers from across the United States related to injection and inhalation and nasal use of these drugs. First on the left, what you see is that there is quite a high rate in the period before reformulation of

intranasal use. That orange line on the left you can see was rising quickly. After reformulation, the blue line on the right shows a decrease in that intranasal use.

However, when we look at injection associated with this what we see is that there is actually quite a bit of a different pattern. Injection use was also on the rise, as you see on the left of that orange line. After reformulation the blue line shows that there was a slight decrease after use. And on this left panel here what you're seeing is these are rates per population so looking at the overall public health impact.

So, in general, we saw that injection rates were rising per population, but they flattened out after the reformulation. More crucial though, on the right-hand side what we see is that when we look at this by the amount of the drug available, amount of prescriptions out there, there was very little impact that was happening by that reformulation. So, what this suggests is that reformulation may have decreased the total number of people who were exposed to this

drug, but those who were exposed, the amount of injection that we saw, was staying about the same.

Not only that, but we also see that now there are these high-risk behaviors associated with it despite the fact there is no decrease in that behavior. So, an in-depth study of Opana ER injecting behaviors was performed in Starke County, Indiana. There were 25 intravenous Opana ER users. And there is -- the study characterized how they used this drug. We looked at extraction volume, how they prepared it, and the rationale for why they were sharing intravenous solutions.

So, few things about how this drug was shared that I think are also important to know. The drug was pretreated. This means that it was browned and heated in an oven for several minutes. Then typically a 40-milligram tablet was split into 4 pieces. Each of those 4 pieces was then mixed with a small amount of water, and what that meant was each of those injections then were split again into, about a quarter tablet led to about 4 injections per 1-ml insulin syringe.

So, what this means is that Opana ER was

extracted in a small volume and split into multiple injections each of less than one millimeter. So again, we're talking about very small quantities, much less than what you would have imagine with a 100 ml large volume extraction.

So why did people share these IV solutions of Opana ER, the volumes were so small. Well, really one of the things that's really crucial here to understand is that oxymorphone is very unique drug. It's 10 times more potent intravenous taken orally. And so, what that means is that a 40-milligram tablet has a huge volume of potential morphine equivalent when given intravenously, and this leads to solution sharing and unsafe injection practices.

And the gelling product that was used to make this abuse-deterrent formulation was not sufficient to deter injection of a desirable intravenous dose, which again, lead to unintended consequences associated with these behaviors.

So just to make this a little bit easier to understand, looking at an Opana ER 40-milligram tablet, up to 16 people could have an injection off of a single

tablet, which is massive. And again, it all comes back to the fact that it's a uniquely potent opioid intravenously, different from other drugs. For example, oxycodone, even if extracted under ideal conditions really only provides enough morphine equivalent for a single person to inject. And this matters when we think about how we do risk-benefit assessments.

So, in conclusion, some learning here. Opana ER was extracted in small volumes, not large, and dose driven was shared -- dose sharing was driven by IV potency and not volume. Intravenous deterrent should be assessed by the ability or difficulty to get an ideal dose intravenously. And the present extraction is not really a clinically meaningful measurement. It really matters how many morphine equivalence you can receive.

Finally, guidance should reflect IV potency as a key factor for influencing IV dose sharing. Post-marketing surveillance is crucial to detecting concerning behaviors, and early planning for surveillance allows detection early and intervention

when unintended consequences occur, because human behavior is unpredictable. Thank you. And I'm happy to answer questions from the panel.

DR. THROCKMORTON: Thank you very much. Let me just ask a question. So, the guidance does speak to -- asks sponsors to evaluate whether increased or decreased risks of a particular product based on its specific characteristics. You know, I think delivery device and type, that sort of figures, but you're suggesting we add something related to pharmacology if I'm understanding?

DR. IWANICKI: Yeah. I think considering bioavailability is really crucial, and it's not something I've seen addressed so far in the guidance to this day.

DR. THROCKMORTON: Sorry; yes, go ahead.

DR. STEIN: This is a related question. Certainly, I've some of these behaviors being regional. Do you have any suggestions? Obviously, yours is a network, so I presume looking at a region and characterizing this behavior in that region. Do you have any suggestions for how the challenge of finding

regional patterns might be addressed? You've given something like the RADARS System, which is looking at one region where you may or may not see this kind of behavior.

DR. IWANICKI: Yeah. So, RADARS System is somewhat unique, because we do have a broad geographic coverage across the country, but I think your point is an important one. I think finding ways to perform signal detection to identify geographic regions when there are issues really is crucial, and the best way to do that, no one network, as far as this research, is perfect. And so, finding ways to combine data from multiple different networks and utilizing that via modeling to look for signal detection I think is the next step in the future.

DR. THROCKMORTON: Other questions? Thank you very much. Meredith, we are at break now. What time should we have people come back?

UNIDENTIFIED SPEAKER: 10 -- 20 minutes…

DR. THROCKMORTON: So back at 10:30 please. Thank you very much.

BREAK

(Recess)

ROLE OF POSTMARKETING SURVEILLANCE

IN OPIOID APPROVALS

DR. THROCKMORTON: All right. Why don't we go ahead and get started again? The first speaker is Dr. Dart from RADARS for Denver Health and Hospital Authority.

DR. DART: Good morning everyone. My name is Rick Dart and I'm the -- thank you.

I'm the Director of Rocky Mountain Poison and Drug Center and a professor at the University of Colorado. And my research for the past 15 years has been on abuse of prescription drugs specifically. I want to join the others in thanking the Agency for doing this because I think opening up the topic of what standards we should apply is extremely useful, and I'm looking forward to getting that task I've started.

I'm also Executive Director of the RADARS System, and the RADARS System provides post-marketing surveillance data for the pharmaceutical industry, but also for government and researchers. And much of this was already covered by Dr. Iwanicki in her

presentation. So that saves me a good 45 seconds of my presentation.

So, what does a pharmaceutical product need for approval? To be approved, it has to show that it can be manufactured appropriately, and that's actually a major advance and why the FDA was initially started. It has to show that it's effective and safe when used as directed. In the past, that safety component has generally been fulfilled by the sponsor establishing a call center that accepted spontaneous adverse event reports, which was a good thing, but it's not the most rigorous approach. It works because most drugs don't really develop major new problems after their introduction.

The problem, as we've discovered in the United States, is that prescription opioids are different. Not all issues can be identified before marketing and not all-important adverse events are actually new adverse events or unexpected adverse events. The current system isn't really focused on trying to detect changes in expected adverse events, it's focused on unexpected events. And for example, for the opioids,

respiratory depression and death have always been expected adverse events for any opioid drug.

So, the problem we have today is not from unexpected events, but from unexpected uses of the drug producing the same adverse events. To their credit, FDA has addressed these issues. For example, this table makes it clear that they plan to consider risks related to both the broader public health and to consider these risks relative to other currently available analgesic drugs.

It may not seem like a big change, but it's important, and I fully support these changes. But there are a couple implications that we should consider. For example, this means there are at least 3 different risk issues now involved in the draft guidance. Individual risk appears to be the same concern we have for any drug. What are the risks for that individual usually using the medication as prescribed, although for opioids there is also dependence and addiction?

The population risk or broader public health is new, and I think really important to add what is the

effect that a drug may have on the broader public health. As we discovered, this is a critical issue for opioids and likely for other drugs as well. The addition of comparative risk or risk relative to other analgesic drugs is extremely important, but also the most difficult to study.

For example, generic drugs are commonly abused. How do we compare a new opioid to a generic? So, I made this table for us. What if we wanted to compare across the oxycodone products for example? Well, right away we're in trouble, because only the branded extended release products have required post-marketing surveillance.

On the left, I provided 5 specific outcomes identified by FDA, although there are many others of course, and then described the requirements. And you can see that because they're essentially all generic, single entity oxycodone products do not have any or minimum. There’re multiple reasons for this situation, but whatever the reason, we can't effectively compare it across these products currently.

This is a big problem because most of the

opioids available, diverted or abused, are immediate-release preparations. The press would have us believe that they're extended release, but the truth is they're immediate. The figure on the left shows the total grams dispensed for immediate release and extended release analgesics in United States. As you can see, 90 percent of the market is immediate release. And this is reflected in actual levels of abuse. The right panel shows that abuse cases as recorded at Poison Centers are also predominantly immediate release.

But this raises the question, how do we gather safety information on generic drugs? I believe the law establishing generic drugs allows them to use safety data from the branded drug. For example, generic hydrocodone acetaminophen products would rely on the brand name Vicodin for safety data.

However, there's essentially no real Vicodin sold anymore; it's all genericized. So, in the end, these companies really don't have a responsibility to a requirement, I should say, to monitor the safety of the drugs. So, my first recommendation is that we need the same post-marketing surveillance required for every

opioid product.

And this echoes what previous speakers have said. This means both extended release and immediate release. It means both abuse-deterrent and non-abuse-deterrent. And it means both branded and generic products. This needs to be required, because the data will not be collected unless it is required. In our society pharma's mandate is to maximize shareholder value and not to do safety monitoring that is not required.

Now some of you may wonder what about the required FDA opioid REMS? This is a good concept, but it primarily addresses educational objectives, assuring that the prescriber and the patient understand the drug. That's great, but it does very little about requiring monitoring for population safety risk or the risk compared to other drugs. But more is needed than simply post-marketing surveillance; standardization is needed. Currently, post-marketing requirements are negotiated individually between FDA and a sponsor at the time the drug is approved. This essentially requires FDA to anticipate what will be different about

these drugs, and this is just impossible for anyone to do.

Furthermore, the draft guidance asks for comparative data, and this is impossible as well when each negotiation results in a different collection of surveillance tools and a different -- very different set of data and analytics procedures on that data. To illustrate this point, this slide addressed the lack of a common data set just for oxycodone.

Let's say the generic producers of single entity oxycodone, for example, Roxicodone 30-milligrams is a very popular drug abuse. Let's say they were required to perform rigorous surveillance. If standards are not developed, then a manufacture of single entity oxycodone might decide to use treatment centers for their surveillance program even if they were required to have surveillance, while the extended release sponsor might decide to say use diversion programs. How would one interpret these results if they differ? And they will differ. It's impossible as you can see. And don't forget, there are literally dozens of products depending on the category, so the

permutations really are endless.

So, my second recommendation is that the same elements of surveillance should be available for each product to improve the quality of comparisons. A common data model would simplify and speed up analysis of data in the future, especially the speed up part, and not mention -- not to mention that it would decrease the expense per sponsor. In addition, common analytical approaches should be provided preferably with the input from multiple and knowledgeable parties, and there are many at the stage in the U.S. because of the epidemic.

My final point is that we must include drugs other than just the opioids. I realize that FDA is already addressing this concern, but I want to emphasize the point that all drugs with CNS affects are abused. Even Diphenhydramine is commonly abused. These data are from the RADARS' analysis of the National Poison Data System from the American Association of Poison Control Centers of 2006 to 2014. Opioids are the highest. I took them off, because of space; they would be the highest on here, but you can

see that after that come the Benzodiazepines, very high, but even Dextromethorphan is very commonly abused in the United States.

And worse, the abuse of essentially all these categories is rising. So, we're currently in the process of exchanging an epidemic of prescription opioid abuse for an epidemic of abuse of other prescription drugs as people switch away from opioids, to heroin, of course, which is a huge problem, but also to multiple other drugs that are available.

So, my third recommendation is that the same method should be required for all drugs with CNS effects. This is a large task, I realize, but is real and emerging and needs to be addressed proactively now. I would add that we at least need to include those illicit drugs as well, illegal drugs that are similar to commercial products, for example, and may lead to abuse such as the amphetamines.

So, in summary, we need rigorous and meaningful post-marketing surveillance that is required of each opioid product. This postmarketing surveillance should be standardized to allow for

meaningful comparisons, and these principles should be applied to all medications with potentially desirable CNS effects. Thank you.

DR. THROCKMORTON: Thank you, Dr. Dart. Questions? Gerald?

DR. DAL PAN: Could you talk a little more about what this common data model that you propose would be, what its scope would be, how it will be used?

DR. DART: That's a big task. The idea would be -- my concept is that there would be a fixed and variable portion to this. In other words, there would be certain data elements that are required of every sponsor, but obviously not every drug is identical. You might for some drugs, for example, using the Opana ER example for some drugs that you're worried you might have a variable portion that you add to that sponsor. So, all sponsors would do a common data set that would allow us to do basic surveillance of that drug. And then if there are special concerns, that could be tailored to each sponsor's individual product.

DR. DAL PAN: So, if I understand, the sponsors then would collect data from various sources

put it into a structured format that would be common across them and then those data could be pooled or analyzed?

DR. DART: That's right. That's right.

DR. DAL PAN: Could you also talk about something we've noticed here, and that's the challenge of identifying what product the patient actually really takes?

DR. DART: Yes.

DR. DAL PAN: And certainly, ingredients might be known, the active substance, then getting down to what product is, we've seen a lot of imprecision in that area.

DR. DART: There is imprecision in that area, and it varies by the data collection method that's used for sure. Some are more reliable than others, but I guess my point is that I think if we put our minds to it we could figure out how to do this. I can think of ways to be able to ascertain products or cross-reference products so that we could get more accurate identification. So, for example, in a drug diversion program, for example, you often have the product and

you can know what the product is because you can actually identify it.

It is true that in a system such as poison centers, you're using the subject's belief in what they took. There is some value in that, I think, because then you know what they think they took, but in those you would have to have either some sampling method or something that -- and I guess my point is really to start working on those rather than just say, we can't really do that. I think we can if we put our minds to it.

DR. DAL PAN: Thank you.

MS. SIPES: Thanks for your presentation. I'm Grail Sipes. I'm the Deputy Director of CDER for Regulatory Policy. I was wondering if you could talk a little bit more about some of the authorities that might be necessary for this activity, particularly the standardization and the surveillance area.

DR. DART: Well, I am not lawyer by any stretch. I'm trying to identify a need, I think, more than to say how to solve it. I don't -- every time I think I understand the -- what the FDA is empowered to

do then I find that I'm wrong. So, I hesitate to get in there. It's just that I think what's very clear to me that is -- and I -- this is -- I'm not trying to be critical of industry, but they're not going to do something they don't have to do, and that's just the way it is. Every company in the United States is like that, and the world is like that, right?

And that's the system we have set up. So, I'm happy living within that. That means in a situation like this, because I think the opioids or CNS active drugs are different, we need to actually be more stringent and require it rather than suggesting.

DR. THROCKMORTON: Dr. Stein?

DR. STEIN: Can you say a little bit more about what kind infrastructure would be needed to operationalize something like this? Obviously, we're going from fairly limited, somewhat more patchy (ph), surveillance to what you're really referring to, very systematic national surveillance and markedly expanding numbers of the agents that we need, that we believe are under surveillance of accumulated (ph) and apply in a large number of non-opioids. How you just -- in

general terms, what are you thinking in terms of the kind of infrastructure necessary to operationalize that kind of larger surveillance approach?

