October 8, 2020 NDA 211179: Joint PDAC & DSaRM Advisory Committee Meeting

Script for FDA Presentation: Stimulant Use and Nonmedical Use

FDA Presenter: Joseph Shearer, PhD, MPH, Epidemiologist

Slide 1

Hello, my name is Joe Shearer and I am an Epidemiologist in Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA). In this presentation I will provide an overview of postmarketing data on the use and nonmedical use (NMU) of prescription stimulants.

Slide 2

I will use this simple diagram to organize the presentation and frame the discussion about potential public health impacts of this product and abuse deterrent formulation (ADF) stimulants, as a whole. I will provide data on the utilization of prescription stimulants, nonmedical use of these products, including routes of nonmedical use, and adverse outcomes associated with those behaviors. I will also provide some data on factors to consider, such as diversion and polysubstance use, including both prescription and illicit substances.

Slide 3

In considering the potential impacts of ADF stimulants on the problem of stimulant nonmedical use, it may be helpful to think about specific populations who may be affected differently by ADF stimulants, including both desired and unintended impacts across different populations. It is important to recognize that individuals may simultaneously fit into multiple populations and may move in and out of populations depending on their current situation.

The first population is comprised of individuals who are not currently using prescription stimulants nonmedically including those prescribed a prescription stimulant for the treatment of attention deficit hyperactivity disorder (ADHD). The desired impacts of an ADF stimulant in this setting is to reduce risk of initiating non-oral use and associated harms. Some potential unintended impacts could include adverse effects from added excipients and potential misperceptions about the safety benefit of ADF stimulants, such as that they prevent addiction.

Slide 4

The second population is comprised of either patients or others who use prescription stimulants nonmedically, but not regularly through non-oral routes. A desired impact here is to reduce risk of transitioning to non-oral use and associated harms. Some potential unintended

effects in this population could include hastening transition to more harmful substances and adverse effects from defeating ADF properties.

Slide 5

The third population comprises individuals who use prescription stimulants regularly through non-oral routes. These behaviors are often associated with more severe substance use disorders and polysubstance use. Similar to the second population, the goal here is to reduce non-oral use and associated harms. Potential unintended effects could include substitution of more dangerous substances and adverse effects from defeating ADF properties.

Slide 6

As opioid analgesics are the only other drug class with labeled ADFs, and since the Applicant based their development program on the ADF opioid guidance, we will also provide some data on utilization, nonmedical use, and harms associated with prescription opioids, and also look to the ADF opioid experience to inform discussion about the potential public health impact of ADF stimulants. Although, it is important to note that the patterns of use, NMU, and harms differ between opioids and stimulants. So, we will present some data for opioids alongside stimulants to provide a general sense of how these patterns are similar or different.

Slide 7

Because no single data source provides a complete picture of stimulant use and NMU, we took a mosaic approach to our data assessment. Drawing from a multitude of data sources from health care utilization data to surveys, to mortality and spontaneous adverse outcome reports.

Slide 8

This included evaluating several Applicant-submitted literature reviews and study reports, as well as conducting a range of independent analyses using multiple data sources available to the FDA.

Slide 9

In its ADF opioid guidance for industry, FDA defined misuse as the intentional therapeutic use in an inappropriate way and specifically excludes the definition of abuse, and abuse being the intentional, non-therapeutic use, even once, to achieve a desirable psychological or physiological effect, such as use to get high. In this presentation, we generally use the term nonmedical use (or NMU) to include either misuse or abuse, although we recognize that terminology varies across studies.

Slide 10

Throughout this presentation, I will come back to this data framework slide to show where we are in the landscape of use, nonmedical use, and harms. I will show this slide, then present our summary of some key findings related to the section, and then show a few pieces of data that illustrate those points. I will first discuss prescription stimulant dispensing patterns.

Slide 11

Some key findings here are that prescribing of stimulant ADHD medications is widespread and increasing. The largest growth in use has been among adults. Racemic amphetamines, such as the product in this application, make up only 0.3% of the CII prescription stimulant market. In 2019, the number of CII stimulant prescriptions was roughly half that of CII opioid analgesics.

Overall, prescription stimulant immediate-release (IR) and extended-release (ER) use is roughly equivalent in terms of prescriptions dispensed, which is quite different from opioid analgesics where IRs make up 90% of the market. For amphetamines, ER use is more common for adolescents while IR use is more common among adults.

Slide 12

Looking at the data for overall utilization of CII prescription stimulants.

Slide 13

As shown by the solid blue line, IR stimulant prescriptions increased steadily from 2014 to 2019, nearly equaling the number of ER stimulant prescriptions in 2019.

Slide 14

The increases in CII stimulant prescriptions were largely driven by mixed amphetamine salts, shown by the dotted dark blue line at the top.

Racemic amphetamines, which would include AR19, represent a very small proportion of the prescription stimulant market shown in dark green triangles at the bottom of the graph.

Slide 15

Here we focus on the strengths dispensed for IR racemic amphetamine tablets. In 2019, 10mg and 5mg tablets accounted for 98% of tablets dispensed. Of note, the Applicant has proposed product strengths up to 40mg which is higher than currently marketed racemic amphetamine products.

Slide 16

Now let's look at utilization by age.

Slide 17

From 2008 to 2019, the largest increase of CII stimulant use was among adults ages 20 to 64 years shown in the white dotted portion of the bars.

Slide 18

Between 2018 and 2019, there were more prescriptions of IR amphetamines dispensed for patients aged 20 years and older, shown in blue bars, while there were more prescriptions of ER amphetamines dispensed for patients aged 19 years and younger, shown in red bars. Highlighted by the gray box, individuals aged 20 to 39 years were dispensed nearly twice as many prescriptions of IR amphetamines as compared to ER amphetamines.

Slide 19

How does utilization of CII stimulants compare to CII opioid analgesics?

Slide 20

From 2015 to 2019, CII stimulant prescribing increased while opioid analgesic prescribing decreased. In 2019, the number of stimulant prescriptions was about half the number of CII prescription opioid analgesics.

Slide 21

Unlike prescription stimulants, which had a relatively equal number of IR/ER prescriptions dispensed, IR products have dominated the opioid analgesics market, shown in gray. As shown by the dotted black line on the bottom, abuse deterrent formulations of prescription opioids continue to represent a very small proportion, about 1 to 2%, of the total opioid analgesic market.

Slide 22

Shifting our attention, I will now describe the scope and patterns of prescription stimulant nonmedical use.

Slide 23

First, a quick summary of key findings. Nonmedical use of prescription stimulants is fairly common, especially in some subgroups. An estimated 5 million people aged 12 years and older used prescription stimulants nonmedically in 2018, with the highest prevalence among young adults and college students. Most data sources suggest that nonmedical use of prescription simulants has remained stable since 2010. In the general population in 2018, the prevalence of nonmedical use of prescription stimulants was about half that of opioid analgesics, although

the percentage of individuals with any use that also used the drug nonmedically is higher for prescription stimulants than opioid analgesics.

Slide 24

First, I'll show some data on the scope and patterns of prescription stimulant NMU in the general population.

Slide 25

Past-year prescription stimulant NMU, shown by the pink line, was fairly stable from 2010 through 2014 and from 2015 through 2018 according to the National Survey on Drug Use and Health (NSDUH), whereas the prevalence of past-year prescription pain reliever NMU, shown by the black line, decreased slightly but remained greater than stimulant NMU across both time periods. Of note, in NSDUH prescription pain relievers are largely comprised of opioid analgesics.

Slide 26

As noted on the previous slide, the estimated number of individuals with past-year NMU of prescription stimulants is less than prescription pain relievers. However, among those reporting any past-year use of prescription stimulants, 28.4% reported NMU, whereas among those reporting any past-year use of prescription pain relievers, only 11.5% reported NMU.

Slide 27

In 2018, both use and NMU of prescription stimulants was highest among people aged 21 to 25 years.

