

**FDA ADVISORY COMMITTEE BRIEFING DOCUMENT****Aximris XR  
(oxycodone hydrochloride) extended-release tablets**

**JOINT MEETING OF THE ANESTHETIC AND ANALGESIC  
DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG  
SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

**Intellipharmaceutics Corp.**

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## List of Abbreviations and Definition of Terms

ADF	Abuse-deterrent formulation
AIDS	Acquired immunodeficiency syndrome
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
APTT	Activated partial thromboplastin time
AUC <sub>inf</sub>	Area under the curve from time 0 to infinity
AUC <sub>last</sub>	Area under the curve from time 0 to the last time point
cc	Cubic centimeter
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
C <sub>max</sub>	Maximum concentration
CRL	Complete response letter
E <sub>max</sub>	Maximum effect
ER	Extended release
FDA	Food and Drug Administration
HAL	Human abuse liability
HCl	Hydrochloride
HIV	Human immunodeficiency virus
HMW	High molecular weight
ICH	International Conference on Harmonisation
IID	FDA Inactive Ingredient Database
IR	Immediate release
IV	Intravenous
LA	Long-acting
LD	Listed drug
LS	Least squares
mg	Milligram
min	Minute
mL	Milliliter
MNC	Mononuclear cell

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MOS	Margin of safety
MTDD	Maximum tolerable daily dose
NDA	New drug application
OD	Optical density
OPC	Opioid Post-marketing Consortium
PD	Pharmacodynamic
PDE	Permitted daily exposure
PEO	Polyethylene oxide
PK	Pharmacokinetic
PMN	Polymorphonuclear leukocyte
PT	Prothrombin time
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk-Evaluation and Mitigation Strategy
RPC	REMS Program Companies
SAE	Serious adverse event
SAR	Structure-activity relationship
SD	Standard deviation
SE	Standard error
SKIP	Survey of Key Informants' Patients
SLS	Sodium lauryl sulfate
SUPAC-MR	Scale-Up and Post-Approval Changes Modified Release
t <sub>1/2</sub>	Half life
TEAE	Treatment-emergent adverse event
TTC	Threshold of toxicological concern
TTP	Thrombotic thrombocytopenic purpura
US	United States
VAS	Visual analog scale

## 1 EXECUTIVE SUMMARY

### 1.1 Introduction

The Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee are being asked to discuss new drug application (NDA) 209653 for oxycodone extended-release oral tablets (hereafter referred to as Aximris XR), submitted by Intellipharmaceutics Corp. (IPC or the Sponsor), with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Aximris XR has been formulated with the intent to provide abuse-deterrent properties, and Intellipharmaceutics has submitted data to support the abuse-deterrent properties for this product. The committees will be asked to discuss whether Intellipharmaceutics has demonstrated abuse-deterrent properties that would support labeling, as well as to discuss the overall risk-benefit profile of the product.

### 1.2 Product Description

Aximris XR is an investigational abuse-deterrent extended-release (ER) oxycodone hydrochloride (HCl) product intended for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Aximris XR is designed to be bioequivalent to OxyContin®. This briefing document summarizes the Sponsor's data, which support that Aximris XR is bioequivalent to OxyContin. The data also support that Aximris XR's formulation provides resistance to common manipulations used by abusers to overcome the time-release mechanism of ER dosage forms and provides resistance to abuse by intravenous (IV) injection, with less drug extracted in injectable volumes of solution when compared with OxyContin. Furthermore, the Sponsor's data also show that, if manipulated for intranasal abuse, Aximris XR is as difficult, and in some cases more unpleasant, to manipulate than OxyContin. Therefore, Sponsor's data summarized in this briefing document support the approval of Aximris XR as an extended release opioid analgesic with properties that can be expected to deter or make the intranasal and IV routes of abuse more difficult or less rewarding.

If approved by the Food and Drug Administration (FDA), Aximris XR will be provided in the following proposed dosage strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg (see [Figure 1](#)). These are the same as the currently marketed dosage strengths for OxyContin®. Aximris XR 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients for whom tolerance to an opioid of comparable potency has been established. The proposed indication is for adults and opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent, which is the same indication as OxyContin. The proposed labeling recommends that Aximris XR could be administered with or without food, since the Aximris has no significant food effect; the full release of the drug from the formulation is achieved irrespective of the presence or absence of food.

**Figure 1: Dosage Strengths of Aximris XR Tablets**

Aximris XR is formulated with a combination of physical and chemical barriers with intent to make the tablet more difficult, less amenable, unpleasant and less rewarding to manipulate for misuse and abuse. During development, FDA provided significant input, particularly in design of the studies to evaluate abuse potential. These studies are referred to as Category 1 (in vitro laboratory physical and chemical manipulation), Category 2 (pharmacokinetic), and Category 3 (clinical abuse potential) studies. Some of the features of Aximris XR that were determined in the abuse potential program are summarized below:

#### Features of Aximris XR

- Aximris XR is formulated to become viscous more quickly with greater particle size reduction on contact with aqueous environment.
- Aximris XR coagulates on contact with aqueous solutions to make IV injection difficult.