DR. DART: Well, the general concept that was alluded to earlier is that you can't -- you really can't get all the information you want from one system at all because there's many different facets to substance abuse, and the people are always trying to hide those activities. And so, you have to identify specific objectives. That's probably the key thing here, and then see which data sources answer that question and then require those data sources of all of the sponsors.

So, there would be a process there where you do that identification of what you actually are trying to measure then agree on how you're going to measure, and then companies would know how to provide that data, and there's several. I think one of the issues here is, so far, it's been so fragmented that there really isn't any -- you know, we're a government agency, there isn't really -- there hasn't been a big interest from the data analytic companies because there -- it's

different for every product. There is no standard product they can roll out. So, I maybe cutting my own throat here, but the reality is you need to have that. And I think if we ever want to know what happens when you pull -- when you take Opana ER off the market, what happens to all the drugs around it, including the non-opioids. We're just not going to know that in the current system. We can get some hints, but we're really not going to know the answer to that. Sorry; I can't be more specific…

DR. STEIN: Okay.

DR. THROCKMORTON: Just ask a couple more questions, so it does seem quite expansive, I agree, especially when you threw in the illicit drugs. You also wanted to have this system. Do you envision a group that would be leading this? Are you thinking this is something that the FDA would lead? Or is it a -- especially with the illicit, I am wondering if there is another mark.

DR. DART: That's a great question. And I have to admit I haven't thought about it. So, I guess the new system ER is sort of a benchmark to compare to

more than I'm actually going to get the detailed data on them for, if no other reason, that they are so variable and so non-standardized. I mean one of the beautiful things about FDA is that you have standard products that are produced, and you know how much drug is on that type of thing when they are produced appropriately. For the illicit, you never have information. And so, I think that would be much less specific, and to be honest, easier to implement in many ways. Kind of goes -- I would be happy to talk more about it because I think it's a more extended conversation.

But the -- for me is that the regulated drugs are going to be -- are going to remain a big problem. They're not going to go away just because of illicit products. You seem to be adding to the problem rather than -- it's not a zero-sum game. What I am seeing is expansion essentially of both markets if you want to view it as a market phenomenon.

In other words, prescription opioids are going down. The other CNS active prescription drugs and OTC drugs are actually expanding substantially, and heroine

is expanding. So I am kind of getting off the topic here but I see that if -- that we're going to need to -- we need to get our hands around the whole -- the whole picture or else we're going to constantly be playing whack-a-mole, and we wouldn't know where we stand, and no agency will be able to say to Congress, hey, we've made progress here. Right now, I don't know if we made progress or not.

DR. THROCKMORTON: Thank you very much.

OPIOID AND ALTERNATIVE PAIN MANAGEMENT EFFECTIVENESS AND OBSTACLES

DR. THROCKMORTON: Next speaker is Ms. Tasha Olson from the Pain Community.

MS. OLSON: Hi everyone. I am Tasha Olson. I am a chronic pain sufferer. Okay, so I come here not representing any organization or cause, other than I represent my own experience and my friends in the pain community that suffer from chronic pain, and some of the obstacles that we still have been running across that we would have hoped had been fixed or we thought had been fixed. So, I'm go bring up a couple of those.

And FYI, I am going to ready my presentation

because I recently had a stroke. So unfortunately, my aphasia isn't doing so well. But let's go on here. Who am I? Right. So, I do still work full time, so I am considered high-functioning as a chronic pain sufferer, but I've worked extremely hard to stay working, suffering from chronic pain. I am very involved one-on-one with other chronic pain communities and other individuals that suffer from chronic pain. I am also a recovering addict and a recovering alcoholic, and that started in 2001, was my recovery birthday, which was before I was injured.

So, a little bit about my journey. You do -- I want you to understand what I have tried, what we do in the pain community, everything that I have to bring into a discussion like this and some of the hiccups that I have seen. Like I said, I've been a recovering alcoholic addict since 2001. But I was injured in 2010. I had multiple skeletal, from an accident, skeletal damage as well as soft tissue and nerve damage, peripheral and motor neuropathy, and I also have several severed nerves.

So currently, the conventional therapies I

have gone through is obviously multiple surgeries. I do frequently have injections, radio frequency, cold laser therapy, ultrasound therapy on soft tissue damage, traction. I do now have a spinal cord stimulator which was put in in 2012. I undergo physical therapy still and also some occupational therapy. Pain psychology has been a very large part of me still being part of my own working community. And of course, medications. As far as unconventional in some -- in some scopes, that is unconventional treatment, I of course have undergone limited chiropractic acupuncture massage.

I do still use binaural beats, which is something that helps distract from pain. Obviously, it worked with nutritionists and anti-inflammatory diets. I have tried essential oils and also meditation and CBD oil. I do want to clarify quickly what I talk about as far as being a chronic pain sufferer.

I think it's critical that this -- to this discussion that you understand what I am saying when I say chronic pain. I define chronic pain as long-term permanent pain, not acute pain. Most of us are -- do

deal with extended release opioids. So, I am not speaking to acute or surgical pain or treatable injury pain. Do know that this definition many times is beyond 12 weeks is chronic pain, and to us in the pain community we do drive that into more sections. There are some of us who have what we call forever pain until someone else comes up with it. But then there is the pain past 12 weeks where you shattered your leg on a ski slope, no offence to any skiers, but that is a pain that eventually may go away and is not necessarily treated long term as we are.

So, we know that we're not, as far as the chronic pain that I have, we are not necessarily a huge community. But one thing we do know is that I have friends that have pretty much given up with some of their restrictions on being able to get opioids that they need. Most of those are extended release, not immediate release, for acute pain.

So, pain patients, they do need the medications that are prescribed by qualified pain doctors. But there is also a need for more alternatives for pain, and we very much encourage

developing the drugs that we currently have on the market to understand more about how we can use them, how we can get them into a severe pain community, and the effect that they have on some of the other medications that were brought up earlier. Some of them aren't considered opioids but may still be dangerous that have -- very much have a -- may have a relationship that becomes very useful.

We would like to think that pain can be effectively treated without these acute. If we can do that, then it's a win-win for everybody that the U.S. would be happy. Pain doctors would feel as though they can -- they can treat their own patients, and that chronic pain community would feel like they were taken care of.

If pain can be effectively treated, I think there is also the question -- if addiction or recovery can also be relieved by some of these pain mechanisms and that the risk-benefit analysis really needs to reflect these kinds of goals. So, pain physicians, here is a few obstacles we've run into. We have several pain doctors that really feel as though they

are being restricted at this point to what they feel they need to give, and that includes the extended release opioids that are so important to the really chronically pain sufferers.

So, we do think that they need a little more authority back, because I do think that as far as pain specialists and pain physicians that are qualified for those kind[s] of pain that they are the ones who do know best. And I do like to see collaboration that comes between regular physicians, but also some of the more unconventional things.

Here is an example. When I have to get my upper back fixed what I do is the day before I go and get injections. I have a chiropractor that works on getting my ribs back in place. I go in. I have the neck injections and upper back, and 6 hours after that, I see an acupuncturist who is able to release these muscles right here. And it makes the treatment far more effective. And that's because of collaboration.

I know nobody wants me to go on about insurance and pharmaceuticals probably. However, I have couple of things to say, most of it is I am going

to give you an example of what I have recently gone through. Recently my pain team made the decision to transition me from some of my previous medications to a Butrans Patch. I don't work for that company, I am just saying the name of the patch, right, an extended release. So, my pharmacy said, oh, sure you can have that for $475 a month, so that's great. Unfortunately, of all the people who may get the most benefit from a nonacute pain patch, how many of them are going to have that kind of money? Four-hundred fifty dollars a month, that's tough.

So, I called my insurance company to ask them, can you please cover this? And they said to me, I wrote it down so I wouldn't forget, we can't cover it or make an exception, but for around $12 a month we can get you oxycodone. Could you ask your doctor if that will work instead? That's tough. And we hear that all the time, and that's tough.

Because I know it's tough on our physicians too when they know that all we can afford possibly is, you know, is something like that as supposed to $450 that will keep us a little more cognitive. I do pay

out of my pocket for that pain patch, unfortunately. We would also like to see multiple dosing alternatives in some of the patches that are currently out there in some of the opioids.

The research on that could be very helpful for us. We do not necessarily need the total dose that is available. So that would be nice, to see an incentive for that. As I said, we -- any testing that's done, long-term transdermal medication is great for us. I don't want to pop pills. I would much rather slap on a patch every week; you know, most of us would. And that also makes it a little bit harder for an addict or someone who isn't in our community to get a hold of those medications and abuse them if they're in a format that is much harder to abuse.

So, we'd also like to obviously see knowledge of alternative pain relief that gets out there for us. I think that beyond that we would also like the accessibility of it. And unfortunately, with our group of people, where people are going to have to ask us, and we would like to be a resource in order to make that happen. And I know I am out of time. Any

questions at all?

DR. THROCKMORTON: You had a couple of last thoughts. Any last-minute things that you wanted to say?

MS. OLSON: Oh, stroke brain, it's not good. These are just some of the incentives I already mentioned that you see on there. We have incentives. We would like to see more cross-treatment. We think it's effective to working away from opioids as far as -- as I talked about, mixing up different kinds of therapy that could be done.

We would love incentives for insurance companies to be able to prove out some of these alternative treatments and to be able to support us getting them. Obviously, we'd like to see the approval and promotion of these by insurers, research on safer transdermals would be great. We like to see the combination and the advantage of using some of our other medications with that, and of course more dosing options. How was that?

DR. THROCKMORTON: Thank you, Ms. Olson. Questions from the panel? Thank you very much.

MS. OLSON: Thanks.

STANDARDS FOR FUTURE OPIOID ANALGESIC APPROVALS AND INCENTIVES FOR NEW THERAPEUTICS TO TREAT PAIN AND ADDICTION

DR. THROCKMORTON: Our next speaker is Dr. Andrew Kolodny from Brandeis University.

DR. KOLODNY: Hi. My name is Dr. Andrew Kolodny. I am an addiction psychiatrist. I am Co-Director of the Opioid Policy Research Collaborative at Brandeis University, and I am also the Director of Physicians for Responsible Opioids Prescribing, which is called PROP.

My comments today are on behalf of PROP and its members. PROP members are from diverse specialties, including pain, addiction, primary care, internal medicine, emergency medicine and public health. I have no industry relationships to disclose, but will disclose that I have received income, helping states and municipalities sue opioid manufacturers for their role in the opioid crisis.

I am going to cover three related topics. First, I am going to just explain briefly why at a time

when deaths involving illicit Fentanyl was soaring why it is still important to focus on prescription opioids. In other words, why this meeting today is important. I am going to next talk about something you've heard already this morning, the need for FDA to apply a new risk-benefit framework for existing products. And lastly, I am going to talk about the benefit side of the risk-benefit equation or really the lack of evidence supporting benefit.

This is a slide that probably looks familiar for several years. It was the CDC's Chief speaking point about the opioid crisis. The green line represents opioid prescribing. The red line represents death. The blue line represents addiction. And the CDC's point was that the soaring increase in opioid prescribing was resulting in parallel increases in addiction and overdose deaths.

We know that things have changed since 2010. This is current opioid overdose death data, national data. The brown line here is fentanyl deaths, and the orange is prescription opioids. Blue is heroine, and we see that fentanyl deaths have surpassed prescription

opioid and heroine. There is a popular narrative to explain what's happening today that's sometimes referred to as the three waves. What you are hearing is that there was a crackdown on the pills which resulted in drug users switching from prescription opioids to heroine, and then they switched from heroine to fentanyl, and the opioid crisis has consistently got worse. And there are problems with that narrative. It's inaccurate, and it masks important differences. For example, it masks the fact that fentanyl does not hit the whole country. Illicit fentanyl deaths have really been affecting mostly the eastern half of United States.

The three-wave narrative also masks important racial differences. In fact, the geographic area where we have seen the largest increase of deaths involving illicit fentanyl is Washington, D.C. which has a large population of survivors with the heroine epidemic in the 1970s who have managed to beat the odds for many years but now are dying because of the dangerousness of the heroine supply.

To really understand the opioid crisis, you

have to understand the epidemiology of the opioid crisis. We have different cohorts of opioids-addicted Americans. We have a young white group that has been switching to heroine after getting addicted to prescription opioids. Their addiction began after 1995. A middle-aged and older white group that hasn't really been switching to heroine. And this older non-white group which are really survivors of a much earlier heroin epidemic in the 1970s. The fentanyl is really hitting this first group and the third group very hard.

Before fentanyl emerged and something that we were seeing with that up until really -- up until 2012 when the heroine supply became very dangerous. The group where we saw the highest rate of overdose deaths were really middle-age, white people, and it was deaths involving prescription opioids. When the heroine supply became very dangerous, mainly because of fentanyl, that's when things really became to change.

In states though that haven't been plagued with heroine and fentanyl, the deaths have really closely tracked changes in prescribing. As prescribing

began to trend more cautiously we saw deaths come down. Sort of a last point about this narrative, the three-wave narrative of a crackdown causing drug users to switch. Lastly, another reason why this narrative is incorrect is that there really hasn't been a crackdown. We are still massively over-prescribing. What you are looking at here in blue is oxycodone consumption in the United States per capita compared to oxycodone consumption in Europe. And what this means, the fact that our opioid consumption remains so high is that many Americans are still becoming opioids-addicted. It means that we still have a high incidence rate of opioid addiction, and with a high incidence rate of opioid addiction, the opioid crisis will not come to an end.

Fortunately, prescribing has continued to trend in a more cautious direction. You would see the waves are peaked around 2011, 2012. But even with the most optimistic forecast, by 2023, we'll still be at about double our opioid consumption; double what it was in the early 1990s.

Now, if you look since 2012, we've seen opioid

prescribing come down. Those in favor of new opioid approvals have argued that, you know, FDA approving new opioids clearly isn't resulting in more opioid prescribing because of the downward trend. But what we don't know is what this graph would look like today had FDA really changed its policies on new approvals long ago, and I think it would look very different. And something that I would hope that FDA understands is that drug makers don't invest millions of dollars to bring a product to market and then sit on their hands and just hope doctors will prescribe it.

They do everything they can to make sure that doctors will prescribe it. In fact, even before a product gets approved there are unbranded aspects of a campaign to prime the market. This is something we're learning about through the opioid litigation, through internal documents that have become public.

We've heard about the NAS report. This morning we heard from Dr. Bonnie. I'd like to point out that the report didn't just call again for new criteria for approval, but it really did call for looking at removing existing products or new criteria

for existing products, and the report was endorsed by Commissioner Gottlieb.