NMU of prescription pain relievers was also highest in young adults, but the peak is much less pronounced. In addition, use steadily increased across age categories, unlike for prescription stimulants.

Slide 28

Now we'll will look at NMU across population subgroups.

Slide 29

Focusing our attention on data collected from an Applicant-submitted online survey of young adults aged 18 to 26 years. Past-year NMU of prescription stimulants was higher among respondents enrolled in college (4.4%) as compared to those not enrolled in college (1.9%). While only comprising approximately 10% of college students enrolled in the study, those who participated in Greek life (i.e., fraternities, sororities) were 3.6 times as likely to report past-

year NMU of prescription stimulants as compared to college students that did not participate in Greek life.

Slide 30

The Applicant-submitted online general population survey provided data regarding NMU of prescription stimulants and opioids among individuals diagnosed with ADHD. As shown by this figure, the percentage of respondents with past 30-day NMU of prescription stimulants was greater among those with ADHD than in those without ADHD. As a comparison past 30-day NMU of prescription opioids was also more common among respondents with ADHD than those without ADHD.

Of note, psychiatric comorbidities, including ADHD, depression and anxiety, were also more common among those who have ever used prescription stimulants nonmedically.

Slide 31

The applicant submitted an analysis of self-reported nonmedical use of selected prescription stimulants among individuals seeking or being assessed for substance use disorder treatment that suggests an increasing trend in this population, although these cases still represent a small fraction of individuals assessed, ranging from 0.5 to 2%. It is also important to note this sample is nonrepresentative and changes over time, limiting our ability interpret and generalize these trend data.

Slide 32

Trends in prescription stimulant nonmedical use look quite different based on our analysis of National Poison Data System cases, which are based on calls to U.S. poison centers. Overall, cases involving NMU of stimulants increased from 2001 to 2018. However, this increase was largely driven by steady increases in cases involving illicit methamphetamine. Prescription stimulant NMU cases peaked in 2011 and then slowly decreased through the end of 2018.

Slide 33

As the proposed ADF stimulant is designed to deter non-oral use, examining nonmedical use by route is critical.

Slide 34

Briefly, to summarize the key findings: the vast majority of people report nonmedical use of prescriptions stimulants via an **oral** route. There is also a sizeable proportion of people who report ***snorting***, but the percent varies by data source and population. In National Poison Data System cases based on calls to U.S. poison centers involving nonmedical use of prescription stimulants, only 6% documented snorting, whereas across different general population surveys

around 20-30% of respondents reported snorting, at least some of the time. Injection and smoking are uncommon in the general population.

There are ***some*** subpopulations using prescription stimulants nonmedically, such as those entering treatment for substance use disorders, where non-oral use is ***more*** common. Snorting was reported by about 40% of people entering treatment facilities, with about 12% of adults and 3% of adolescents reporting injection of these products.

Slide 35

First looking at non-oral use, in the general population.

Slide 36

Among adults aged 18 to 49 years enrolled in the Applicant-submitted online survey of the general population, more than 90% of respondents with lifetime NMU of prescription stimulants reported oral NMU and 27% reported NMU via at least one non-oral route. Similar to prescription stimulants, oral NMU of any prescription opioid was reported most often; while, overall non-oral use was lower compared prescription stimulants. However, this crude comparison of the two drug classes doesn't tell the whole story.

Slide 37

First, the observed differences in non-oral use were primarily driven by snorting, which was reported nearly twice as often for prescription stimulants as compared to prescription opioids (24.7% vs. 11.8%). Use via other non-oral routes (e.g., smoking, injecting) was similar between both classes of drugs

Slide 38

Second, there is quite a bit of variation in the routes reported in nonmedical use cases, depending on the specific drug. This figure again shows data from the National Poison Data System cases, which are based on calls to U.S. poison centers. For the opioid analgesics, in particular, you see that although the majority of route mentions were oral across the class, the proportion of cases mentioning a non-oral route varies considerably by the opioid active pharmaceutical ingredient.

Slide 39

And finally, we also see that the route used depends on whether the product is single-ingredient, or a combination product. This figure shows National Poison Data System mentions of route for abuse cases involving Oxycodone ER, single-entity IR, combination ingredient IR, and oxycodone not otherwise specified. Non-oral routes were reported more often for single-entity IR and ER products and less often in cases involving combination oxycodone products.

These low-dose opioid/ acetaminophen combination products represent a large proportion of the opioid analgesic market.

Slide 40

Next, we'll examine non-oral use in people being assessed for or entering treatment for substance use disorders.

Slide 41

Among people be assessed for treatment for substance use disorders, the general patterns of routes reported for past 30-day NMU were similar to what was observed in the general population, with the predominant route for NMU being oral, and a sizable minority of individuals also reporting snorting. For your reference I have highlighted IR amphetamines in blue, which is the category the proposed ADF stimulant product would fall under.

Slide 42

In a comparable population in 2017 and 2018, similar nonmedical use route patterns were reported for some opioid analgesics (e.g., oxycodone, hydrocodone) as what was observed for prescription stimulants; however, other opioids looked quite different from the pattern observed for prescription stimulants, with much higher injection rates for morphine in the bars with blue boxes and very low rates of non-oral use for tramadol in the bars with gray hashes.

Slide 43

Other factors like polysubstance and drug use pathways, diversion of stimulants, motivations for NMU, and drug use culture are also important to consider, in part because they complicate our ability to identify patients likely to use prescription stimulants nonmedically.

Slide 44

Polysubstance use is common among those that use prescription stimulant nonmedically, with illicit drug use the most common substance used prior to NMU of Rx stimulants. Also, oral NMU of prescription stimulants *usually* proceeded non-oral use.

Multiple data sources suggest diversion of prescription stimulants is common, perhaps even more so than opioid analgesics in at least the general population, in terms of the percent who report a source other than their own prescription. Most NMU of prescription stimulants is related to improving performance at work or school, staying alert or awake, or to help with concentration.

Slide 45

First looking at polysubstance and drug use trajectories.

Slide 46

In the general population, polysubstance use is more common among individuals with past-year NMU of prescription stimulants compared to those without. The most common additional substances used by individuals with past-year NMU of prescription stimulant were alcohol (94.1%), marijuana (72.1%) and tobacco (67.5%). Prevalence ratios were highest for cocaine, sedatives, and benzodiazepines when comparing substance use among those reporting NMU of prescription stimulants to those without NMU of prescription stimulants.

Other data submitted by the Applicant showed even higher rates of polysubstance use among those reporting NMU of prescription stimulants via non-oral routes.

Slide 47

Drug use trajectory studies also support the notion that polysubstance use is common among individuals who use prescription stimulants nonmedically. An Applicant-submitted general population online survey suggested approximately 90% of individuals who reported lifetime NMU of prescription stimulants also reported lifetime NMU of illicit drugs and/or prescription opioids. Of those individuals, approximately 70% initiated their NMU of drugs with something other than a prescription stimulant. For most individuals, their NMU of drugs was initiated with an illicit substance, largely marijuana.

An additional Applicant-submitted survey of individuals with a history of NMU of prescription stimulants via a non-oral route, also showed frequent use of illicit drugs, with nearly 82% of respondents initiating their NMU of drugs with an illicit substance prior to prescription stimulants.

Slide 48

Most individuals with non-oral use of prescription stimulants also report oral NMU. An Applicant-submitted survey comprised of individuals with lifetime NMU of prescription stimulants via multiple routes, showed 89.1% of respondents initiated NMU via an oral route and 10.9% initiated with snorting. The most common initial non-oral route among respondents reporting multiple routes was snorting (97.9%).

Slide 49

Although the data are limited, drug use trajectories leading up to non-oral use of prescription stimulants appear to be diverse. Among an Applicant-submitted survey of individuals with a history of non-oral use of an ADHD prescription stimulant, 61.5% of respondents reported using a prescription stimulant nonmedically via an oral route prior to their first non-oral use. While,

18.3% reported NMU of a substance other than a prescription stimulant only, and 20.2% reported no substance use prior to non-oral use of a prescription stimulant.