This is just a section from the report urging FDA to do a full review of all marketed products, looking at the need for revised labels, formulations, post-marketing requirements and to consider withdrawing some products entirely from the market. After FDA endorsed this report, almost immediately a petition was filed with FDA from organizations including public health commissioners, consumer safety advocates, my organization PROP, [and] addiction advocacy organizations, urging FDA to now apply these new criteria and really to begin with the most dangerous opioids that exist. If you're going to really think about what products should be withdrawn from the market, the ultra-high dosage opioids are the most sensible place to start where we appreciate that FDA held a meeting on this topic a few months ago. And we remain hopeful that FDA will act on the petition's request.

Lastly, I want to talk a bit about the safety -- the efficacy side of the equation, the effectiveness

side of the equation, something you've heard from Dr. Bonnie in a comment to an FDA docket and from Dr. Kesselheim is that despite clear evidence of harms related to opioids, we lack evidence of benefit. This is something you've heard from former FDA commissioner. He said this publicly on 60 Minutes, that the FDA made a mistake in allowing opioid manufacturers to promote opioids for chronic pain.

FDA heard this. It was really part of an AH -- an AHRQ review that looked at all of the evidence supporting opioid use, long-term use, and concluded that we don't have evidence that this helps people when used long-term, but we do have evidence of serious harms.

Lastly, I just want to talk quickly about the use of enriched enrollment, randomized withdrawal which is really where FDA is getting the bulk of its information on efficacy of opioids for chronic pain. And the use of this clinical trial methodology didn't come from a public hearing like this one or from FDA consulting experts. It came out of private meetings with industry, and this was a presentation by Bob

Rapaport crediting impact, these private meetings with enriched enrollment.

Let me just finish up by explaining why enriched enrollment, randomized withdrawal should not be used. It's certainly something that drug makers like, because when you try to do a clinical trial the appropriate way, when you compare opioids to placebo you see a very high dropout rate. And over 12 weeks, many of the patients who get the placebo, their back pain will improve. Enriched enrollment, randomized withdrawal, the methodology there was to give all of the patients opioids in a 4- to 6-week open label phase. And then you see the drop outs or maybe half the patients drop out because they don't tolerate opioids.

And then you have the remaining group that are asked, let's say, half of the patients are asked, did you find opioids helpful for your low back pain? If they say no, they are also removed. Then that's your enriched sample. Then, you randomize half to be switched to placebo. The group being switched to placebo is of course going to have an increase in pain

because they are going through withdrawal and increase in pain is a symptom of opioid withdrawal. You now have lost the double-blind. All of the patients, if they are switched to placebo, know it. People who performed the study know it, and you've now created a situation where the placebo group has increased sensitivity to pain; something that's not controlled for. So, I do not believe that FDA should consider enriched enrollment randomized withdrawal to meet the requirement for adequate and well-controlled studies. And, you know, when the risk side of the equation is so clear, FDA really should be requiring better evidence of efficacy for the benefit side of the equation. Thank you.

DR. THROCKMORTON: Thank you, Dr. Kolodny. Questions from the panel? Thank you, sir.

WHAT RESEARCH TELLS US THAT CAN IMPROVE FDA APPROVAL STANDARDS AND REMS FOR OPIOIDS

DR. THROCKMORTON: Sorry, Dr. Zuckerman. Find your name. Next person is Dr. Diana Zuckerman from the National Centre for Health Research. Thanks.

DR. ZUCKERMAN: Thank you very much. I just

want to say the National Centre for Health Research does not accept funding from pharmaceutical or device companies, and we're also not involved in any lawsuits. The Center conducts research, scrutinizes other peoples' research, and tries to explain the research results to the public, to medical professionals and to policymakers. My personal perspective, I am trained in epidemiology, I was on the faculty at Vassar and Yale and a researcher at Harvard, and then I worked at U.S. Congress for a dozen years before becoming President of the National Centre for Health Research.

As everyone here knows, the usual perspective for what's safe and effective means -- for prescription drugs means that the benefits outweigh the risks for most patients under certain circumstances if prescribed for approved use, if used as directed, and if -- and based on studies that are particular number of weeks or months or years. And we -- and of course for opioids now the FDA is looking at how they can reduce the likelihood of doctors prescribing inappropriately, which is not an issue that is usually raised and what can FDA do to reduce the chances of patients abusing a

drug.

And we agree with the guidance that FDA now wants to consider how opioids might be abused or used inappropriately and have that be part of the equation. And we believe that better research and more specific labeling can, in fact, reduce the chances of addiction, and FDA has an important role in that. I just want to start with a simple issue, and that is what words we used and how some of them have PR value more than public-health value. The term abuse deterrent has often been misinterpreted to mean that people are less likely to become addicted to those products.

And, in fact, research shows that almost half of physicians misunderstand the meaning of abuse deterrent. And I'm sure patients and family members do as well. So, if a drug is crush resistant, call it crush resistant, and don't call it abuse deterrent. And if it's tamper-resistant, it should be proven to actually reduce tampering in the real world. These are just simple terms that should be clear, and they should only be used when they mean what people think they mean.

In terms of new research requirements, we believe that proof of abuse deterrent or tamper-resistant or less addictive. The issue is compared to what and under what circumstances. So, types of patients should be the same as those that are in the indication. The risks and the benefits in the short term and the long term should be established before approval, not after. And I'll go into a little more detail on this. So, in terms of long-term and short-term efficacy, we know now that research shows that many patients with chronic pain that for many of them, opioids are no more effective than over-the-counter painkillers.

So, FDA should require studies that compare new opioids with non-opioid painkillers, not just with other opioids. And the studies should compare short-term use as well as long-term use, and short-term use can be a week or less; it can be 3 days, it can be 5 days. Long-term use, you know, I'm not going to say what exactly that means, but certainly more than a month is something that is very important.

And the labels and all the advertising should

have clear black box warnings and clearly marked contra-indications and warnings. And those warnings and those -- that information should include information that what happens if this drug is taken for more than 3 days or more than 5 days or more than a week, more than 30 days. It should be very specific in terms of the times and how addiction is more likely after specifically used for a period of whatever number of days. And when we're looking at the risk to benefit ratio, we have to look at which patients we're talking about. Some types of patients might be more likely to become addicted, and that wouldn't be just sex or race or age. It could be comorbidities and other issues, and that should be studies and specified. And the FDA should not be approving opioids for types of patients that they didn't study.

Only the types of patients that were studied should have an indication. And if that were true, we think that more companies would have more diverse populations in their studies. I just want to use one example which was an opioid implant from 2016. This is at a time when FDA already knew about what was

happening with opioids, and yet, there was an application that was based on a single 6-month control trial with major design flaws. I don't have time to go through all of them.

But, for example, patients receiving the device who discontinued the study without providing efficacy data were excluded from the intention to treat analysis. That should not happen. My personal favorite was when patients who missed their urine, drug tests were considered negative instead of positive. Obviously if they missed their test, you know, you should think, well, maybe there is a reason. And in addition, in this particular -- for this particular product, 84 percent of the patients were white, and it was not that big a sample. And yet the decision was that FDA approved that product.

I want to end up by talking about the REMS program, which of course, enables FDA to approve products that would otherwise be considered too risky. And for opioid REMS, we agree with the FDA that REMS should be offered for all opioids and for all health professionals dealing with pain management. I want to

point out that an analysis provided to the FDA by Josh Sharfstein and Caleb Alexander of Johns Hopkins indicates that the REMS for turfs, that's the immediate of these fentanyls, were not effective. It was clear that these products were being wildly used by patients who should not have gotten them. There were all these red flags that the REMS were not working, and yet, the red flags were ignored.

Just briefly going to talk about the previous REMS programs that FDA had for long-acting opioid prescribers. Only 20 percent of those prescribers completed the voluntary training. Only 59 percent of prescribers were even aware that the training was available. And I am just going to quickly go through some of the results of what they -- what the doctors learned who took this training.

The blue is correct answers, the grey is incorrect answers. Here is a basic question, what is the recommended way to safely confer an opioid tolerant patient to extended release opioids? You can see most of the doctors got that wrong. Oops, I don't know what happened there.

Then, there were a bunch of other questions about is the family history of mental illness relevant? Are there specific federal limits to the quantities prescribed? You can see that vast majority are getting some of these answers wrong. Should prescribers perform a comprehensive physical exam? Got that wrong. Should they systematically perform drug screening and follow up visits? Almost everybody got that wrong.

So, the question is, how well are these REMS working? And how can we make them work better in the future? In the past many doctors don't know about the training. Half the doctors who started -- excuse me, started training didn't complete it. Eighty percent of the long-acting opioid prescribers weren't getting trained. And even the doctors who were trained weren't learning everything they needed to know.

So -- and another thing is that the sponsors are the ones that are evaluating. So, they tend to say, look, the opioid crisis is decreasing, and so, our REMS are working. But we all know that there is lot of other reasons why things are changing. And we don't think that sponsors should be evaluating the REMS.

So, will guidance -- your guidance improves REMS? I hope so. We think that, yes, training would be for all doctors, that's good, and all pains -- health professionals, that's important. It would be specific; the REMS would be specific to the specific opioid product. We think that's good. But there is a big problem. If it's voluntary, there still would be a lot of health professionals not getting it. And if there are no clear incentives for doctors to complete the training and actually learn, in other words there should be certification to prove that they have learned what they need to learn. And of course, the big question, who is going to evaluate the impact of the REMS, and it shouldn't be the sponsor. Oops, I am sorry; I do have just a couple more things.

So, when you look at the guidance, and you think of what's there, which is great, and what the reality is, you need to know who is going to monitor risks of prescribed opioids in the real world and how many of these drugs will be used off label versus for the indication that FDA has approved it for. And you know the sad story about who is going to actually read

the labels, even the black box warnings, who is going to be influenced by the ads.

So, in conclusion, I just want to say that although I am focused on new opioids in my talk, I agree that the old opioids on the market also need to be studies, absolutely, need to be studied, the generic ones need to be studied. I was very impressed with Dr. Dart's remarks, thank you very much. And the -- especially the enriched enrollment, which is something that just was mind boggling to me I have to say. But thank you very much for the opportunity to be here, and I'm glad to answer any questions.

DR. THROCKMORTON: Thank you, Dr. Zuckerman. Questions from the panel.

MS. SIPES: Thanks for your presentation. I wanted to go back to your point about when you were talking about the risk-benefit ratio, and you're talking about how the drug should not be approved for any types of patients that were not studied. I was wondering if you could comment a little bit more on that in terms of how that would work in a practical level, how the trial will be designed and how the

groups would be defined.

DR. ZUCKERMAN: Sure. And that's a great question and something that comes up a lot with FDA approvals where sometimes these people in the studies are mostly white or mostly man or mostly women, but then the product is approved for everybody. With opioids, we can't know every single group. Obviously, you can't study every single group. But there are certain major groups that we think should be studied. Obviously major racial groups, men and women, age is important. Sometimes drugs are approved that have only been studied on people under 65, and they should be studied on people of all ages. And comorbidities are really important as I think especially mental health and some other groups that have tend to -- have a tendency to self-medicate. So, you want to make sure that the product is going to be safe and effective for those major groups. And obviously, you can't do every single possible demographic health group.

MS. SIPES: So, the underrepresentation of some of these types of patients, is this something that you perceive to be unique to the opioid area? Or are

you seeing this in other therapeutic areas? And how would you propose that clinical trials be conducted so that you can actually bring in a more diverse population of patients?

DR. ZUCKERMAN: I know that sponsors usually say we're trying to have a diverse population. This is what we've got. But we also know that when sponsors design their studies, they want the best possible outcome for their studies. And so, there is a tendency to have the healthiest sick people in whatever group it is. This is an issue that is not just opioids, it's just that because of the problems with opioids it's sort of a bigger problem. But, yes.

So, if -- we believe that if the company has an incentive to have a more diverse patient group and do subgroup analysis, that's what's really important. You don't want five African Americans in a group of a thousand patients. You want to have enough of each of these major groups that you can separately analyze them to see to the benefits outweigh the risks for that particular group.

MR. STEIN: In terms of the content of the

REMS, you mentioned making -- including more product-specific information. Are there other recommendations you have regarding what you see as particularly important to add to what's in the current training that the REMS provides? Are there areas that you think need to emphasize more or need to be included that aren't included?

DR. ZUCKERMAN: I think what -- you know, that the REMS would look different if it was specific to specific products. And so that take -- you know, that's a harder question to answer and one that I think is an important one that you're looking into. But I think that the biggest problem with REMS is the voluntary nature and the lack of certification, and I know FDA doesn't like to tell doctors what to do and require certain training. But I think the opioid crisis is one that is serious enough that training should be required, and certification should be required.

DR. THROCKMORTON: Thank you very much.

INCENTIVES FOR NEW THERAPEUTICS TO TREAT PAIN AND ADDICTION: AN INDUSTRY PERSPECTIVE

DR. THROCKMORTON: And our next speaker is Dr. Danielle Friend from a Biotechnology Innovation Organization.

DR. FRIEND: Good morning. I first want to thank the FDA for hosting this meeting and allowing us to share our thoughts. I'm Danielle Friend, Director of Science and Regulatory Affairs at the Biotechnology Innovation Organization or BIO. BIO is the world's largest trade association representing biotechnology companies, state biotechnology centers and other related organizations within the United States and across the globe. Thank you.

The focus of my comments today will be on the last question included in the docket, in mechanisms for spurring investment and development of novel and safer therapies moving forward. In February of 2018, BIO released a report on the State of Innovation for Highly Prevalent Chronic Diseases, taking a look at the current investment trends and pipeline for pain and addiction therapies. You can find this report on our website. I'm going to briefly step through some of the data that was included in that report and discuss why

it's important for us to provide some regulatory certainty and some incentives for companies that are developing pain and addiction therapies moving forward.

Perhaps one of the most striking figures that was included in that report was a chart that looks at investment, venture funding as a function of U.S. healthcare spending. What I hope you can appreciate, in the lower right-hand corner, is what you see for both pain and addiction. So, compared to many other therapeutic areas, pain and addiction impacts a wide range of people, resulting in high amounts of U.S. healthcare direct costs. However, venture capital spending for those therapeutic areas is relatively low.

Another way that we can look at investment in R&D in a particular therapeutic area is to take a -- take a look at Phase I clinical trial starts. This chart is examining Phase I clinical trial starts in the context of pain, and each bar represents the Phase I clinical trial starts for a given year. What I hope you can see is from 2013 to 2017 there was a reduction in the number of Phase I clinical trial starts for pain therapies. We have seen a slight uptick in 2018, and

we're hopeful that that trend continues.