Slide 50

Looking at the data related to diversion of prescription stimulants.

Slide 51

In 2018, the National Survey on Drug Use and Health estimated nearly 80% of individuals with NMU of prescription stimulants in the past-year got prescription stimulants from friends or a relative while an estimated 50% with NMU of prescription pain relievers (i.e., opioids) cited their source as a friend or relative.

Results of multiple Applicant-submitted studies in different populations were consistent with this finding.

Slide 52

In general, the motivations cited for NMU align closely with the drug's indication.

Slide 53

Data from NSDUH in 2018, showed the most common reasons for stimulant NMU were related to studying, alertness, or concentration. About 10% reported that their most recent reason for nonmedical use was to feel good or get high, and this was similar to prescription pain relievers.

Similar findings were observed in multiple Applicant-submitted study reports, although individuals using prescription stimulants non-orally were more likely to report that their motivation was to get high.

Slide 54

Next, I'll present some data on adverse outcomes associated with nonmedical use of prescription stimulants, with some analogous results for opioid analgesics for context.

Slide 55

In summary, harms associated with prescription stimulant nonmedical use are far less frequent than for opioid analgesics. For example, only about 3% of emergency department (ED) visits for nonmedical use of pharmaceutical products in 2016 involved prescriptions stimulants whereas about 36% involved prescription opioids. Fewer than 1% of people entering substance use treatment centers in 2017 reported prescription stimulants as their primary substance of abuse, which was again far lower than the percentage reporting prescription opioids as their primary

substance. Overdose deaths involving psychostimulants are increasing, but deaths involving opioids still dwarfed deaths involving stimulants in 2018. However, our analyses of death certificate literal text have shown that the vast majority of psychostimulant deaths involve illicit methamphetamine. Unfortunately, we can't comment on the contribution of non-oral use to these deaths as that information is not routinely available on death certificates.

Slide 56

We know that non-oral routes are associated with some adverse outcomes not associated with oral nonmedical use. In particular, injection is associated with serious harms such as infection complications. However, because oral nonmedical use is so much more common, oral nonmedical use contributes far more to the public health burden of harms than non-oral use.

Slide 57

So, what kind of adverse outcomes do we see with NMU of prescription stimulants?

Slide 58

Based on calls to U.S. poison centers, National Poison Data System single substance exposure cases involving NMU of prescription stimulants from 2001 to 2018 shows over 95% of cases reported either a minor or moderate effect as a result of the exposure. Shown on the table to the right, the top 3 clinical outcomes from these cases were tachycardia, agitation, and hypertension.

Slide 59

Emergency department visits involving NMU of pharmaceutical products was also examined. Shown in this published report by Geller et al., only 3.1% of all emergency department visits in 2016 involving NMU of pharmaceutical products involved prescription stimulants, while visits involving prescription opioids accounted for approximately ten times the number of visits observed for prescription stimulants. It's important to keep in mind that these data systems are unlikely to capture non-acute adverse effects of nonmedical stimulant use, including psychosocial harms.

Slide 60

Overdose deaths involving psychostimulants and opioids increased from 1999 to 2018. However, as of 2018, the number of psychostimulant overdose deaths was markedly lower than the number of opioid overdose deaths. An important note is that these data group CII prescription stimulants under the same International Classification of Diseases, Tenth Edition (ICD-10) code as other stimulants, including methamphetamine and other illicit stimulant drugs, such as ecstasy (T43.6: psychostimulants with abuse potential). The category of all opioid overdose deaths also includes illicit opioids such as heroin and illicit fentanyl.

Slide 61

Because of limitations related to differentiation of prescription and illicit stimulants from publicly available mortality data, we supplemented national data on stimulant-involved mortality using death certificate literal text, made available to the Agency by the National Center for Health Statistics. Based on available data for 2010 to 2014, methamphetamine was involved in the largest number of stimulant-involved deaths (19,268 decedents), followed by amphetamine (3,493 decedents), although it is unclear what proportion of amphetamine deaths specifically involved a CII stimulant containing amphetamine salts and what proportion involved the general amphetamine class of drugs.

Slide 62

To help provide context for the mortality data, results from a previously published report by the National Vital Statistics System are shown here of the 15 drugs most commonly involved in overdose deaths. In 2016, other than methamphetamine (most likely illicit), amphetamine was the only other stimulant API in the top 15 drugs mentioned on overdose death certificates and was documented as being involved in 1.9% of overdose deaths. As a comparison, opioid analgesic APIs (e.g., hydrocodone, oxycodone, morphine) were documented as being involved overdose much more frequently. It is important to note that these comparisons do not account for differences in prescription volume for these products. Prescriptions for opioid analgesics, as a class, outnumbered those for CII stimulants approximately 2.5x in 2016. Rather, these comparisons are intended to provide contextual information on the relative public health burden of mortality associated with these two classes of prescription drugs.

Slide 63

As this ADF stimulant product is aimed at deterring non-oral use it is important to examine how adverse outcomes of prescription stimulant NMU can differ by route.

Slide 64

National Poison Data System Single-Substance Exposure Cases involving NMU of prescription stimulants mentioning a non-oral route (Nasal/Inhalation or Injection) reported a larger percentage of moderate or major effects when compared to cases mentioning an oral route. However, 90% of cases involving NMU of prescription stimulants with moderate or major effects mentioned oral routes.

Slide 65

Review of medical literature detailing potentially life-threatening adverse reactions associated with nonmedical use of CII prescription stimulants via injection describes complications associated with accidental intra-arterial injection, infectious disease, exposure to excipients,

and generalized adverse systemic effects. These severe adverse reactions are listed and include embolism, sepsis, and renal failure.

Slide 66

Likewise, adverse events associated with inhalation of CII stimulants to include smoking and intranasal routes of administration relate to excessive exposure to stimulants and ingestion of excipients and contaminants. Some of these severe and potentially life-threatening adverse events include aspiration pneumonia, eosinophilic lung disease, and pulmonary and alveolar hemorrhage.

Slide 67

In summary, use of prescription stimulants is widespread and increasing. Nonmedical use remains prevalent but appears relatively stable in recent years. These patterns are different from opioid analgesics, where both use, and nonmedical use of opioid analgesics have decreased in recent years but remaining more prevalent than prescription stimulants. Nevertheless, nonmedical use of CII prescription stimulants is a serious public health concern, particularly among young adults and college students, where the prevalence is far higher. This differs from opioid analgesics where the prevalence of nonmedical use doesn't have the same sharp peak in young adulthood. Individuals who use prescription stimulants nonmedically may not be the same as those being prescribed a stimulant, as most individuals report receiving their prescription stimulant for NMU from diverted sources, such as a friend or relative. Diversion as a source of prescription stimulants for nonmedical use is even more common than what has been observed for opioid analgesics. In general, individuals appear to be using prescription stimulants nonmedically primarily for purposes that are related to the indication for the drug rather than to achieve a high. The proportion of people who reported nonmedical use to get high, about 10%, was similar for prescription stimulants and opioid analgesics.

Slide 68

The frequency of measurable harms from Rx stimulant nonmedical use, such as emergency department visits, moderate-to-severe NPDS cases from poison center calls, substance use disorder treatment admissions, and deaths, is substantially lower than that associated with prescription opioid analgesics.

The majority of people report nonmedical prescription stimulant use via the oral route; however, a sizable minority report snorting them, and a considerably smaller proportion report injecting. The nonmedical use route patterns are qualitatively similar for opioid analgesics, although route patterns vary widely by opioid drug and formulation. There are a number of serious adverse effects specifically associated with intravenous and nasal routes of administration. However, oral routes account for more severe outcomes as oral use is the most common route for nonmedical use, by far. Individuals who use CII prescription stimulants

nonmedically also frequently report nonmedical use of a wide range of other prescription products and illicit substances, this is particularly true for those reporting non-oral use.

Slide 69

As I mentioned at the beginning, opioid analgesics are the only class with products labeled as abuse-deterrent. I will share some observations from the postmarket experience with abuse-deterrent opioids. First, ADF opioids have had very low market penetration, and all the marketed products have been extended-release/ and long-acting (ER/LA) products. The low utilization has limited our ability to assess the effectiveness and public health impact ADF opioids in the postmarket setting. In addition, there have been challenges with data quality and difficulty attributing causality to observed changes in abuse patterns due to the constantly changing substance use patterns and other interventions to address nonmedical use of opioids.

We recently convened a joint advisory committee meeting to discuss the results of postmarketing studies evaluating the effectiveness and public health impact of reformulated OxyContin. The FDA review team concluded that the evidence was fairly compelling that OxyContin's reformulation deterred abuse by non-oral routes, which *is* what they were designed to do, but this effect was primarily seen in the small subset of people with more advanced substance use disorders.

And, in the end, the overall public health impact of the reformulation remains unclear. We saw no clear reduction in overall abuse or opioid overdose. We really had no data on whether the ADF prevented people from *initiating* non-oral abuse or reduced the risk of developing an opioid addiction. Polysubstance use was found to be very common, and there was some evidence suggesting unintended adverse consequences, primarily related to substitution of other opioids, including more dangerous illicit opioids.

Slide 70

So, could ADF stimulants provide a meaningful public health benefit, in other words, a reduction in harms to patients and others who access the drugs? Stimulant products formulated with properties to resist crushing and make injection more difficult might reduce use by riskier, non-oral routes, although they do not address the most common route of nonmedical use—swallowing the pills whole. Marketed ADF opioids have a similar limitation.

Again, it is important to consider the potential for different impact in different populations. One question that could be asked is which patients might benefit from ADF stimulants? Although we know that college-aged adults have the highest rates of nonmedical use, we also know that most individuals who use prescription stimulants nonmedically obtain them from relatives or friends rather than from their own prescription, making it harder to target those who might benefit. It is also unclear whether ADF stimulants could reduce initiation of non-oral routes or the risk of developing an addiction. And finally, could there be unintended consequences for some, including substitution of more dangerous illicit stimulants or excipient-related harms if

the ADF is defeated and the product is injected. You'll hear more about this safety issue in a later FDA presentation.

Many of these considerations have arisen based on the postmarketing experience with ADF opioid products, but as we have described in this presentation, patterns of use, nonmedical use, and harms for prescription stimulants and opioid analgesics differ in some important ways. We look forward to hearing the committees' thoughts on this important question of the potential public health impact of abuse-deterrent stimulant products.

Slide 71

Thank you for your time.

October 8, 2020 NDA 211179: Joint PDAC & DSaRM Advisory Committee Meeting

Script for FDA presentation: In Vitro Studies of Proposed Abuse Deterrent Properties for NDA 211179 AR19 (amphetamine sulfate) capsules.

FDA Presenter: Andrei Ponta, Ph.D., Chemistry, Manufacturing, and Controls Reviewer

Slide 1

My name is Andrei Ponta. I am a chemistry, manufacturing, and controls reviewer in the Office of New Drug Products, Office of Pharmaceutical Quality. I will be presenting, "In Vitro Studies of Proposed Abuse Deterrent Properties for NDA 211179 AR19 (amphetamine sulfate) capsules."

Slide 2

The proposed drug product is AR19 (amphetamine sulfate) capsules. It is an immediate release capsule available in strengths from 2.5 to 40 mg. The proposed drug product is to be administered orally as a capsule or by opening the capsule and sprinkling its contents over food.

The drug product contains excipients such as poly(ethylene oxide) (PEO) which impart the drug product with its abuse deterrent properties. The molecular weight of the PEO used in the formulation is seven million.

The Applicant has performed in vitro abuse deterrent studies, referred to as Category 1 studies. An FDA approved amphetamine sulfate immediate release tablet was used as the comparator. Single tablets of the 10 mg comparator strength were used.

Slide 3

The overall goal of category 1 studies is to evaluate the ease with which the potential abuse deterrent properties of a formulation can be defeated or compromised.

Category 1 studies include four major types of studies.

Physical manipulation studies aim to manipulate capsule contents to reduce particle size to produce a powder amenable to insufflation.

Extractability and syringeablity studies are performed to determine whether a syringeable material can be produced. Common solvents are used to extract drug from an abuse deterrent dosage form. The amount of drug present in the extract is measured and the syringeability is determined using needles of various gauge.

For this NDA the Applicant also performed large volume extraction studies which produced a drinkable solution of the product. Smoking studies assess whether a smokable product can be produced.

Slide 4

Physical manipulation studies were performed using a variety of tools readily available in any household or easily obtained in stores or online. Multiple tools were used, representing cutting, crushing, grating, and grinding methods. In these studies, physical manipulation was performed with and without pretreatment. Examples of pretreatment include heating or cooling the capsule contents prior to the physical manipulation.

Note that a particle size of less than 500 microns is generally considered to be amenable to insufflation; however, particles less than 1000 microns may also contribute to the overall drug available when insufflating.

Slide 5

Selected results are included in the table on the right.

Physical manipulation of the comparator produced 82- 98% of the particles less than 500 microns, with 90 – 100% of the particles being less than 1000 microns. The results of the comparator are without pretreatment. Because almost 100% of the comparator was insufflatable with no pretreatment prior to manipulation, physical manipulation studies of the comparator with pretreatment were not performed.

When 40 mg AR19 capsule contents are manipulated with the most effective common household tool, up to 75.6% of particles produced were less than 500 microns and up to 88.8% of the particles produced were less than 1000 microns. Overall, pretreatment did not cause a significant increase in particle size reduction. However, pretreatment combined with the same manipulation method just discussed resulted in 87.8% of particles less than 500 microns and almost 100% of particles less than 1000 microns.

Note that if 75% of a 40 mg capsule is reduced to less than 500 microns, that provides approximately 30 mg of insufflatable amphetamine.

Slide 6

The Division of Pharmaceutical Analysis , Office of Testing and Research, performed confirmatory physical manipulation studies. Results were largely in line with the Applicant’s results. Pretreatment had little impact on further reducing particle size.

Drug substance recovery was at least 95% regardless of manipulation tool, meaning that after physical manipulation of the 40 mg capsule, at least 95%, or 38 mg, of the amphetamine sulfate was recovered when totaling all of the particles.

Slide 7

Extractability and syringeability studies were conducted to assess the potential for syringeability and injectability of the manipulated drug product. Both small and large volume extractability studies were performed. Testing included both pretreated and non-pretreated, intact and manipulated capsule contents extracted in solvents at room temperature and elevated temperature. Multiple solvents were tested as well as varying extraction times.

Large volume extractions using 10 mL or more were also performed. Studies performed were similar to small volume extraction studies; however, after extraction, the volume was reduced to an injectable amount.

Slide 8

Conditions were confirmed in which up to 95% of amphetamine sulfate from the comparator was extracted. Without pretreatment, up to 15% or 6 mg of amphetamine from the AR19 40 mg strength was extracted.

Slide 9

Additional extractability studies were performed with various pretreatments. Conditions were confirmed where up to 50.2% of amphetamine sulfate from a 40 mg strength capsule could be isolated and potentially injected. This is equivalent to 20 mg of amphetamine sulfate. There were also multiple conditions where approximately 10 mg of amphetamine sulfate could be extracted.

All the results described on this slide use common household solvents.

Slide 10

The Applicant performed large volume extraction studies where a larger volume is used to extract the drug substance. As the resultant extract is not readily injectable, the volume is reduced to a syringeable amount.

Conditions were confirmed where up to 31.5%, or 12.6 mg, of amphetamine sulfate present in a single 40 mg capsule could be isolated and potentially injected.