In, you know, in taking a look at these investment trends and what is in the current pipeline, one of the things that we also looked at was clinical trial success rates. And so, this chart takes a look at clinical trial success rates for all therapeutic areas compared to clinical trial success rates for pain therapies. The gray bars represent all therapeutic areas, and the orange bars represent that for pain. And what I hope you can appreciate is that across the board in Phase 1, Phase 2, Phase 3 pain therapeutics have a lower clinical trial success rate as compared to all other therapeutic areas.

Lastly, I just want to point out the last set of bars, when we take a look at therapies that advanced from Phase 1 all the way to approval, most therapeutic areas are, I guess, taking into account all therapeutic areas together. There's about a 10 percent clinical trial success rate, which is 1 in 10. However, for pain therapies, it's much lower; it's 2 percent or 1 in 50. I just wanted to mention here the current pipeline for addiction therapies as well. The far right-hand

column is a chart looking at the currently available options for treating opioid use disorder. The left-hand column -- excuse me -- the right-hand column is the current pipeline. And you can see that there are only four therapies currently in the pipeline for treating opioid use disorder. And you'll see just below that, two therapies are now not active or discontinued.

So, taking all of this data, BIO pulled together a working group, which is now made up of approximately 30 of our member companies, really to identify what were the barriers for preventing investment in R&D into pain and addiction therapies moving forward. We identified three key pillar areas. I will just discuss one of those today, but I think others have talked about some of the reimbursement issues, and that certainly discourages investment and R&D for these therapies.

But for the purposes of my talk today, I'll focus in on really some of the policies that would be helpful in the regulatory space. So, my following slides have a couple of recommendations, and we'll just

step through those very quickly here. Just want to mention that BIO plans just in that formal comments and the dockets will have much more extensive information for the FDA in that public docket.

But one of the first recommendations we would like to just highlight is that some of our companies have indicated that there have been delays in their ability to engage with FDA, particularly for the division of anesthesia, analgesia and addiction products. I do want to emphasize that we recognize that the FDA has been inundated with meeting requests to an unprecedented number. And I also want to recognize that our member companies have indicated that this division in particular has been extremely transparent and as flexible as they can as far as requests go.

But we would like to request that the FDA prioritize fully staffing and resourcing this division so that they can appropriately engage with and review pain addiction products moving forward. Our second recommendation focuses in on providing guidance for sponsors that are developing pain addiction therapies.

I will say the FDA has announced its intention to withdraw the 2014 draft guidance on analgesic indications, and Commissioner Gottlieb indicated, you know, his concern regarding some of the barriers for innovation in that guidance. Our companies are sincerely looking forward to the release of that guidance and, you know, strongly believe that it will help them develop their pain therapies moving forward.

I will step through a couple of areas that we would like to hear more from the FDA on. We certainly believe that these areas will spur innovation and help companies that are currently developing products in the pipeline. So, with this request, we ask that FDA hold a series of public stakeholder meetings to discuss several topics and then develop or update guidance as relevant.

So, one topic in particular is opioid-sparing. We recognize the FDA held an advisory committee meeting in November of 2018, and we appreciate that. We are looking forward to further conversations around opioids-sparing, specifically in the acute and chronic pain space, as well as the evidence that might be

needed in order to reference opioids-sparing and labeling products and the length of clinical trials and desired design of clinical trials to demonstrate opioids-sparing.

Similarly, I think it's important for there to be further conversations around mechanisms for evaluating pain. I think many stakeholders understand that the current 1 through 10 scale, you know, certainly doesn't capture the entire picture of an individual's pain. So, having public stakeholder meeting around mechanisms for evaluating pain is important.

Similarly, innovative clinical trial designs that might be used for developing pain therapies. Also want to recognize that the FDA recently included a pain protocol in the innovative clinical trials pilots. We appreciate that, and we're looking forward to learnings.

In the addiction space, we would also like to have more stakeholder discussions and develop an updating of guidance on reduction of opioid use and specifically how the reduction of opioid use can be

used as an endpoint. Also recognizing the FDA release guidance on efficacy end points for medicated-assisted treatment. We're looking forward to seeing updates to that guidance and hopefully finalization, as well as further discussions around possible innovative clinical trial designs that can be used in the context of addiction therapies.

Our third recommendation that I want to mention today is asking the FDA for clarification around how companies can take advantage of existing expedited approval pathways. It's our understanding that companies developing pain and addiction therapies can actually use expedited approval pathways. However, in speaking with our companies, it remains unclear to them some of the eligibility criteria for both pain and addiction therapies, including the level of evidence, the public health benefit and ability to address unmet medical need, as well as the expected engagement with the FDA.

So further clarification from the FDA via guidance would be greatly appreciated. One quick thing that I do want to mention in the context of expedited

approval pathways is that in speaking with some of our companies that work in the acute pain space, they are very interested in breakthrough therapy designation.

However, because acute pain therapies advance through clinical trials so quickly, the additional engagement that one will receive through breakthrough therapy designation, they are not actually able to take advantage of that additional engagement given the speed of the trials in particular. So, I just wanted to highlight that.

And then our last recommendation, just for the purposes of the talk today is to mention that we know that the NIH is working very hard with our HEAL Initiative. And then in particular, they have their EPPIC-Net Program which is a clinical trial program which will allow the testing of pain therapies in particular through this EPPIC-Net Program.

We certainly think that the FDA has value to add in those conversations regarding potential clinical trial design for the assets, as well as selection of endpoints. And we encourage the FDA to be vocal and clear about how they're engaging with NIH on the EPPIC-

Net Program. Further, as FDA continues to advance their policies, we encourage them to interact with other federal agencies as relevant. As I mentioned, BIO will be submitting more extensive comments to the docket in November. But at this point I'm happy to answer any questions that the panel may have.

DR. THROCKMORTON: Thanks very much. I'll begin just to point out that the 2014 guidance has already officially withdrawn, so.

DR. FRIEND: Sorry, if I wasn't clear. Yeah, we're looking forward to seeing the update on that…

DR. THROCKMORTON: Yeah, that was done recently, but it is in fact accomplished. Other questions from members of the panel. Peter?

MR. STEIN: You went over the low rate of Phase I to approval for novel pain medications. Can you speak about some of the barriers in particular as to what leaves them really (inaudible)? And I'd also be curious, obviously there are many reasons for the -- on the prior slide for the low investment relative to the U.S. direct healthcare prospective. If you could speak more about some of the background as to what you

think contributes in particular to that low rate of investment?

DR. FRIEND: Sure, sure. So, to your first question regarding the low clinical trial success rates, I think there are several factors that contribute to that, but one of the key things that we hear from our member companies is the issue with placebo effect in the context of pain. That that is a huge issue, you know, with running the pain clinical trial. So, I would say that it's probably the most significant impact that we hear in that space.

As far as, excuse me, the lack of investment for pain and addiction therapies. You know, certainly the -- my comments today have focused on regulatory certainty and making sure that that exists. Some of the other pillars that Bio has focused on include really looking at the payment and access space. So, for example, novel pain and addiction therapies, there are reimbursement and access barriers that prevent those therapies from being reimbursed by insurers, and so that is actually determined from investors entering that space as well as companies. And then the other,

the one key -- the other people pillar that I also did not mention due to the limit of amount of time I had to speak is focused on really the, you know, basic neurobiology of pain and addiction. And that's where we see that NIH can play an important role. And certainly, again, just emphasizing the importance of FDA engagement with NIH on those efforts.

MS. SIPES: Okay. Thanks for your presentation. Could you expand a little more about -- you were talking about expedited pathways and questions arising about public health benefit and ability to address unmet medical need. Could you expand on that a little bit?

DR. FRIEND: Yeah. So, we will be providing some more extensive comments within the comments that we'll be submitting to the docket, but there just seems to be some confusion from companies as to whether pain and addiction therapies can qualify given the, some of the current definitions, such as unmet medical need and benefit.

DR. THROCKMORTON: And so, I -- Others? I'll follow up. I have a question about your heal

initiative slide, and this may be something that you will be submitting a comment to it. Exactly what outcomes you'd like to see from that engagement between the FDA and NIH around the HEAL Initiative would be really useful.

DR. FRIEND: Sure. We'll be happy to submit those to the docket as well.

DR. THROCKMORTON: Thank you very much.

And with that, we are at the end of the morning session. I will have us back at 1:00 o'clock, Meredith, for the beginning of the afternoon session. Thank you very much.

LUNCH

(Recess)

DR. THROCKMORTON: We have a list of speakers that have registered, and then we'll move from there to the open public hearing speakers. At present we have three people that have signed up for the open public speaking part of the afternoon. The first person that's going to be talking this afternoon is Mr. Matthew Iorio. Apologies in advance. Please, sir, you're welcome to come up. Thank you.

MR. IORIO: Thank you. First off, thank you very much to the FDA for allowing me to come up and make this presentation. My name is Matthew Iorio. I have my Regulatory Affairs Certification and my master's in Regulatory Affairs and Health Policy. I also have 9 years of experience as an executive at a generic contract manufacturing organization of controlled drugs, and I am currently the President of Eighty Eight Pharma.

So as a disclosure, this discussion is a perspective of a for-profit pharmaceutical company, and we are actively developing products in this space. Eighty Eight Pharma is a startup. We were founded in 2017. We operate out of the Mansfield Bio-Incubator in Mansfield, Mass. So, we're going to be one of the smaller companies that the Agency has interactions with. We don't have manufacturing facilities, so we outsource all the different manufacturing that we do, and that structure allows us to be a native part 4 company, which is a term I just made up to describe that we don't go into drug devices or biologics. We

can go into any direction or combination depending on what suits a product development so that unique structure allows us to develop innovative products like this guy, which is a fixed point in a unit of use, a container that holds 15 tablets. Each one of those has a spring-loaded hammer with the cavity that has naltrexone, and when you push the button, it will be -- we're deploying. So that's the sort of products that we're developing.

So, the opioid epidemic has acted like a tracer dye injected into the United States. People who were invisible are now the focus on the nation. I find it breathtaking and hopeful to watch the new developments every day as the most powerful nation in history develops unheard of -- or deploys unheard of resources to help Americans struggling with opioid use disorder. The focus extends to many vulnerable groups, including people who are incarcerated, people with OUD, who are struggling with mental illness or who have HIV and HCV. We now see people with OUD who live in rural communities, urban communities, tribal communities or people who are struggling with despair.

Finally, the focus extends to people who are in chronic pain and need to navigate this complicated and stigma-laden medicine. I see tangible efforts like to SUPPORT Act that's fixing longstanding problems. For instance, historically methadone treatment has not been covered by insurance. If you needed treatment for OUD, you had to show up at the methadone clinic with cash in your pocket. That was a stigma-based regulation born out of the belief that showing up to a methadone clinic is not an opportunity to get better. Now all FDA-approved medication assisted treatments are covered by Medicaid -- will soon be covered by Medicaid.

Switching gears to another critical legislative effort, broadband. We're talking a lot about telehealth, telemedicine and telepsychiatry to very remote areas. And for these to work, we need to make sure that the federal plan to expand the broadband infrastructure is doing what it's intended to do. To do telemedication assisted treatment, we need Internet connections sufficient to clearly see each other through video chat. So that's where we need to get to.

Jumping right into the guidance. My understanding is that the reasoning for the guidance is sort of a preventative action for future epidemics. So, my thought is that most improvements in that benefit-risk profile would be by reducing risk with minimal to moderate production efficacy. So, I was a little bit surprised to see in Section C, does this analgesic drug offer any advantages relative to available approved analgesic drugs for each indication with regard to effectiveness or duration of response?

I see that as an opening to create a higher potency or extended release drugs. And while that might satisfy making a drug safer in some aspects, I don't think that that's sort of what is the expectation that's going to come out of this guy. Just wanted to mention that.

Moving on. Does the Agency have the authority to require -- to address these issues? So, 21 CFR 820.3, this, of course, is in the device side, design validation shall improve software validation with risk analysis where appropriate. So, if you've ever done device hazard analysis, you know that you have to

consider second-order hazards. So, switching back to the drug side, you've got ICH Q9 quality risk management. If you're doing quality by design, you should be doing hazard analysis. And so, you should have a lot of this baked into your development already. So, I don't think that actually any new authorities are required.

I think the existing authorities could be used. You've got your ICH Q9 with your hazard analysis. You've got the risk-benefit assessment described in a recently issued draft guidance, which is sort of pointing in the direction of what your hazard analysis should include. And then most importantly, the Agency has the ability to withdraw marketing approval of unsafe drugs, and that's something that we've talked about, or I've heard talking about quite a bit today. And I think in a way, that would be helpful to the industry because you could remove some of the less safe products and their generic equivalents, Don't forget about those when you have available more safe products that would eventually have generic equivalents. I think that would be helpful.

Alternatively, you could go to a straight standards approach, sort of new legislation modeled after something like the Federal Motor Vehicle Safety Standards. But these iterative standards apply better to devices then drugs. But if you start to look at some of the things that we're packing on to these opioid analgesics with the REMS program and prescription drug monitoring programs, we're getting well beyond just that, you know, the molecule. So, whoever put this question in, thank you. This is going to make one of my points perfectly. So please consider that existing opioid market consists largely of relatively inexpensive generic drugs. So, this is from the Surgeon General's Spotlight on Opioids. The effect of the opioid crisis are cumulative and costly towards society, an estimated $504 billion a year in 2015, placing burdens on families, workplaces, the healthcare system, states and communities."

And then from the *Wall Street Journal*, "The Ohio Trial is slated to take place before the U.S. District Judge in Cleveland, who is overseeing the consolidation of some 2,000 cases brought by cities,

counties, Native American tribes and other entities seeking to recoup the public costs of opioid addiction and abuse. So, you've got $504 billion, which is the opioid crisis cost to society divided by 216 million opioid prescriptions and that equals $2,333 cost to society per opioid prescription. So, you have to ask yourself are these $15 bottles, or are these $2,348 bottles? And then who pays this cost and who should pay this cost?

Now of course, this is the elephant in the room because for as long as we're going to be stuffed with these $15 bottles of generic opioids, nothing is ever going to be able to come in that's going to be safer because it's going to be more expensive, and it's not going to get coverage.

If you look at it, more features mean more cost. More cost means more reimbursement. And here's what we're really looking for proof of net savings, so you get lower reimbursement, and that means lower penetration and to make the product viable companies raise their price. So, you've got high priced therapeutics chasing high risk individuals and the end

result is a lower overall impact on that $504 billion. And if you want to see this in action, as some of you who came before me was talking about, how they went in for a buphen (ph) patch that costs $400 a month, which is the safer alternative. Their insurance may not cover it. And they offered them a $12 prescription for oxymorphone. That is exactly why it's difficult to bring in your safer innovative products because you are always undercut by this extremely cheap, and they're effective generic opioid medications. They're just not as safe as we would like them to be.