Extraction from multiple capsules was not readily feasible due to increased presence of excipients such as PEO resulting in increased gelling. The addition of a second capsule led to an

addition of 3 mg amphetamine sulfate extracted. Addition of a third, fourth, and fifth capsule did not lead to any additional amphetamine extracted.

Slide 11

Large volume extraction studies evaluated the ability to produce a drinkable solution of drug product with a high amount of extracted drug substance (amphetamine sulfate). Close to 100% of the amphetamine sulphate was extracted from both the comparator product and AR19 capsules. This is expected as the two products are immediate release oral drug products.

Slide 12

Smokeability of manipulated comparator and manipulated drug product was assessed using a smoking simulation device. Low amounts of amphetamine sulfate were volatilized from manipulated comparator and manipulated drug product. Smoking is not expected to be a widely used method of non-medical use.

Slide 13

In conclusion I would like to highlight the following data.

Between 82.5 – 98.4% of the comparator product could be reduced to particles less than 500 microns.

Without pretreatment, up to 75.6% of the proposed AR19 drug product could be reduced to particles less than 500 microns and up to 88.8% of particles less than 1000 microns.

With pretreatment, up to 87.8% of the proposed AR19 drug product could be reduced to particles less than 500 microns and up to 99.7% of particles less than 1000 microns.

These data are significant as insufflation is the most common route of non-medical use of this drug and dosage form.

Slide 14

Continuing with conclusions. With respect to extractability and syrgineability I want to highlight the following data.

Up to 90% amphetamine sulfate was extracted without pretreatment from the comparator product.

Without pretreatment, up to 15% of amphetamine sulfate was extracted from AR19 capsules. However, with pretreatment, up to 50% or 20 mg of amphetamine sulfate was extracted from AR19 capsules.

Extraction from multiple capsules was not readily feasible.

For large volume extraction studies, syringeable amphetamine recoveries were similar or lower than those using small volumes

Slide 15

A drinkable solution containing high amounts of amphetamine sulfate could be produced using both the proposed product and the comparator product which is expected for an immediate release dosage form. Neither AR19 nor the comparator product produced significant amounts of volatilized amphetamine sulfate.

October 8, 2020 NDA 211179: Joint PDAC & DSaRM Advisory Committee Meeting

Script for FDA Presentation: Evaluation of the Purported Abuse-Deterrent Properties of AR19

FDA Presenter: Shalini Bansil, MD, Medical Officer

Slide 1

My name is Shalini Bansil. I am a medical officer with the controlled substance staff at the FDA. You have heard a detailed discussion of the in vitro manipulation studies, and I will be discussing the overall abuse-deterrent evaluation performed by the Applicant, to support their claims that AR19 has properties that deter abuse by the intranasal, intravenous, and smoking routes

Slide 2

Prescription drug products, including stimulants, can be abused in a number of ways. For example, they may be crushed and snorted, or they may be crushed, dissolved, and injected to achieve a desired effect. Abuse-deterrent formulations, referred to as ADFs in this presentation, of **opioid** analgesic products have been developed with the goal of making those products safer, and our experience thus far has largely been in that space, where technologies have been incorporated into those products with the goal of making abuse by a particular route more difficult. One example is physical/chemical barriers that make the formulation more difficult to crush or gelling properties that make the formulation more difficult to inject. Two critical concepts to appreciate are that the meaningfulness of any ADF effect must be evaluated in the context of an appropriate comparator and that the improvement over the comparator may not be absolute.

It is important to note that, because ADF products must still release the active ingredient for the benefit of patients, they are not abuse proof. This point is even more relevant when evaluating an immediate-release product because these products, by design, must release all of the active ingredient at once.

Slide 3

To date, only opioid analgesic products have been approved with labeling claims describing abuse-deterrent properties. Those products are supported by data describing the abuse-deterrent effects and are evaluated consistent with the principles outlined in the FDA guidance for the evaluation and labeling of abuse-deterrent opioids, which was finalized in 2015. It was discussed with the Applicant that the Guidance, although specific to opioid analgesics, describes premarket methodologies that may be applied to other drug classes such as stimulants for the ADHD indication.

The first three Categories of studies are commonly described as “premarket,” because these studies assess the abuse-deterrent properties of a formulation under experimental and controlled clinical conditions. However, we believe that these studies are predictive of the expected abuse-deterrent effects of an opioid formulation.

The first category consists of in vitro manipulation and extraction studies aimed to evaluate the ease with which the abuse-deterrent features of the ADF can be defeated or partially compromised relative to a comparator. These studies are followed by pharmacokinetic studies, or Category 2 studies, designed to understand the in vivo pharmacokinetic properties of the manipulated ADF product relative to comparators.

The third category of studies consists of an evaluation of the abuse potential or “likeability” of the manipulated ADF relative to comparators in human subjects.

For safety reasons, human abuse potential studies are not generally conducted for the intravenous route because subjects would have to be administered a manipulated form of the formulation containing excipients and other impurities. Thus, the abuse-deterrent evaluation for the intravenous route relies on the results from Category 1 studies.

Category 4 studies are based on postmarket data to assess the impact of an ADF on actual abuse.

Slide 4

Abuse-deterrent formulations can be designed to deter abuse by different routes. The Applicant is proposing abuse-deterrent claims based on the premarketing studies for the intranasal, intravenous, and smoking routes.

The Applicant is not proposing an abuse-deterrent claim for the most common route of abuse, the oral route, and, thus, no studies were performed to support deterrence via this route.

In order to support abuse deterrence via the intranasal route, the Applicant conducted a human abuse potential study, using a sample manipulated according to the conditions identified in the Category 1 in vitro studies.

In vitro Category 1 studies were submitted in support of an abuse-deterrent effect for the intravenous and smoking routes. These studies are covered in more detail in Dr Ponta’s presentation. The relevance of these findings is based on an understanding of what would be a minimum reinforcing dose of intravenous dose of amphetamine.

Slide 5: The Applicant did not conduct a pilot study to determine what would constitute a reinforcing dose of amphetamine sulfate when rapidly injected intravenously over a 30-to-60-second period, which would be a reasonable injection time based on the published results of a

survey conducted in people who inject drugs. When assessing the subjective effects of IV-administered drugs, both the rate of injection and the dose injected are relevant.

Data from the literature showed that 10 mg of dextroamphetamine, administered in 1 mL over 60 seconds to volunteers with a long history of illicit intravenous cocaine abuse, produced similar subjective effects to a 16 mg dose of intravenous cocaine, a dose typical of real world abuse. However, AR 19 is a racemic mixture that contains equal parts of dextroamphetamine, which is considered to be the more psychoactive isomer, and levoamphetamine, which is considered to have more prominent cardiovascular effects. Therefore, the main limitations of these data are that they did not directly inform the reinforcing effects of the racemic mixture or whether doses lower than the 10 mg tested would also be reinforcing.

Even so, we considered a 10 mg dose of amphetamine administered in 1 mL over 1 minute to be a reasonable dose that will produce positive subjective effects for the purposes of this evaluation.

As discussed by Dr. Ponta, in vitro manipulation studies demonstrated that, with AR19, it was possible to form a solution containing 10 mg or greater of amphetamine for intravenous use.

Vaporization studies demonstrated that only small amounts of amphetamine were volatilized from manipulated AR19, similar to that of the marketed comparator product. Therefore, abuse-deterrent properties by the smoking route will not be further discussed.

Slide 6: Study AR 19.001 was a randomized, double-blind active- and placebo-controlled, two-part study to evaluate the intranasal abuse-deterrent effects of AR19 compared with amphetamine active pharmaceutical ingredient (API) administered to nondependent individuals who recreationally use stimulants

Slide 7 The study included subjects with a history of stimulant abuse and abuse of drugs via the intranasal route. These subjects would most likely be able to distinguish the drug liking effects of stimulants via the intranasal route and, based on history, are already being exposed to the potential toxicities associated with insufflation of drugs.