So, we get to justify higher prices for safety innovation. This is something that we're going to need to do or at least I will need to do if I'm going to get my products to market. How should comparative advantage be defined and can be quantified? Really it must be quantified to be persuasive to payers and the public about their merits and their advantage. You have to quantify it in order to justify the increased cost of your safer innovation. So how do you justify it or how do you get your slightly -- your products with more features, more safety improvements in market?

Either the Agency just root for us, hold off the other products, or you go to a process of cost benefit justification with all that economic data.

So, you could set up a system where at launch -- this is going to be at launch, you would have N communities. You randomly select interventional and control communities, which is problematic because you've got informed consent on second-order people so that might make this a challenging thing to justify it. Pick your endpoints that payers care about. Figure out what payers care about. Figure out what the Centers for Medicare & Medicaid Services care about, which interesting enough is a meeting on Friday, so we'll figure that one out. And then what epidemiology tools can be used, and who hosts them.

And actually, there's another discussion also on RADARS. This actually will define this sort of thing. Then you ask yourself through low cost phone surveys, chat-room monitoring, and community data be acceptable to support endpoints. There's never really been sufficient for the Agency, but if it's used broadly for economic data, that might be possible.

That is the end of my time. So, I will take questions if you have any?

DR. DAL PAN: Yeah. About this Phase IV prospective observational study that you're proposing -- random intervention and control book, what are the interventions you're talking about?

MR. IORIO: Sure. So, you've picked your communities to deploy your intervention -- you pick 10 communities, you would launch in 5, and 5 you decide not to launch into. And so, you have that differential where you could make some determinations using a randomized sort of style, and hopefully, be able to get the power to make some of these determinations.

MR. PAN: That I get, but what is the intervention that will be randomized of particular medicine, some other treatment strategy, an educational program?

MR. IORIO: It could be any one of these. So, let's for instance say you had a proposal fixed quantity unit-of-use blister packs, and the Agency moved forward with that, which actually I think is a really good approach trying to limit some of the excess

medication on the market. You want to determine if that is effective at preventing this and subsequent harms that having excess medication in tablets to happen. You can pick your communities that you're going to launch, you randomly pick out of your -- and the ones that you're going to launch those blister packs into and the ones that you're not going to launch the blister packs into. And then maybe over time, you can sort of see some of that get that differentiation and see if you're making that happen.

MS. SIPES: And thanks for your presentation and on the same topic that Dr. Dal Pan was just asking about, do you view this as you sort of suggesting this as something that companies would undertake, or would this be a requirement? If so, how would that work?

MR. IORIO: So, there are potentially some claims that if a company might want to make they would have to go through this route. I mean this is a little bit extreme and, but you could. If we're looking at say an abuse deterrent technology, and we're trying to determine if it's actually had an effect in the community on lowering abuse, you have to set up some

sort of a -- some sort of a way to determine that. And this would be a way that in the post-marketing phase if you try to figure out if your abuse deterrent technology is working. You know, there's been challenges right now with figuring out if abuse deterrent technologies work with a product like the one that we're developing. We're trying to limit excess medication so at some point, we have to actually make determinations; is this effective? And we have to set up some sort of a trial. And this is sort of my best approach, of course, in taking feedback, you know. How can we set this up? How can you actually do these sorts of studies? You know, these are done to some extent in academia and the academia -- there's some approaches with say vaccines and different things that have used these sort of approaches, but just sort of how do we use this now for some of these innovations that we feel like we're going to have an impact, we want to justify their impact. How do you start to do this?

This is important for the second-order effects. The first-order effects you enroll your

subjects, you track them, you know what they are going to do. How do you then track the other people in those communities who you're assuming are having some sort of an effect, if it'll be a positive or negative? You have to figure those second-order effects out and so you have to sort of dig down to the community level for these second-order effects. But I think that's sort of squeezed dry. If you're trying to actually make, I mean, maybe a claim or at least a health economic justification about the second-order effects, how do you get to those? I think that's challenging.

DR. THROCKMORTON: So just to continue in the theme so in the guidance that -- the draft guidance that we have, are we to talk about the use of data of this kind mostly in terms of understanding it and under the abuse or misuse populations those kinds of things? Are you suggesting that we think about requiring these kinds of data in different settings than those or use them to support different kinds of endpoints than we talk about in the guidance?

MR. IORIO: So, it most likely discussion about how are we going to establish some of these

second-order effects? Let's say we launch a product and we anticipate it's going to have some sort of a beneficial effect on the patients and on second-order, on the community. If we just launch the product and then you look at the overall trends, that's not as persuasive as having some sort of a randomized aspect to it. So, what we're currently looking at is launching a product, tracking it and looking at the effects. Well, with a little bit of forethought if you can actually deploy strategically as you're monitoring, you might be able to pick up some of these more solid effects, potentially some of these second-order effects just trying to get down to that. It's just a question of when you launch, you know, a little more strategic about how you're launching so you might be able to pick up some of these. Of course, it does get back to some of these -- said issues, some of the challenges with it. But when you're looking at the second-order pieces, how do you get down into those? It's challenging and actually proves -- may not prove, but actually get it some of that persuasiveness that having a randomized element to it will get you that.

DR. THROCKMORTON: Great. Thank you very much. Our next speaker is Dr. James Campbell from Centrexion Therapeutics.

FDA SUPPORTING INNOVATION IN PAIN THERAPEUTICS: AN INDUSTRY PERSPECTIVE

DR. CAMPBELL: So, hello everyone and it's a real pleasure to be here and thanks so much for the opportunity to talk to you today. So, I'm going to represent a biopharma perspective, and my remarks are going to pertain to the issue in particular of incentives.

Centrexion Therapeutics is a company whose sole focus is developing non-opioid, non-addictive novel therapies for the treatment of chronic pain. Our portfolio, I'll just mention in passing, includes products in Phase III going all the way to pre-clinical. We actually have six products in our pipeline. And again, all of these are focused on the issue of chronic pain. Our lead Phase III product is an injectable capsaicin, which is injected into the knee for purposes of controlling the pain associated with painful osteoarthritis.

It's -- with that we're here talking about novel therapies in the context of a meeting that is -- has to do a lot with the use of opioids. So, I've started actually in the pain field as a medical student at Yale back in -- some decades ago. And the conversation then was about use of opioids for pain. And it's striking that the conversation still today is very similar. So, we're in a field where there has been remarkably little innovation, and we need to reflect; and when I say, "we," I mean industry, academia and at the policy level in terms of our government institutions like the FDA and NIH about why this is.

But I think a positive thing that we can do about the situation revolves around use of incentives. So, this slide is just a reminder slide about how biopharma company sits within a very complicated matrix that involves lots of things working. So, this wheel of intersecting components involves science, IT, regulatory issues, patient issues, payers, and then investors. All of these components have to work in order for us to innovate. So specifically, I want to

address my remarks to questions posed to us in the context of this meeting in particular. Do incentives -- are they needed? Which incentives would be most effective? And I want to get into the issue of what should be the criteria for designation in terms of how these incentives should be implemented.

So first of all, are pre-approval incentives needed? And actually, before getting into that, there are a couple of things to be said about regulatory processes that we think would be impactful in terms of bringing about innovation, bringing investors into the pain development process. So, one of those has to do with nimbleness of interactions. So, investors pay a lot of attention to the processes that occur in terms of drug development, in terms of what is the nature of the interactions. So quite often they deal with great formal interactions that involve for example, type C meetings, which lead to further type C meetings because there are certain things that are not clear. And so, one way to put this is to refer to a nimbleness of interactions as being a component of what would be an incentive ultimately to investors.

The second component of this revolves around resources. So, more funding, more bodies are going to be an incentive ultimately to investing because it establishes the priority. So, if we have an under resourced agency dealing with the applications for novel drugs for pain, we're going to see a prolongation of the approval process, and it's simply going to be more cumbersome, and it's going to take longer and cost more. And so, I think this is a very important component as we consider the whole issue of incentives.

Another question that was brought up in the context of this meeting is what new incentives would be most effective? And so, it's pretty easy to generate this. And so, one of the incentives has to do with this nimbleness, if you will, of feedback. And I'll get into the issue of breakthrough designation momentarily and this is another area for us to consider. But there are other incentives that are going to have a great impact on whether investing in new novel pain medications is going to make sense from an investor perspective. So significant tax credits for investment in non-opioid drug development would be

one of those incentives. A waiver of FDA filing fees would be another incentive that would be meaningful. And then, there is the incentive of market exclusivities.

So, in terms of incentives, one of the brilliant innovations in terms of designatory process that's been impactful for a number of diseases is the orphan product designation. So, this 7-year data exclusivity provision by the -- this orphan product designation has brought forward a number of novel therapies for diseases that just otherwise would not have been investible. So, it's to apply this to the field of chronic pain would have wonderful comments for having meaningful impact. And so, a suggestion would be that the 10-year market exclusivity provision would be a very decisive statement at the government level that, "Hey, this isn't important, and there has been a possibility of innovation, and we need to do something about this. And this is a part of our way of dealing with this opioid crisis and our way of leading to innovation where there has been very low over decades."

Somewhat related to this is another incentive,

and this relates to a voucher, a drug priority review voucher. So, this has been impactful in areas like pediatrics and for tropical diseases. And this would be of -- if this was applied to the development of novel non-opioid drugs chronic pain, this would have a -- this would make investment in the chronic pain area immediately highly desirable on the part of investors who would really stimulate innovation.

And finally, the third question is about how the -- these designations might be deciding. And we note that in the description of breakthrough designation that there is some level of clarification that would be very helpful. For example, in the breakthrough designation presently, there's reference to preliminary clinical evidence. Well, what is preliminary clinical evidence mean and if that preliminary clinical evidence only applies to a late stage Phase II product, what kind of impact on development is that going to have? And what does substantial improvement mean? And then thirdly what are meaningful controls in terms of deciding that a therapy is a breakthrough therapy? In a sense a

therapy that works over placebo is almost by definition a breakthrough therapy. So, this is another idea I think that would be helpful guidance in terms of making better use of this breakthrough designation. So those are my remarks, and I'll stop there.

DR. THROCKMORTON: Great. Thank you very much. Could you clarify that, the last comment that you made there about a product that beat placebo be by definition a breakthrough?

DR. CAMPBELL: Right now, I think there are a couple of things just for clarification, so I think getting fast track status is relatively easy in the -- within the analgesia division. One further issue is that there needs to be a greater clarity with regard to what the impact of breakthrough would be over a fast track? And right now, I think there is some uncertainty about what that exactly means in terms of the processes within the intervention division. And we get a sense that there is some difference of opinion in leadership about that issue.

In terms of take a problem like painful osteoarthritis of the knee well, if you have a drug

that works, it's almost by definition a breakthrough for osteoarthritis of the knee. It's almost by definition a breakthrough because right now we are stuck with steroids, which have issues of toxicity. We have HA's which are uncertain in the terms of their efficacy. We have NSAIDs, which are a problematic class in terms of long-term of therapy and morbidities related to cardiovascular disease and GI toxicity and kidney impacts; so how well suited are these for long-term therapy? So, if you have a therapy that works in that broad pain category, isn't that a candidate to be a breakthrough therapy. So, I think it would be helpful to clarify what the standards for breakthrough should be.

MS. SIPES: On slide 6, you mentioned, first of all, FDA commitment to a series of meetings, feedback prior slides. Can you explain a little bit whether -- because we have a series, different categories of meetings, are you actually still talking within those categories your type A, B, C, your CPIN meetings, were you proposing something --?

DR. CAMPBELL: I'm sorry, I didn't quite

understand clearly the question?

MS. SIPES: You mentioned that on slide 6 -- I'm sorry -- FDA commitment to a series of meetings and feedback. And I'm just asking a clarification because we have different categories of meetings the type A, B, C and your CPIN meetings that you mentioned here, are you proposing some other form of meeting?

DR. CAMPBELL: So, I think the intention is that there needs to be order and there needs to be some rules based for interactions. But on the other hand, if there are questions, and for example, that lead to a type C submission and then there is a response that takes a long time, and some of the issues are pretty easily clarified and could be clarified even with a phone call. But then because there's lack of clarification there, how the company goes back to the division to get this done. Right now, it almost looks like there needs to be another type C meeting, which then the clock continues on. In the meantime, how to deal with a pretty straightforward issue might be handled quite differently and much more nimbly if you will in a way that would save time and suit the needs

for helping the drug properly towards the ends of safety and efficacy studies.

DR. THROCKMORTON: Just to follow up on that. So, one way of heard that intention discussed was in terms of regulatory certainty versus speed of response. So, if you are looking for an informal response that maybe exactly that, that's something that a phone call could potentially get you. But that if you are looking for something that would be -- you could act on from a regulatory perspective, they're needed to be more formality. The question was how to find the right degree of formality recognizing that with speed comes a loss of some of that interaction -- loss of that certainty.

DR. CAMPBELL: Yeah. I think you're describing the situation. I think a -- we don't see informal contacts occurring, and I think if there were to be informal contacts, there could be clarification on what the issues are so that when it comes time to come up with the -- a more informal interaction then we can make sure things are outlined, so it's bit more efficient process. So, I think there is a place for

this recognizing that there -- ultimately there is a need for a formal process, and there is a need for formality. We see -- the feedback we get is that there is inconsistency between divisions on this -- and that's understandable. We would see the process to be more efficient if it was more interactional is maybe the word I am acting on.

DR. THROCKMORTON: Other questions? Thank you very much.

DR. CAMPBELL: Thank you.

DR. THROCKMORTON: Our next speaker is Dr. Judy Ashworth from Pinney Associates.

ASSESSING THE VALUE OF NOVEL OPIOID ANALGESICS

DR. ASHWORTH: Good afternoon. To begin with, I would like to thank the Agency for the opportunity to be here and speak today, and for holding this public hearing. By way of disclosures, I'm the chief medical officer at Pinney Associates, where I advise pharmaceutical companies that also that includes biotechs, and primarily with those working on CNS sided drugs and in new analgesic development. We advise on clinical and regulatory strategies. And, with an

emphasis particularly at Pinney Associates, with regard to abuse liability assessments and how companies can be guided through the expectations of the FDA and the DEA during the course of their development of compounds.

I also serve as the chief medical officer at Harm Reduction Therapeutics, which is a non-profit pharma company that's working for an affordable naloxone product on the OTC market. Although, I and my colleagues at Pinney Associates provide consulting services for many companies developing other medications, we neither solicited nor received any outside input into this presentation, nor did I receive any reimbursement for my travel or any compensation for being here.

My colleagues and I agree with the principle that a new opioid analgesic should be able to demonstrate some level of incremental improvement with respect how to use potential, or to some other relevancy to the outcomes, such as disparate pressure compared to existing schedule to opioid -- opioids that are currently on the market. However, today's healthcare system, even if a novel opioid product were

to be able to demonstrate an incremental benefit such as one of these, around policies around product labeling as well as scheduling under the CSF -- the CSA offers little basis for differentiation of these products. So as a result, third party payers have minimal motivation to accept these new opioids into their formulas and because they are more expensive than generics, of course, and also healthcare providers have little information regarding these potential benefits within the label.

So, from the FDAs proposed topics for today's discussion, I want to address two. And the first one I want to address is actually more to should sponsors of new opioid analgesics be required to demonstrate some comparative advantage relative to the existing opioids on the market.

For 17 years I worked at Grunenthal, which is a German pharmaceutical company in the development of analgesic medications including Tapentadol, as well as if you use the term formulations. As you know it's longer than the expectation of EMA, the European Medicines Agency, that sponsors do include active

comparators in the development of their analgesics.

So, given that Grunenthal was at that time collaborating with Johnson & Johnson here in the US on that development program with Grunenthal our global development program did have an active comparator in every single trial except for one, in the chronic pain and acute pain program. And I'm talking about the trials for submission and this, of course, was again it was needed because we went and -- we had to also submit in New York.

Thus, within the respective NDAs that was submitted to the Agency for Tapentadol, the FDA had substantial amount of data in its hands regarding the comparison of Tapentadol to other opioid antagonists with regard to efficacy, as well to safety in both the treatment and the clinical issues.

Unfortunately, even though these data were converged, randomized multi-pronged trials accepted by the Agency's basis for -- in these indications, the Agency didn't allow any comparative data into the labels. These all confirmed these trials not because they were elected or from -- it is just a simple matter

of policy, we don't allow comparative data describing these.

Though even if a sponsor gets it for a novel analgesic which has demonstrated benefits over schedule 2 opioid currently on the market without allowing any of this relevant data into the label, and I'm not saying big plates, just to have the data, the relevant data into the label, two things happen. Companies are left to educate the healthcare providers on these benefits for verifications, posters, conference calls, all of which will increase the need to scrutinize and consider suspect even when the data originated from trials and deemed acceptable for improving the drugs from third party payers and other organizations have learned a reason to encourage uptake of these products usually on a differentiated label.

So, when you ask what the FDA can potentially consider changing, in order to incentivize sponsors to develop novel opioids with better safety profiles, is to provide comparative data during that development and allowing these data into the label, is one area where I would point out to consider. This would help shift the

driving away from more commonly prescribed in the media, immediate releases schedule 2 opioids as being retracted for abusive origin. They account for the major prescription opioid abuse (inaudible).

With regards to topic 9, the FDA specifically asks for ideas regarding free-marketing incentives to encourage sponsors to develop and release better opioids.

The company use incentive, which was also just discussed by the Agency in the free-marketing space's expert reviewed mechanisms, which was back already reviewed in breakthrough therapy. And I think most companies have developed these two formulations they've gotten faster at. And that made that movement to a traditional line a bit more quickly than have they not have that. So, don't take it away, I'm not saying that.

But, the biggest challenge that these companies are facing is in the post-marketing world. It's not getting to the market, it's getting market access. Market access has proven to be an absolute nightmare for ADF (ph) companies as they currently

constitute only minimal fraction of the opioids in the market. This has sent a loud and clear signal to other companies and to investors to think twice before investing in any novel opioid analgesics.

The progress in bringing the policies to third party payers who favor an immediate release schedule 2 opioids over safer products such as ADFs have impacted the potential for these products and make any impact with respect to the products. This includes the VA whose policies continue to discourage the use of these products because they are more expensive than the over-the-counter -- I'm sorry, the generic IR opioids. And this is counter to the FDA's efforts to transform the market to a safer environment.

The VA is likely to correct its claim that abuse rates were, actually in their population, low, and, again we know that the abuse is just foundations and specifications, are being well monitored. It is the diversion of these drugs which is the material aspects of society.

Even for morphine schedule 3 partial agonist with a lower risk for -- more risk for, I guess, for

depression, is only allowed by unique payers to be prescribed after a patient has filled two schedule 2 drugs. And I don't know what that means to pay along those. But you can even get a schedule 3, safer compound at the service and that was mentioned in the -- this morning.

Due to these challenges, with regard to the access even with expedited review, there remains a substantial disincentive for companies to develop safer opioid products. I spent the last few years of my time in Grunenthal in section evaluation. I was involved in assessing the newest analgesics, which are novel opioids, and that any associates, as I mentioned, continue to work with and advise more companies and pharma companies are involved in this space.

There's a lot of pharmacy signs out there for our understanding of the opioid system and how to better target these receptors and interact with them concerning most of (inaudible). The companies working in this space are struggling to find investors, development partners, and due to this -- it's all due to the constraints on market access.

Again, I look at countless assets and look better to have some benefits, and they were turned down usually before due diligence because it was due to market access. So, we all seen [sic] what's happened to the ADFs and differentiated opioids like Tapentadol, Buprenorphine and that's what's scaring away most of it.

So, to summarize what can the FDA do, number one, allow comparative data into product labels. I know this is what you think, but the FDA can't solve the opioid epidemic by itself, but it can play an important role, in regard to the abusive prescription products and making sure that safer and better products get to the market that allow that relevant comparative data gets into the labels so that prescribers and payers can recognize the differentiation from (inaudible).

Work with DHHS and VA and third-party payers to encourage prescribing products for, which clinical studies and increasing billboard advertisement, suggest progress for abuse and overdose.

And lastly, work closely with other relevant

federal agencies to provide white papers that elucidate the issues and prescribe which -- what federal agencies can and cannot do, so there is better understanding and continue to encourage sponsors to develop applications and so forth. Thank you very much.

DR. THROCKMORTON: Thank you very much. Any questions from the panel? Thank you very much. Next speaker is Dr. Chris Storgard from Heron Therapeutics.

OPIOID-SPARING INDICATION, A PRE-APPROVAL INCENTIVE FOR NEW THERAPEUTICS TO TREAT ACUTE PAIN

DR. STORGARD: Good afternoon. Thank you for the opportunity to participate in this very important meeting. My name is Chris Storgard. I am the Senior Vice President of Clinical Development with Heron Therapeutics. I will be discussing pre-approval incentives for non-opioid acute pain treatments.

To encourage drug development in important public health areas there are existing incentives that should also be applied to encourage the development of non-opioid acute pain treatments. These include automatic fast track and priority review designations,

extension of patent exclusivity, and the granting of a priority review voucher. As these require legislative action, they would likely take time to implement. To address the opioid crisis facing our nation today, immediate action is also needed.

The pre-approval incentive we propose could be implemented now. This is for FDA to provide a clear development pathway to obtain an opioid-sparing indication for new, non-opioid pain, acute pain treatments. This could be implemented now because it is aligned with current regulations. The indications and usage section recognize that a manifestation of a recognized disease or condition is appropriate for an indication. The requirement for opioids is a serious manifestation of ineffective pain relief in the post-operative setting.

This is also aligned with current guidance that states applicant should consider whether other information, in addition to the disease or condition as warranted, be included. Opioid-sparing warrants inclusion because it will alert prescribers of what the product can do. It would immediately and unequivocally

inform prescribers that the product reduces or eliminates the need of opioids per FDA standards. This is important. It provides assurance for prescribers that they can reduce opioids without compromising pain control. This assurance is essential to impact opioid prescribing habits.

It also provides a clear differentiation between products based on solid evidence of opioid-sparing benefits. This benefits the patients, because when prescribers are better informed patients get better care. This is not about promotion. This is about how to best inform prescribers to help patients. Prescribers are much more aware of a product indication when they are updated in the clinical study section. And as I will demonstrate the information in the medical study section regarding opioid-sparing, maybe at a varying quality, and the relevance to prescribers is less clear. Including opioid-sparing in the indication is more likely to affect patient access and coverage. This directly impacts patients. If it's not on the hospital formulary, it is not covered by payers, patients don't have access to the treatment.

Last November at the advisory committee meeting on assessment of opioid-sparing outcomes in trials of acute pain, the FDA presented four products with relevant labels. All four products include mention of opioid-sparing information in the clinical study section. None have an indication statement referring to opioid-sparing. All four products included randomized, double-blind placebo-controlled trials however none included an active control. And with regards to opioid-sparing, results were not replicated for studies for non-statistically rigorous.

Here are the opioid-sparing statements from the clinical study section from three of the four products. The first two indicate clinical benefit has not been established or not demonstrated, and in the last the statement is actually included twice with the percent reduction in opioids. But there is no information on whether this reduction conferred any benefit. It's unclear how a prescriber should use this type of information in the clinical study section when treating patients.

But there are some potential challenges with

providing opioid-sparing indication, and they include: are there unintended consequences; what degree of opioid-sparing is needed; and can we generate the appropriate evidence in the confines of the clinical trial? We can address these challenges. But without a clear development path, it is uncertain if overcoming these challenges will result in the granting of an opioid-sparing indication.

At the November advisory meeting the FDA identified potential unintended consequences of opioid-sparing, such as what if a prescriber habits do change and there is decreased analgesic benefit, increased poly-pharmacy , or now a new analgesic with abuse liability? What if prescribing of opioids does not change and there are more leftover pills? And, what if the labeled opioid-sparing effect does not confer benefits in clinical practice? We believe these concerns can be mitigated. First, opioid-sparing must not compromise pain control.

In the acute, post-operative pain setting, the use of multi-modal analgesic regimens is already recommended and well-established, abuse liability

assessments are already required and in place. Leftover pills, this is where we believe an opioid-sparing indication could have the greatest impact, because an indication statement most effectively informs prescribers, and this can help change prescribing habits.

Lastly, we believe that the evidentiary rigor required to obtain an opioid-sparing indication means it should be as likely to confer benefits in practice as any other indication.

To what degree of opioid-sparing warrants an indication? This is important to define because it forms the basis of evidence generation and study design. There is agreement that the more opioids a patient consumes the more opioid-related adverse events they are likely to experience. However, there is no consensus on what degree of opioid reduction, in and of itself, is clinically meaningful.

The approach often proposed is to link opioid reduction to a reduction in the incidence of opioid-related adverse events. However, the impact of these events can be difficult to demonstrate for many

reasons. First measurement of these events is not standardized, nor validated. Most of the common adverse events from opioids can also result from surgery or anesthesia. And, most of the significant events are too infrequent to power a study of it all.

So, to overcome these challenges, we proposed post-operative opioid-free status as a clinically relevant endpoint for obtaining opioid-sparing indication. Opioid-free is an unequivocal, easily quantifiable, objective measure of opioid-sparing benefit. Opioid-free means no adverse events to opioid. Opioid-free means no risk of transitioning from acute to chronic opioid abuse. And importantly, opioid-free means no opioid discharge prescriptions, so there's no leftover pills to fuel the opioid epidemic.

The opioid-free endpoint is feasible to assess in clinical trials. As with all the efficacy endpoints, the definition must be pre-specified, but it may be different depending on the situation. The durability of the effect should be confirmed. And it should be compared to an active control, in order to be clinically relevant. And as I mentioned before, it

must demonstrate that opioid-free does not come, as a result of increased pain.

We believe that a pathway for inclusion of opioid-sparing in the indication statement will incentivize development of innovative non-opioid pain treatments. We believe this can be implemented now, because no modifications to the current FDA standards and requirements for granting an indication statement are needed. To warrant an opioid-sparing indication, the existing evidentiary standard statistical rigor should apply. We have proposed that opioid-free is a clinically meaningful endpoint, it's clinically feasible in clinical studies, and supports an opioid-sparing indication.

Providing a development path to obtain an opioid-sparing indication, will incentivize development. But more importantly, it will benefit prescribers. They will be more informed, and this will benefit patients and they can facilitate the needed change in opioid prescribing practice.

DR. THROCKMORTON: Gerald?

DR. PAN: So, if I understand your proposal

correctly, you would perform a clinical trial development program in a post-operative setting. In the point of your outcomes here, is they discharge opioid-free. How does this address the widespread outpatients of opioids for conditions where opioids might be needed for a longer period of time, or at different doses?

DR. STORGARD: So, this proposal is specifically for an acute pain treatment. So, it may not be applicable to the chronic pain situation, but even managing the acute situation is critical, because we do know that six percent of patients who get opioids in the acute setting become chronic users. When you take a look -- the number surges in the current year -- that's about 2.5 million patients, and of that, nearly a hundred -- sorry, half a million become actually addicted. So, although six percent may seem small, given the number of surgeries, it's a very important sizable population, where this approach would actually have application.

DR. STEIN: Thank you for these thoughts. But, a question about criteria for opioid-sparing. So,

you've gone through a detailed presentation on sort of the opioid-free as criteria. Are there other criteria that you considered -- obviously there's been discussion of different approaches to decide, you know, opioid-sparing, and you didn't comment on some of the other types of approaches. So, for example as patients are discharged earlier from a trial, plus procedure, and might need -- still might need opioids at discharge. Are there other kinds of criteria that you would consider as relevant to reduction in the requirement for opioids even patients who were discharged on opioids?

DR. STORGARD: There are certainly other criteria to look at. The reason we're proposing opioid-free is that it's clear-cut. The challenge for some of these other criteria, as I mentioned, there are challenges in measuring them. The adverse events are often confounded just from the event itself. And when you look at simply percent reduction, well, what percent is meaningful? So, this is a very clear-cut endpoint. If you are not taking an opioid and there are settings, such as bunionectomy and herniorrhaphy,

or others where that should occur right after the surgery.

So, you could be measuring this inpatient, you can follow the outpatient. So, it's a very clear-cut endpoint that we believe has real applicability. There are other endpoints to consider, maybe challenging, and I think that may be contributing to why we haven't had that opioid-sparing indication today.

MS. SIPES: Thanks for your remarks. One quick question, getting back to sort of where that would be the degree to which an opioid-sparing indication would incentivize development, you also mentioned that inclusion of an opioid-sparing claim in the indication is very important for access and coverage on your presentation. How do you think -- can you walk through a little bit more on how you think -- peers would react to inclusion of that opioid-sparing claim in the indication given the continued availability of other types of opioids?

DR. STORGARD: So, I can't speak for them, but I can only assume. And, I think that if we can offer payers the fact that this new medication has [been]

proven to allow patients to be mobile and free, either immediately, and long-term after the surgery, then we've seen the cost effects of opioids, 504 billion a year. So, I believe to be able to show definitely -- this with the medication you can avoid opioids, six percent of those patients who get exposed in the operative setting become chronic users, there is an economic benefit. More importantly there is, actually, you know, the benefit to [the] individual patient and the benefit to society as well.

DR. THROCKMORTON: Thank you very much. Next speaker is Dr. David Hewitt from Karuna Therapeutics.

CONSIDERATIONS FOR ACCELERATING THE DEVELOPMENT OF NONOPIOID ANALGESICS

DR. HEWITT: Thank you very much for allowing me to speak today. I am just thinking -- get this stuff over there. So, I'm going to be talking a little bit about some considerations for accelerating the development of non-opioid analgesics. Let me know if you can't hear me -- this may not be working always that well.