Slide 8 Part A of the study consisted of dose selection to identify a dose of intranasal amphetamine that would produce drug liking effects. Amphetamine API was tested at three dose levels: 20, 30, and 40 mg. Based on the pharmacodynamic results, 40 mg of amphetamine was selected for use in subsequent phases of the study.

Part B of the study consisted of a Qualification phase and a Treatment phase. The Qualification phase was performed to identify subjects able to discriminate between the active control amphetamine API powder and placebo using standard criteria.

The treatment phase was randomized and double-blind. Amphetamine sulfate API powder was selected as the active comparator for this study, as opposed to a marketed immediate-release

amphetamine drug product. 40 mg of manipulated AR19, 40 mg of amphetamine API, and matched placebos were administered in a crossover fashion. Now that I have discussed the design of Study AR19.001, I will move on to a discussion of the results.

Slide 9

The study included PK sampling at pre- and post-dosing time points and relevant PK parameters were calculated for single-dose intranasal administration of 40 mg manipulated AR19 and 40 mg amphetamine sulfate API powder. As seen in this figure, following intranasal administration, manipulated AR19 resulted in lower systemic exposures to l-amphetamine and d-amphetamine compared to that of amphetamine sulfate API powder. However, it is critical to recognize that PK findings alone are not sufficient to determine abuse-deterrent effects. The pharmacodynamic measures are integral to the assessment of abuse deterrence in this study.

Slide 10

Pharmacodynamic, or PD, assessments were performed using visual analog scales, which are also known as a VAS. Each VAS was scored from 0 to 100.

Drug Liking, Overall Drug Liking, and Take Drug Again were measured on a bipolar VAS where the neutral point was located at the 50 mark. Whereas, High VAS was measured on a unipolar VAS where the neutral point was located at the 0 mark..”

This slide depicts the VASs, along with the prompts, that were used for the PD assessments in the study. As an example, Drug Liking was used for the primary endpoint and was assessed on a bipolar VAS using the prompt “At his moment my liking for this drug is”, with 50 representing the neutral point of “neither like nor dislike,” 0 representing strong disliking, and 100 representing strong liking.

Slide 11

The Primary Endpoint was the maximum, or peak, effect for Drug Liking known as Emax, assessed as “at this moment, my liking for this drug is ” on the bipolar VAS.

The Secondary Endpoints were the maximum effect, or Emax, for Overall Drug Liking, assessed as “Overall, my liking for this drug is” on the bipolar VAS, Take Drug Again, assessed as “I would take this drug again” on the bipolar VAS, and High, assessed as “At this moment, I feel high” on the unipolar VAS.

Slide 12

In contrast to traditional efficacy and safety studies, human abuse potential studies include a validation test to ensure that the subjects enrolled were able to reliably differentiate the effects of the positive control from placebo. This test is performed on the results from the Treatment

Phase prior to analyzing the results for the test product. Because subjects that do not differentiate the positive control from placebo will not provide a reliable measure when evaluating the effects of the test drug, study validation is an important step to make sure that the study is sensitive enough to detect any differences in subjective responses between active treatments, if they exist.

The study validation step was based on meeting a mean difference of at least 15 points in maximum drug liking between the positive control and placebo among all subjects who completed all three treatments. In this case, the completer population consisted of 37 subjects out of the 40 that were enrolled. The study was not validated based on this analysis as displayed on the next slide.

Slide 13

Amphetamine 40 mg did not separate from placebo using a minimum margin of 15 points, as evidenced by the fact that the p-value on this statistical test exceeded the prespecified level of 0.025. As you can see, the lower limit of the 95% confidence interval is 13.1, which crossed the prespecified limit of 15. Therefore, the study failed the validation test.

Slide 14

Prespecified criteria may be used to remove subjects from the analyses, including analysis for study validation, who did not provide reliable responses; however, the Applicant did not prespecify these criteria. The Applicant and the Agency conducted additional exploratory analyses on the results of the study.

The Applicant determined that one subject was a likely contributing factor to the study not being validated and conducted the validation test with this subject excluded. Although the Applicant reported that the validation test passed with this subject excluded, we do not agree with their statistical approach because of differences in opinion regarding the normality assumption.

The Agency also conducted an exploratory validation test by excluding four subjects with unreliable responses using what would have been acceptable prespecified criteria. This population was considered to be the modified Completer Population, which consisted of 33 subjects, and was used for further exploratory analysis on the primary and secondary endpoints. Although statistical analyses were undertaken on this population, any “statistically significant” results can only be considered ‘nominal’, and are designated as such in this presentation, since these results are from post hoc exploratory analyses

Slide 15

A heat map is a useful tool to display the results on a PD measure for individual subjects to better understand, in graphical form, why a study may not have passed a validation test. The

heat map displayed here is a hypothetical example for an abuse-deterrent product for illustrative purposes. This heat map depicts the magnitude of Drug Liking Emax for individual subjects and for each treatment, using a colored scale. At the top of the slide, you see a scale for the Emax of Drug Liking VAS scores. The blue part of the scale represents various degrees of Drug Disliking, 0 to 49, the white represents a neutral response, 50, and the pink part represents various degrees of Drug Liking with the darker the pink the more the Drug Liking, 51 to 100. The three columns represent the three treatment groups, as shown at the lower part of the slide, that is positive control, test drug, and placebo. Each row represents a single subject. Placebo responses usually fall between 40 and 60. The top row of the heat map displays a subject who gave discriminative responses, that is, high drug liking for the positive control, lower drug liking for the abuse-deterrent test product, and a neutral response for placebo. The remaining subjects gave inconsistent responses and are deemed unreliable. Specifically, the second subject from the top gave a neutral response for all three treatments. The third from the top gave high drug liking responses for all treatments, including placebo. The subject at the bottom of the heat map gave a higher liking response for placebo than for the positive control. Now let us examine what happened in Study AR19.001.

Slide 16

This is the heat map generated from the actual data collected in Study AR19.001. As can be seen here, there were a number of subjects that did not provide reliable responses. The data for the four subjects excluded from the Agency's exploratory modified completer population are highlighted in the boxes and with arrows. As an example, the subject at the bottom of the figure gave a neutral score for the amphetamine 40 mg positive control, as indicated by the white color, whereas this subject reported similarly high drug liking scores for placebo and manipulated AR19, as indicated by the dark pink color for those treatments.

Among the 37 completers, 6 subjects, or 16.2%, did not respond to the positive control as they had a Drug Liking Emax score of less than or equal to 60, and 8 subjects, or 21.6%, responded to placebo with a Drug Liking Emax greater than 60. In all, 15 out of 37 subjects, or 40.5% of the population, had a difference in maximum liking between positive control and placebo of less than or equal to 15 points. This heat map clearly demonstrates that a substantial proportion of the subjects did not provide reliable responses and provides a graphical explanation for why the study failed the validation test.

Slide 17

We undertook two broad types of exploratory analyses on the data collected for the primary and secondary endpoints using the modified completer population in order to further explore if there are any differences between AR19 and Amphetamine API that would be consistent with an abuse-deterrent effect. These analyses were generally consistent with the approach the Applicant took for the prespecified analysis on the primary endpoint, Drug liking Emax, that is, using a minimum threshold of a 10% reduction for manipulated AR19, as compared to amphetamine 40 mg. In the Applicant's prespecified primary analysis, it was not adequate to

simply show that AR19 had statistically significant less liking than amphetamine, but instead a statistically significant at least 10% difference in drug liking. The second type of analysis was a responder analysis. The Applicant conducted a responder analysis on the Drug Liking endpoint using the hypothesis that the majority of subjects, that is greater than 50%, would be responders, defined as having at least a 10% reduction in maximum Drug Liking for manipulated AR19 compared to amphetamine 40 mg. We used a similar approach for the responder analyses on the primary and secondary endpoints for the modified completer population.

Slide 18

The Agency's exploratory analysis on the primary endpoint of Emax of Drug Liking was conducted on the modified completer population that, as a reminder, excluded the four subjects based on our criteria. The results of this analysis are displayed in the table. The comparison of the means between positive control and placebo reached nominal statistical significance consistent with having passed the validation test. Importantly, this exploratory analysis did not demonstrate a nominally significant difference between manipulated AR19 and amphetamine API 40 mg in this population, which is consistent with lack of an abuse-deterrent effect for AR19 for the intranasal route. Drug Liking Emax for manipulated AR19 was greater than that of placebo.

Slide 19

Human abuse potential studies are evaluated based on an approach that considers the totality of the evidence. Consistent with that approach, we considered the results of the exploratory analyses conducted on the primary and secondary endpoints. All of the results of our exploratory analyses are summarized in the table on this slide.

The analyses that passed the nominal statistical test for the comparison of AR19 to amphetamine API are highlighted in green, whereas those that failed are highlighted in red. As you can see, the results of the exploratory analyses conducted on the modified completer population are mixed, with the study importantly having failed the exploratory primary analysis between AR19 and amphetamine API using this population and failed on the exploratory responder analysis of the primary endpoint.

Slide 20

In all, analyses were performed on three different populations in Study AR19.001. The first was the prespecified completer population. However, as you have seen, the study was not validated in the analysis of this population. Therefore, it is not appropriate to analyze the data for this population further. Regardless, the Applicant has reported that the difference in mean Drug Liking between AR19 and amphetamine API for the entire completer population was not statistically significant at the prespecified 10% threshold but that it did reach statistical significance at the 9% difference level. Two additional post-hoc exploratory analyses were performed. The Applicant excluded only one subject as previously discussed. However, we do

not agree with the Applicant that the exclusion of this subject led to a validated study because the Agency did not agree with their statistical approach. Therefore, further analysis of the data from this population is not appropriate. The Agency also conducted a post hoc exploratory analysis, the results of which have been previously described, based on excluding four subjects that provided unreliable responses, using criteria that would have been acceptable for this purpose. The analysis using this population passed the validation test. However, the primary analysis using this population did not reach nominal statistical significance. Nor did the responder analysis on the primary endpoint reach nominal statistical significance.

Slide 21

AR19 was formulated with physical/chemical properties intended to deter abuse. Based on the immediate-release properties of the AR19 formulation, AR19 was not intended to, and will not, deter abuse by the oral route, which is the most common route of amphetamine prescription product abuse.

In vitro manipulation studies demonstrated that it is feasible to obtain a solution for injection containing a reinforcing dose of amphetamine, under the conditions reported by the Applicant.

The intranasal human abuse potential study does not provide convincing evidence that the formulation employed for AR19 has significant abuse-deterrent effects, as compared to amphetamine sulfate, when administered by the intranasal route.

Thank you for your attention.

October 8, 2020 NDA 211179: Joint PDAC & DSaRM Advisory Committee Meeting

Script for FDA presentation Nonclinical Safety Assessment of AR19 Capsule Excipients: Nonclinical Safety Assessment of AR19 Capsule Excipients

FDA Presenter: Shiny Mathew, PhD, DABT, Pharmacology/Toxicology Reviewer

Slide 1

Good Morning. I am LCDR Shiny Mathew. I am a Scientist officer within the United States Public Health Service serving as a Nonclinical Reviewer within the Division of Pharmacology and Toxicology-Psychiatry Division. Today I will discuss the nonclinical safety assessment of AR19 capsule excipients.

Slide 2

From the beginning of this presentation, we would like to make it clear that there are no nonclinical safety concerns with AR19 excipients when the product is used as intended via the oral route. However, there are safety concerns if the product is manipulated for use via unintended routes of administration. In particular, there are two excipients in the AR19 drug product: polyethylene oxide 7 million daltons (from here on referred to as PEO 7 million daltons) and talc that raise specific safety concerns if they are administered by unintended routes.

The Applicant provided their own proprietary and published data to assess the risks associated with the excipients in AR19 when misused via the intravenous and intranasal routes.

Under the conditions used in the submitted study, the data provided by the Applicant indicate that IV injection of one extract of AR19 once a day for 7 days did not result in clear evidence of thrombotic microangiopathy, or TMA, or other toxicities that were observed with reformulated Opana ER. However, the current data have limitations which will be discussed in detail later in the presentation.

Overall, the FDA cannot rule out the possibility that adverse events could occur with other drug product extracts that were not tested. In addition, we cannot rule out the possibility that adverse events could occur with more frequent and/or prolonged administration of the manipulated AR19 product by the IV route.

Slide 3

FDA has regulatory guidances for the safety assessment of excipients when administered by the intended route and guidances for assessing safety when oral products are to be reformulated

for use by other intended routes such the IV route. However, FDA does not have a formal nonclinical guidance for evaluating the safety of oral drug products administered by unintended routes of administration.

Prompted by unanticipated postmarketing concerns that arose with reformulated Opana ER, FDA now evaluates potential risks associated with excipients in abuse-deterrent formulations of opioids when these products are manipulated for misuse via alternative routes of administration. Considering previous experience with opioid products, we employed a similar approach for this program due to the potential for misuse.

Slide 4

This slide provides some details on the first excipient for discussion today: PEO 7 million daltons. Just to clarify the nomenclature, polyethylene glycol or PEG is a term that is reserved for polymers that are less than 100,000 daltons molecular weight; the nomenclature polyethylene oxide or PEO is reserved for larger polymers that are greater than 100,000 daltons molecular weight.

There are some basic concepts about PEOs to keep in mind for this presentation. PEO polymers are available at various molecular weights, and toxicities appear to correlate with their molecular weight. High molecular weight PEO polymers have been employed in some abuse-deterrent formulations to impart characteristics intended to deter abuse. Based on the current data, high molecular weight PEO greater than 1 million daltons specifically raises a concern for potential TMA. The current data are limited on the hemolytic potential of PEOs that are less than 1 million daltons, and on the hemolytic potential after prolonged duration of treatment with PEO greater than 1 million daltons. Heating manipulations can degrade high molecular weight PEOs to lower molecular weight PEOs, thus reducing their hemolytic potential. And finally, both reformulated Opana ER and AR19 contain PEO 7 million daltons.

Slide 5

As a reminder, after the market approval of reformulated Opana ER, there were unanticipated clinical outcomes in individuals who manipulated the formulation by IV route. These adverse events include anemia, TMA, acute kidney injury, retinal damage, and cardiac toxicity.

Slide 6

Following the postmarketing reports, FDA conducted and published mechanistic studies in animal models to better understand the clinical adverse findings. In this study published by Hunt et al., guinea pigs were injected with PEO 7 million daltons plus several other excipients that were specific to the Opana ER reformulation. It is important to point out here that the material used in this study was not subjected to manufacturing processes which may include heating and curing steps. However, injection of the uncured excipients into these animals resulted in toxicities that were consistent with the adverse events reported in humans.

This published study also demonstrated that the hemolytic toxicity observed was not due to a lack of blood compatibility but rather, it was likely an indirect hemolytic effect due to an increase in sheer stress in the blood vessels and deposition of free hemoglobin in tissues. The results of the Hunt investigations illustrate the utility of an in vivo study to evaluate the potential toxicity of high molecular weight PEOs.

Slide 7

A key point relevant to the discussion today is the fact that high molecular weight PEOs have been used in multiple oral drug products, some of which include labeling for abuse-deterrent properties. These include OxyContin, Hysingla, Arymo, Zohydro, and Concerta, a controlled-release stimulant. Evidence of TMA has not been noted for all of these products. In fact, we are aware of only 6 reports of TMA following manipulation of reformulated OxyContin for intravenous administration. To our knowledge, there are no reports of TMA with these other products. This is in distinct contrast to the incidence of TMA reported with reformulated Opana ER. As such, we do not believe that all PEO-based drug products have the same risk for TMA. Differential risk could be based on several differences between these products and Opana ER. For example, there may be differences in the manufacturing process, such as curing methods, differences in the molecular weight of PEO used to manufacture the drug products, differences in methods of manipulation needed to extract the drug substances, and/or differences in patterns of abuse which may contribute to the risk of TMA.