So, we talked earlier about what some barriers

are to the development of novel analgesics. Now, I just thought I'd go over some of my favorites. One is it's a very highly genericized market, pain is. And I say this from being both inside big pharma, and also have been in a -- you know, being at a CRO, I've gone to see some of these statements. Opioids are inexpensive and, as we saw, there are a lot of opioids that are generic. The benefit-risk of novel analgesic therapies is something that really hasn't been discussed that much. I think there is guidance when we talk about the benefit-risk of opioids, but non-opioids are more problematic.

It's not clear where that standard would be relevant to the opioids, or it really had more of a discussion of the benefit-risk posed to individuals and the society overall. Or one could ask oneself is whether we could have a side-effect profile, a benefit-risk profile of a non-opioid analgesic that would be similar to an anti-psychotic or an anti-convulsive. And, I think that's a debate that we can have. I'm not sure how much baggage for the benefit-risk would look, compared to those.

Another barrier was the current non-opioids and antacids work really well for a large number of people. And, a lot of companies actually don't always perceive, and on that need, I didn't recently look at the top 50 companies, just now, that are looking at drugs for analgesia, not a lot out there so. And, obviously that is one of the perceptions.

Interestingly, pain is a target obviously for both proven and unproven alternative medicine approaches, there's also a large number of medications that are OTC, as you're aware, and that cannabinoids are now becoming more used commonly. They have the benefit of -- working on both the sensory discriminative point of pain, which is what most of our drug approvals are based on, but it probably also works on the sensory effect component of pain which we really don't have great measures, which we could talk about later.

There is a -- there are a large number of pain indications which is a good thing because it helps you differentiate your drug. But also, if you want to get a joint pain indication, it's a lot of work. It's a

lot of work and it may be a bit of disincentive. So, I'm not saying we shouldn't have them the way they are right now, but I do think we should think about why we need such a large number.

And, of course, every time you have a negative study in pain, it's the same as a negative study in CNS or depression. Negative studies are uncommon because of the high placebo effect. And so, we're always sort of dealing with that big issue. And, then there is the question of predictive value of pre-clinical models. I like preclinical models, but a lot of people are calling to question their value. And I can tell you that for large -- a number of pharmaceutical companies -- it's become a big issue.

There's also the value of translation on medicine approaches, which I think are also very valuable. They could be very useful, but they're really not available to -- they may not be good for making 'go,' 'no-go' decisions in terms of further development. They may be good at making 'go,' 'go slow' or 'go gung-ho', but they're not very good at making, you know, the decision to actually drop a

study, or not.

So, I wanted to just talk about a few things we might be able to consider to speed up development of novel, non-opioid analgesics. One is we should consider enhancing use of existing accelerated development programs, frugal pathways, including breakthrough status, which have been discussed already, and streamline the development requirements for novel, non-opioid analgesics. Sometimes, it feels like, you know, that it's got a bit of a high bar. We should designate priority review. I think this also have been discussed for NDAs of non- novel, non-opioid analgesics. We should focus more FDA resources to work with industry to develop additional accelerated developmental approval pathways. Being part of this would be coming up with better endpoints scales. We don't have great scales for pain. They are still basically 0 to 10 scales, with the assumption that pain is luminal (ph) we know it's probably logarithmic, like taste is and hearing, and our other sensory inputs. So, I don't think our instruments really are completely valid to represent the pain experience.

We should develop new pre-approval incentives to provide accelerated development with more limited pre-approval study packages, and a great dependence on host proven studies, including real world evidence. I think this is a very hot area. We should be thinking about double-blind placebo control studies that give you certain amount of information, but they don't really paint the whole picture. There should be a consideration for additional incentives to target indications, specific indications, as well as the at-risk populations or susceptible populations. Ideally, it would be great if we had a biomarker and we could say that this biomarker they're going to -- this person is going to have addiction problems, or they are not going to have addiction problems. But, we don't have that right now, but we may in the future.

But there are target populations we should be considered about. When a soldier comes back from war, and they've got significant traumatic pain, and there's a little bit of PTSD associated with that as well, we should be targeting our therapies to that important population, because they're going to be living with

that pain for a very long time, and putting them on an opioid for significant amount of time could be problematic, as well for reasons, we could discuss that many people know. Again, I think we need to ensure the appropriate benefit-risk assessment relative to opioids. This is at the top debate we have, and as I mentioned before, limiting the number of trials required for a lot of pain indication.

We talked previously about wanting to look in a number of different populations, and certainly, we should, but I also think that sometimes it seems like maybe too many populations. I mean, for example, we could argue a low back pain is not different from osteoarthritis, since a lot of low back pain is osteoarthritis, for example. So, one, I mentioned one potential -- I'm going to be mentioning a couple of indications I think are really more for debate and discussion than something to be just stressed too strongly, but I think they're valuable to think about. One is the indication for sub-acute pain.

We kind of touched on that previously, but this will be potential treatment of pain lasting three

months or less, but we could talk about this and more, maybe it'll be plus or minus. And, it should recognize that many pain syndromes are limited in duration. Now as many of -- some of you may know, I actually did a pain fellowship, and one of the things I was talking in my pain fellowship is that chronic pain is a disease, and it is a disease. But, it's not always a disease, and that's an important thing to figure out. You don't always know when it is chronic disease and when it's not a chronic disease. So maybe, having a sub-acute pain indication will help us start to think more intelligently about that.

Also, if an opioid or a drug doesn't work forever -- you know chemotherapy doesn't work forever. Lots of drugs may not work forever. You've got to stop antidepressants. It's good you re-examine whether your drug is working or not. And so, a sub-acute indication will help you do that. So, we would encourage a re-assessment of the pain syndrome, the condition the disease causing the pain, and some of the underlying psycho-social factors that might be driving the pain, and really reconsider the development of the plan.

And, of course, one of the biggest questions is, is this pain medication helping you or is it not helping you. And one of the things -- I used to be a pain doctor at Emory, so I saw quite a few pain patients.

And sometimes, the only way to know whether the pain medication is working or not, is to actually ask the spouse or ask a friend because you don't always get the whole story. You know, you got to treat a whole family, and its part of the bond cycle of social model, which I'm not sure where that stands these days in medical education, but it's very valuable. And we would encourage development of therapies that would block the chrornification of pain.

You know this is a big issue is why in that post-operative, some people think 15 percent of pain becomes chronic. Post-operatively for herniorrhaphy, we don't understand why, we just need to understand this better and one could imagine developing new analgesics that break and prevent the chronification of pain, you know. Pain may be chronic, may be a disease but that -- but like all diseases that doesn't stop us from thinking about how we might cure it. Stop?

I also want to talk a little bit about increasing the duration of accessibility. This has been hit on before, so I'm going to give you my angle on it. I think we should provide an additional period of market exclusivity, that is patent extension for the development of these novel, non-addicting therapies. And this includes compounds that analgesics is a potential, but of lost composition of matter patent protection that would provide sufficient period of marketing exclusivity to incentive development.

One of the things many people from this may know is that with all the mergers of all these big pharmaceutical companies, there are a lot of drugs in the walls sitting on the shelves that could be developed but haven't been developed. And, they could be pulled and utilized, if there was an incentive. And that incentive would be, you know, some exclusivity associated with it.

We could facilitate the development of compound currently, as I said, sitting on these shelves and some of those were stopped not for any of the -- any safety reasons, but because of priority. In big

pharma you got this thing called PTRS, which I could explain later. But it helps you decide incremental fractions between what drugs you decide to develop and what drug you do not decide to develop. So, there are some drugs that just didn't make the cut.

There are compounds that were initially being developed for the treatment of pain, but they were not being used for the treatment for -- developed for pain -- but those mechanisms are now seen as potential analgesics. And we can talk about that as well. And, in there are compounds that are known to be analgesic, but they have never been approved for the treatment of pain. And, those include some of my favorite drugs like Ativan Nortriptyline, the tricyclic antidepressants, as well as some of the anti-epileptic drugs anticonvulsives, which you know, obviously, some had been approved for certain pain issues, but there are others that could be interrogated.

Another indication I want to mention is -- actually was just discussed, was the opioid-sparing for acute and chronic pain. I think this is a fascinating issue. I will add my two cents into it and you could

imagine the development of a lot of comments to really limit the risk of opioid therapy. Now, we're talking chronically, I guess he was talking acute, there is so much chronically that, if we could limit the amount of opioid therapy, it would be great. We could recognize that limiting the dose of an opioid, either acutely or chronically, it could have value. I think that was discussed. And, we could just advance the development of targets. And, they're maintaining analgesic effect of opioid for a long period of time.

As many of you know, or some of you know, that when you give an opioid, about six months later, people have, in general, increased their opioid dose by about 30 percent. This was a study actually brought to the economy many, many years ago. But, the other thing that this could do is enable the tapering or discontinuation of opioids chronically. And, of course, the cynic here would say, well, any analgesic, that's a good analgesic, has the potential to decrease the analgesic that's not working. And, that's true. But, I do think there is the opportunity to start thinking in these novel ways that could help us.

So, in conclusion, you know, opioids have been around since the Neolithic age, it's over 7,000 years. And, it's worth thinking about that. They've been around a very, very long time. The ancient Sumerians basically recognized both the euphoric as well as the analgesic capacity of these drugs. And clearly, we need better analgesics right now that are non-addicting, and do not have death as a side effect.

I've discussed some of the challenges to the development of non-opioid analgesics, and I've touched on, and I think we have further discussions on the incentives and some of the creative thinking that we need to develop novel non-addicting therapies moving forward. So that concludes my talk. And thank you for your time. And I'll take any questions.

DR. THROCKMORTON: Thank you very much. Questions?

MS. SIPES: Thanks for your comments. Going back to your, I think your first slide, or second, I was wondering if you could talk a little more -- you did talk about this a little bit, but I was wondering if you could address a little bit further, your comment

about benefit-risk profile for novel analgesics as a potential barrier, and how you would see that working differently or what you think would need to occur in that space?

DR. HEWITT: Yeah. Well let me give you a couple of examples. I should tell you that a part of what Karuna Therapeutics does, we're creating a new anti-novel anti-psychotic. So even though I'm just a neurologist and have been spending most of my time with pain, I've learned a little bit about anti-psychotics, and they have a lot of adverse effects associated with them, including diabetes.

So, I mean, I think the questions -- and I don't know the answer to this -- I'm not presuming to say that we should have a side effect profile similar to diabetes. But, there is certainly, one could say, that that might be something that we -- that should be in the debate. And, I think one of the things I'm always worried about, particularly in drug development, when you're in the big pharma suite, is they're all but asking for the impossible. They're asking for a drug that's really effective, as effective as an opioid, but

with the side effect profile of a placebo. You know, that's a huge problem. Of course, placebos have very high side-effect profiles. They usually don't cite this too, but that's another story. But that's sort of what I'm thinking.

And, then the other thing I'm thinking about, frankly is, is that there are drugs, I won't mention any, that have been approved for analgesia for OA in Europe that weren't approved in the United States, because the side effect profile was considered unacceptable. I don't think it'd be appropriate for me to now mention a name of a drug or something you might know what I'm talking about all that. So, that would be an example of that, is that maybe we should look back and see whether the bar was too high. You know, at the same time, people might argue that the bar was low for proving opioids and there are congressional legal reasons why the FDA approves opioids, I totally understand that. I don't disagree. There is also a feeling that there may be a too high bar for nonopioids. And, we need to go back for this profile.

DR. HAI: So, the question on Slide 3, where

you mentioned limiting number of trials required for broader pain indications and limiting pre-approval study package for novel non-opioid therapies, I'd like to hear your thoughts in terms of the context of what we require for substantiating its effectiveness. Are you looking to other sources of data than typically two studies? What are you suggesting there?

DR. HEWITT: Well, you know, obviously, I'm referring basically to the pain guidelines that we've just withdrawn. And the idea, I won't go through all of it. But you know, need two indications and painful diabetic neuropathy plus or minus PHN, and you can see that it becomes a whole list. Meaning for a general pain indication, it's something like 12 studies or 13 studies. Is that seven? I'm lost there. I mean it's a lot. So, I think, there's -- so there are two ways to solve that problem. One is you could do a study of syndromes that are very similar.

For instance, I did a study of -- a proof of concept study using individual and randomized withdrawal design, using Craig Avalon (ph) as a proof to -- to use that model for proof of concept studies.

And I use a basket of different proof of neuropathic pain syndrome. So, the question was, you know, is diabetic neuropathy small fiber, idiopathic and PHN?

And so, one could imagine, you could look at them all in one particular and large study, you could create it as just a mesh (ph) or you could actually create it as a basket study as well and develop studies that way. And then you wouldn't necessarily have to do so many studies, but you could cover your bases. I think somebody actually mentioned this in terms of we should study more. So that would be one thing. I'm not sure the pathophysiology of some of these pains are that different. One argued in the past that the underlying pathophysiology of the pain syndrome may not be related to conditions associated with that pain syndrome.

So, the hyper allergies and the allodynia, for example associated with certain neuropathic pain is certainly part of other -- it's not just related to diabetic neuropathy or postherpetic neuralgia, it's like there are other neuropathic pain conditions, as well, including phantom limb pain. And I should have

thrown that in there as well. That's a pain that I think it's completely under-treated. I kind of alluded to it when I was talking about traumatic injury in soldiers. But that's what I was thinking about in part. You still need to have large studies and you need to have substantial evidence in placebo-controlled studies. But, I do think, you know, these real-world evidence studies can be very useful to supplement those at the end as well. And you know, the risk of being wrong that would get it is lower. It is less problematic if you're putting drugs that don't kill you, and don't make you addicted. And so, I think there's a reason to think that it's -- you can be wrong and approve drugs, and maybe they won't, over time, be an effective cross over all conditions. But you can do those studies post-hoc and then see them. I think a lot of this also has to do with sort of the education of physicians, as well and their ability to really interpret the data that they're seeing.

And I think one of those problematic things we had out there we don't talk about is really physicians' ability to look at the data and not just the label, the

data for all my decisions.

DR. THROCKMORTON: Thank you very much. And next speaker is Dr. Beatrice Setnik from Altasciences.

ABUSE DETERRENCE AND OTHER NOVEL APPROACHES TO ADDRESS THE PRESCRIPTION OPIOID EPIDEMIC

DR. SETNIK: I'd like to thank the Agency for giving me the opportunity to speak today. I wanted to address some of the abuse deterrence and other approaches to address the prescription opioid epidemic.

As a disclosure, I am a full-time employee at Altasciences and I do consult with various pharmaceutical and biotech companies. And the opinions that I express today are solely my own.