Slide 8

I would like to now go through the approach that the Applicant took to characterize the potential risks associated with PEO 7 million daltons by the IV route.

Slide 9

As previously presented by my colleagues from the Chemistry team, there are likely many ways to manipulate AR19 capsules to extract the active ingredient, amphetamine. We cannot predict or test them all. However, the table on this slide shows the Applicant's nine representative conditions that they explored in an in vitro hemolysis assay. Here, the data are compiled to summarize the data provided by the Applicant in the NDA and in their briefing document. The columns on the table show the syringeability, injectability, and extractable levels of amphetamine and PEO greater than 1 million daltons. These data are based on extraction from one 40 mg AR19 capsule. Note that the data here does not distinguish between the various molecular weights of PEO that are greater than 1 million Daltons.

The Applicant notes that all nine extracts are syringeable, meaning that they can be drawn into a needle at high temperatures, but not all are injectable because they congeal when cooled to physiological temperatures suitable for injection. Highlighted in green are the five extracts that were deemed by the Applicant to be injectable at physiological temperatures.

Also note that based on the data submitted to the NDA, the limit of quantitation of PEO in these studies vary. The less than symbol indicates that PEO was not quantified at this level; however, we cannot exclude the possibility that PEO was present up to the limit of quantitation. For example, Condition 6 resulted in 5 mg of amphetamine and possibly up to 5.23 mg of PEO greater than 1 million daltons. The important take home message from this slide is that in at least one manipulation condition, a measurable quantity of PEO greater than 1 million daltons is present in an extract that is both syringeable and injectable. Although the amount of amphetamine present in this condition is not likely to be reinforcing dose and, thus, would not likely be repeated, injection of high molecular weight PEO has the potential to cause harm.

Slide 10

Using an in vitro assay model intended to mimic sheer stress-induced hemolysis, the Applicant demonstrated that Conditions 3, 4, and 6 produced 15, 14, and 11% hemolysis respectively compared with the positive control, PEO 8 million daltons. Condition 6 was considered injectable, contains a low dose of amphetamine, and showed some evidence of hemolysis in this assay suggesting the potential presence of some high molecular weight PEO below the limit of quantitation. Also illustrated by this table, the extract from Condition 3 had the highest yield of high molecular weight PEO of the conditions tested; however, the Applicant noted that this extract was not considered suitable for injection given that its viscosity increased as the manipulated extract cooled to physiological temperatures.

Slide 11

This slide narrows down the extract samples that the Applicant considered suitable for injection. Of these, the Applicant chose to conduct further nonclinical testing using only extract from Condition 8. Condition 8 had the highest amount of syringeable amphetamine, but it had no quantifiable levels of high molecular weight PEO. No evidence of hemolysis was observed for Condition 8 in the in vitro assay under the conditions tested. Interestingly, Condition 8 utilized a manipulation step which employed high heat pretreatment thus potentially degrading the PEO in the extract.

Slide 12

In this table of only the injectable extracts, we note again that all five extracts yield amphetamine and may contain high molecular weight PEO greater than 1 million daltons. Due to limitations in the sensitivity of the analytical methodology, we must conclude that some of these extracts may have had as much as 5 mg of high molecular weight PEO. Based on the data provided, Condition 1 may be the “worst-case” scenario here with respect to quantifiable, injectable PEO greater than 1 million daltons. Condition 1 also did not utilize high heat pre-treatment but rather the extraction was done at room temperature. The data provided indicate that the Condition 1 extract, which includes some amphetamine, contains PEO greater than 1 million daltons. Because this was not tested in in vivo toxicology studies, we do not know if injection of this material would result in TMA.

Therefore, based on the data we have to date, we cannot rule out the possibility that an individual who manipulates the product using these conditions in order to obtain amphetamine may also inject some PEO greater than 1 million daltons.

Slide 13

To characterize the toxicity associated with AR19 Condition 8 extract, the Applicant conducted a series of preliminary studies that were not conducted in accordance with Good Laboratory Practices, and pivotal studies in accordance with GLP using in an in vivo animal model. Preliminary studies were used to inform dose selection of Condition 8 extract and a PEO 7 million daltons positive control for their pivotal study. The preliminary dose range-finding studies for PEO 7 million daltons demonstrated similar toxicities as reported in the literature, including mortality.

Unfortunately, in the pivotal GLP study, the doses of PEO 7 million daltons produced more significant toxicity than was predicted from the dose range-finding studies, suggesting the positive control dosing regimen was not optimized for the pivotal study. However, considering that the pivotal study used a larger sample size of animals and because it was conducted under GLP, the data from the pivotal study is most informative, so I will describe it in detail here.

In this pivotal study, New Zealand White rabbits were administered Condition 8 extracts equivalent to up to 3 AR19 capsules per day for 7 days. In this study, the Applicant included a positive control arm of rabbits treated with a dose of PEO 7 million daltons. However, all positive control rabbits prematurely died or were euthanized within minutes of the first dose administration due to severe clinical signs. Therefore, there were no survivors for the positive control group for the duration of the pivotal study for histopathological comparisons. In the premature decedents, there was clotted blood in the heart, pulmonary artery, and/or vena cava, but no other histopathological findings to demonstrate clear TMA. In this study, IV administration of three doses of AR19 Condition 8 extract per day for seven days did not produce evidence of adverse effects.

Slide 14

Although the Applicant's pivotal toxicity study to characterize the toxicological potential of AR19 Condition 8 extract did not show adverse effects, there were a few limitations in the assay.

First, the full chemical content of the syringeable Condition 8 AR19 extract was not characterized and approximately 15% of the material was described as impurities of unknown chemical composition. Therefore, it is possible that in addition to the amphetamine, PEO, talc, and starch that the Applicant quantified in this material, the extraction conditions could have resulted in the formation of unknown degradants of amphetamine and/or other excipients. It is not known if 7-days would be an adequate time for toxicities of these unknown compounds to manifest.

Second, five other extracts were considered injectable at physiological temperatures and yielded amphetamine but these were not tested in in vivo toxicology studies. Therefore, some of the injectable extracts potentially containing higher high molecular weight PEO were not evaluated in vivo. In fact, the Applicant assessed only Condition 8 extract which appears to contain heat-degraded PEO.

And finally, the in vivo studies were limited in terms of duration of treatment and number of injections and dosing conditions are not expected to reflect all potential human patterns of abuse, should the product be approved.

Slide 15

Next, I will go through the approach that the Applicant took to characterize the potential risks associated with intravenous and intranasal talc exposure.

Slide 16

Based on nonclinical literature, talc is known to cause a number of toxicities via the IV and intranasal routes including pulmonary and systemic granulomas, lung fibrosis and talc-induced pneumonia. The Applicant's extraction studies demonstrated that only small quantities of talc were present when AR19 was manipulated for use via intravenous or intranasal routes. Despite the low levels, talc could still be deposited in tissues, accumulate, and cause chronic toxicities with repeated IV or IN misuse of this product. Therefore, we believe that the risk with talc in AR19 is likely similar to the risk observed for other non-ADF oral formulations that contain talc.

Slide 17

In summary, the data provided by the Applicant have limitations and do not alleviate the FDA's concerns about the safety of the excipients in this product. If AR19 is manipulated in a manner that results in injectable high molecular weight PEO, we cannot rule out the possibility of thrombotic microangiopathy. Talc exposure via injecting or snorting manipulated AR19 capsules likely poses a concern similar to other non-ADF oral formulations containing talc.

Slide 18

This concludes the Overview of the nonclinical assessment of the excipients in the AR19 drug product. Thank you.