So, the status quo we've been talking about the opioid epidemic in 2017, the NSD wage report and, again, 11.4 million people misused opioids. And pain reliever misuse primarily was for the reasons of really being in physical pain, followed by the feelings, of course, of feeling good and high. And about half of the respondents in the survey did report that they obtained the last pain reliever they misused from a friend or relative. And this has been fairly

consistent over the years with NSDUH, with diversion from friends and family as being one of the primary sources of opioids.

The approach to the prescription of opioids, and I applaud the FDA for coming up with the benefit-risk assessment. However, not addressing currently approved and marketed opioids is not going to change the needle from the statistics we see today and will continue in that fashion until we decide to do something with the currently marketed opioids. So, in as much as a risk-benefit analysis as the dire need for approvals of opioids and analgesics, it also needs to be implemented in the assessment of the currently approved and marketed opioids.

And the status quo, as we've been hearing from all the speakers today, we have a market that is flooded with inexpensive, generic opioids. And, those are the go-to because they are economically priced and accessible for patients and make an economical choice for the treatment of pain in a cost-effective manner. As long as we have this conundrum, we're not going to be able to shift the needle in terms of where

prescription opioids are concerned.

The many marketed opioids don't have any types of features that will prevent problematic use or use by unintended relative administration that causes more societal consequences. And we do have now, since the onset of abusive trends and other types of approaches, some studies that have been showing evidence that these formulations can impact certain aspects of safety, including abuse and fatalities.

And of course, the ongoing studies are required to continue determining the effectiveness of different types of approaches of abuse deterrents, where the risk ratio, benefit ratio may be improved, in terms of reducing some of the risks associated with opioid abuse. I think one of the problems and we've spoken, and it's been alluded to today, is also the market penetration and signal of these types of studies. In order to prove abuse deterrence, one needs to collect data. Without a sufficient market penetration, it becomes very difficult to identify and follow and track signals in the real world to determine whether these types of approaches are effective in the

real world.

And as much as we have a clear path for approving abuse deterrent or other types of innovative technologies that allow for a more, a better risk-benefit ratio, the data that's collected for approval is not the same data to compel insurers and payers to bring these types of drugs on to formularies. And, until we change the fact that the funneling and the representation of the opioids that are currently marketed are very much in the hands of the payers, because they ultimately will decide what the patients will receive. And that will always be based on an economical choice, rather than for the benefit of society.

And, until we can force the hand to allow safer opioids or analgesics or non-opioid analgesics onto the market that have an improved risk-benefit, we are always going to be stuck with the fact that the economical choice will over power the societal benefit and what should be the right choice for society and for the pain patients.

Now we know that opioids are the most potent

class of pain relievers. So, until we have the onset of non-opioids that are as effective and as potent, we will always have this problem. A moratorium on removing all opioid approvals will simply block innovation and will prevent other analgesics that have a more favorable risk-benefit profile to coming on the market.

So, it simply doesn't address today's issue. And it blocks potential solutions to improving the problem with prescription opioid abuse. So, this is a problematic solution I think we need to be more creative than that.

The idea of opioid-sparing has been brought up today. And, I think we do need a very good definition of opioid-sparing. I think the ideal would be to be opioid free. However, that's not always a reality. The other approaches to opioid-sparing can be the switch from a more potent opioid to a lesser potent opioid, a reduction in dose, a shorter duration of opioid use, or a movement from a higher schedule to a lower schedule, or to an unscheduled non-opioid analgesic. I think all of those can be representative

of opioid-sparing and could have benefits to the patient.

And, there have been very good incentives and programs to implement supplement medical education, reducing the amounts of refills and durations for acute pain. The provision of non-opioid interventions, I think, are also very important. And, our earlier speakers had alluded to other things like acupuncture or other modalities that could also enhance opioid-sparing.

The risk reduction, mandating, I think in the end, if you want to solve the problem, there does need to be the risk-benefit applied to approve new approved opioids as well as marketed approved opioids. And there needs to be some mechanism of taking out the opioids that have a high-risk profile off the market and allows you to collect data and to make those decisions, faster response times, and continuous data to collect to determine which opioid should be removed. For example, like the OPANA example, where that was taken off the market because of identified signals of safety. Those types of actions need to be taken. But

the flood of generics that don't have any safety features, those need to be seriously considered with replacement of opioids that may have an improved safety benefit, safety risk profile.

The other issue is also the data collection, or the metrics. And these do have to be collected by the brand, if you're simply collecting information, and, I realized there are difficulties in sometimes understanding what type of drug was given in certain situations and poisonings, and this type of thing. But if you want to determine if a safety feature of an analgesic is effective, you need to be able to follow the data by brand.

And, I think, Dr. Dart alluded to the solution, there can be a solution perhaps. And maybe we make pills a little bit more recognizable, some features, so that when we have surveys or reports of overdose, or other incidents, that there may be a more reliable recall of what that patient had taken at the time, so that you can identify the brand and the type of opioid taken.

So, the economics play a big part of it.

Novel formulations are more expensive. With the replacement of safer types of analgesics, there does have to be that consideration of the cost to the patient. And, I think, if there is ultimately a replacement of safer opioids, that part of that incentive will be a larger market share. However, there does need to be consideration, careful consideration, of cost, particularly because generics would have offered cheaper alternatives.

The managed care formularies as I mentioned, they do pose barriers. I think they pose barriers, not only to the accessibility of safer analgesics, because of the economic choices that are made for the payers, but also, a lot of the time, there's an impediment to get going? other opioid-sparing therapies, acupuncture, all types of other things that may be effective for an individual patient level. But, increasing coverage for other opportunities to treat pain are just as important as having analgesics that are safer.

And lastly, I think there are a lot of opportunities for research grants and funds. However, given the extent of this crisis, having more available

funding for research in innovation, and ongoing research for both pharmaceutical and non-pharmaceutical interventions of pain, I think, would be very helpful as well. And that is all I had. Thank you.

DR. THROCKMORTON: Thank you very much. Questions for the panelists? Thank you. That brings us to our break. I believe Meredith is spot on time. So, we'll reconvene in 15 minutes at 2:45 for the open public hearing. Thank you.

BREAK

(Recess)

OPEN PUBLIC HEARING

DR. THROCKMORTON: Speakers. And I'm going to call them just to come up in order and give their remarks. The first individual is Dr. Lih Young.

MS. YOUNG: Good afternoon. My name is Lih Young. I think I repeat everywhere to comment on the social issues. This is one of them. And my name is Lih Young, and I'm a Ph.D. in economics by training. I'm a genuine reformer advocate, activist. I've been in a TV program, speakers, producers, including series shifted times (ph), freedom times (ph) and it's about

100 episodes. Each in one hour per episode.

And I have run for public offices since '94 from local to federal, including the U.S. Senate, U.S. Congress, both several times, and Maryland state Comptroller. And, I run as Senate Rockville city mayor. And as I said, I'm concerned about social issues very much, including in government function.

I have been so far, for several decades, I think our civil rights are practically, are totally ignored, or you should say, violated from local to global. I think you can see how USA intel the global-wide issues our system is rigged, the election is rigged.

So, I think the most urgent issue we have problem here and overseas is what I call robber-ism [sic] though you can put several words linked together with a hyphen: Official-misconduct, government-gain, abuse-murder, fraud, crime, injustice in world operation. This means, including three branches, from local to federal, and again to global, and whether at judicial level or in the administrative level is basically is "big-guy" propaganda to benefit and

promote them self and victimize others.

It's not just black or brown, it's elderly, it's young and means, and old, and you can see whether it's a grandma or just baby, granddaughters, it's all the same treated, they are victims.

So, what we always heard is that capitalism is justice and freedom and fairness democracy, as we were told, and I don't think so. So, this system is continuing, ongoing, and spending penetrating every segment of our life, including civic, nonprofit, women or minority or churches, nonsense studies proposals, World Bank think tank, education institutions, and including the public-private partnership. This has been propagandized like a new fashion without addressing the important issues, whether they should be medically necessary or serious cost-benefit analysis.

PPP have been related to extreme serious war and crime, abuse of power and resources. Again, just like that, robber-ism and are causing social issues, including in the Rockville Town Center, which is basically 100 percent by the taxpayers and output is 100 percent private owned. So, you called that as a

public-private partnership. That is total misleading. It's just the opposite, and its relation not owner victimized individual, it's not just one project only.

Basically, they use abuse of power, victims are everywhere, and every people, every victim is every possible way you can think of. And it's just the same with -- if you have been to the Rockville city project. And you can see and this morning we just heard in the National Academy of Science engineering medicine, they conspire with police, with 11 attorneys, conspires together with all kind of fraudulent criminal operation. So, you just keep them out of our society and serious problem. And so, we must turn this around. Otherwise every one of you will be victimized.

For I think the most important issue is that they will victimize it -- if you've heard the data itself is really underestimated because all the institution, their data are force, including they see your personal medical record, they don't even give you the medication, or they give you awkward medication. So, in a way --

DR. THROCKMORTON: Dr. Young, could you finish

your comments, please?

MS. YOUNG: Huh.

DR. THROCKMORTON: Could you finish your comments please?

MS. YOUNG: Sorry. Okay. I think my time is almost up. I'm sorry. I've submitted a written statement. And it's a lot of files and attachments, and they've all been together. And I have put them everywhere and I hope it works this time. And so, I ask to read every word, because every word is very condensed with behind these serious stories. So, I will submit the written statements. Thank you very much.

DR. THROCKMORTON: Thank you very much. Our next speaker is Mrs. Carrie Wentworth. Mrs. Wentworth? The next speaker is Ms. Carrie Barnhart.

MS. BARNHARDT: My name is Carrie Barnhardt. Thank you for allowing the stakeholder meeting and allowing me to speak. I hold a master's degree in leadership renewal and change and I'm the founder of Pain Advocate Warriors in the state of Virginia, co-leader for Don't Punish Pain Rally, and a member of the

American Pain and Disability Foundation. And I'm an ally with the US Pain Foundation.

I've been a science teacher and I've worked for three pharma companies in quality assurance before I became fully incapable of working. I'm a chronic pain patient, volunteer lobbyist, a pain advocate, and listen to suicidal pain patients. I am a great mom of a team that also has the same conditions I do, including the pain. None of my diseases have cures, most don't have any treatment. I'll spare you the details and diagnosis and only speak about one here. I'm dependent on pain medication.

And the pain level, pain index is much better than the 0 to 10, and I live between 36 to 40 daily , which is about 7 or 8 on the old scale. When patients living in this agony hear the words opioid epidemic or opioid crisis, we're triggered. Yes, a medical PTSD triggered. Medical abandonment, medical harassment, profiling by pharmacies, laws, with doctors, extremely questioned about why we need these meds. Harassed by the general public, family, friends, as you know, the stigma of opioids follows everywhere.

Have you tried this? Have you done yoga? I shall pray for you. Have you changed your diet? It's in your head. Here's an antidepressant. So, Six percent become chronic users, like myself [sic]. Why are 94 percent denied pain relief, denied the rest, denied quality of life when they need pain meds stronger than NSAIDs and ibuprofen? Sixty percent of veteran suicides, about 22 a day, are due to un-treatment, or under-treated physical pain. Only 0.6 percent of anyone that has been over-prescribed an opioid become addicts. There's a difference between being dependent and an addict. So why is it an epidemic?

Too many chronic pain patients are denied pain medication, at the discretion of insurance companies and state legislation, based on the 2016 CDC guidelines. State governments and every single insurance entity took the guidelines as gold and in-doored [sic] cancer patients and chronic pain patients, like myself.

Every month, there are patients fighting for their meds, they're fighting the MMEs. And, we're

fighting to also keep our vendors, too. We shouldn't have to choose between anxiety and mental health or our physical pain.

I was lucky to have a great pain management doctor. We had a great relationship. We worked together. And he even involved my family, which was really important. When I wasn't benefiting as much as I needed to anymore, he would increase or change my meds. Then I moved states. Now, I'm starting all over. And I've already been in the hospital seven nights out of the last two months because of pain.

Patients are dismissed from pain clinics because the DEA has intimidated the pain management doctors into no longer prescribing opioids. Too many pain docs are quickly closing doors or have been shut down by the DEA. We, pain patients, have too many agencies in our doctors' offices. We are deprived the very medication that keeps us out of bed, that keeps us functioning, and that keeps us constant -- from constantly thinking about ending our pain by ending our lives.

We instead are forced into other treatments

that have been proven to fail us. For example, steroid injections, these actually degrade many patient's connective tissues further with those that have rare diseases, like Ehlers-Danlos syndromes, like I have. EDS requires aggressive high dose pain therapy because, given the progressive centralized breakdown of connective tissue, patients developed intractable pain that leaves them unable to function.

So there needs to be this idea cemented in everyone's minds that pain management is not a one size fits all. I've had 28 surgeries so far, and not because my docs want to keep cutting me open or prescribing me more meds. My surgeries are simply to attempt to preserve what little ambulatory steps I have left. EDS requires me to have my meds, and I can't even get numbed at the dental office because I don't respond to Lidocaine.

So, it's not even just opioids. It's all medications. We pain patients acknowledge addiction and that battle that addicts go through. We, too, would like acknowledgement from the FDA and the CDC to get an understanding of our fight to live. We want the

World Health Organization to recognize an inherent right to live pain-free. We acknowledge that our pain meds do not eliminate our pain 100 percent. We deserve adequate access to appropriate pain management.

The WHO is fully committed to ensuring that children, as well as adults with severe pain, have access to effective pain control medication, including opioids, when needed. We hope to work with the FDA and CDC and develop a way to ensure that chronic pain patients get care that the addicts receive in their independent proper care.

Thank you for your time and I'll answer any questions you may have.

CONCLUDING REMARKS

DR. THROCKMORTON: Thank you very much. That ends the open public hearing session of this hearing. And, on behalf of the FDA panel, I'd like to thank all of the presenters and everyone in the audience, whether you've attended in person or by webcast, for participating in today's hearing.

On responding to the opioid crisis, while addressing the need for appropriate access to pain

management, remains a central focus of the FDA and the highest priority for us. We greatly appreciate your attention and your interest to this important topic and to today's presentations.

In addition, I'd like to recognize the FDA staff that participated in organizing the work, the meeting today, including the staff in the great room, the panel participants, and the many individuals within the Center who collaborated on this important hearing.

As a reminder, we strongly encourage you to submit docket comments by November 18, 2019. If you'd like details on how to do this, we have placed copies of the doc, the Federal Register notice in -- for this hearing -- at the registration table.

A transcript from the hearing shall be posted to the meeting website in approximately 30 days and we will provide copies of today's presentations on request. Please see the registration desk for that information.

And on that note, I am closing this public hearing. Thank you, very much, and safe travels.

CERTIFICATE OF TRANSCRIBER

I, MURALIDHAREN K.V., do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and

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MURALIDHAREN K.V.