- Intact and manipulated Aximris XR is resistant to chemical extraction for IV injection across a range of conditions and solvents.
- When manipulated and subjected to an aqueous environment, Aximris XR creates a viscous material that is difficult to syringe or pass through a hypodermic needle, with less drug extracted in injectable volumes of the liquid when compared with OxyContin®.

- Aximris XR is resistant to dose dumping in the presence of alcohol.
- Aximris XR resists heat manipulation for purpose of vaporization and smoking.
- Manipulation of Aximris XR for abuse can result in difficulty in snorting and local irritating effects (facial pain/pressure, throat irritation, and nasal congestion), which may make manipulation for oral and intranasal abuse less attractive.

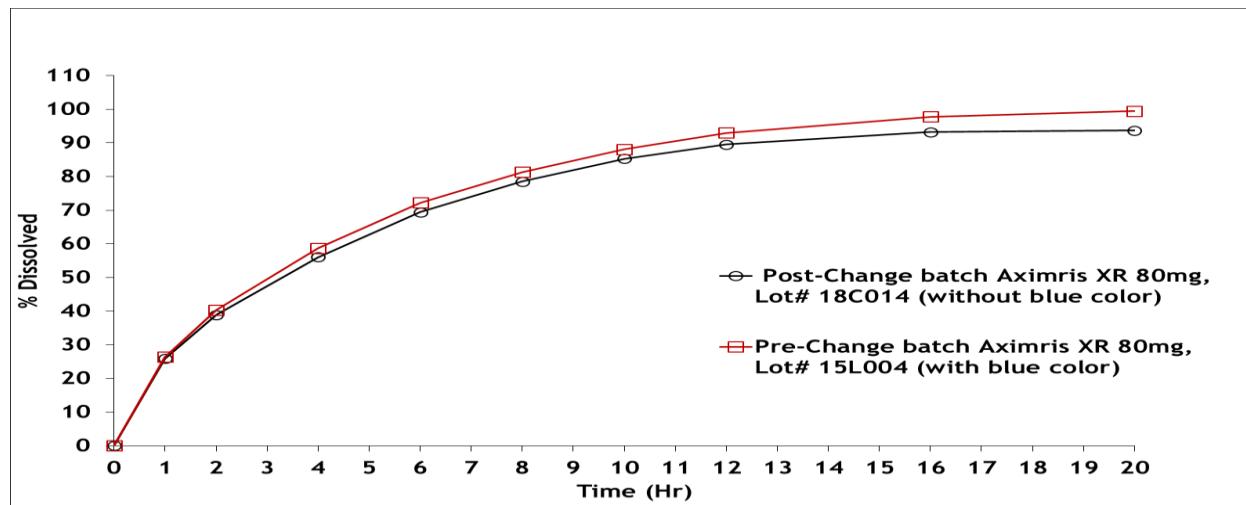
### 1.3 Regulatory History

In November 2016, Intellipharmaceutics submitted a New Drug Application (NDA) for approval of Aximris XR to the FDA. In this original application, Aximris XR was formulated with FD&C Blue No. 1 Aluminum Lake to impart a blue color to the drug product. In September 2017, Intellipharmaceutics received a complete response letter (CRL).

In February 2018, Intellipharmaceutics engaged with the Agency in a Type A Post-action meeting to discuss and gain agreement on Intellipharmaceutics' plans to address deficiencies in the NDA. In February 2019, Intellipharmaceutics submitted an amendment to the NDA addressing deficiencies identified in the CRL based on advice from the Agency. It is important to note that, in response to FDA's comments in the CRL, Intellipharmaceutics changed the Aximris XR formulation to remove FD&C Blue No. 1 Aluminum Lake prior to submission of the February 2019 NDA amendment.

The function of this excipient was solely to impart color; the material did not have any release controlling property and did not impact the quality attributes of the product. Similarity Factor (F2) of 80 and similarity of dissolution profiles of pre- and post-change Aximris XR (which were submitted to the Division and in the Type A Post-action meeting minutes, February 28, 2019) support this conclusion (see **Figure 2**).

**Figure 2: Dissolution Profiles Oxycodone Hydrochloride ER (Aximris XR) Tablets, 80 mg Pre-change Exhibit Batch (with blue color) vs Post-change Batch (without blue color) in Acidic Media**



There was no change in the manufacturing process, critical material attributes, or the controls of the manufacturing process when this excipient was removed. In the Type A Post-action meeting, the Agency agreed that the removal of the FD&C Blue No. 1 Aluminum Lake dye is a Level 1 change per the Scale-Up and Post-Approval Changes Modified Release (SUPAC-MR) guidance (CDER, 1997), and hence, there is no need to conduct new or repeat pharmacokinetic bioequivalence studies previously conducted. Therefore, in the current Aximris XR NDA, Intellipharmaceutics is relying upon data from studies (including pharmacokinetic [PK] bioequivalence studies and Category 1, 2, and 3 abuse deterrence studies) conducted with the product both pre-change (containing blue dye) and post-change (blue dye removed).

Aximris XR was developed using the 505(b)(2) regulatory pathway with OxyContin as the listed drug (LD). This NDA uses data on bioequivalence of Aximris XR and OxyContin to support a scientific bridge to the Agency's prior finding of safety and efficacy of OxyContin. Pharmacokinetic bioequivalence studies under fasting, fed, and steady states comparing Aximris XR and OxyContin support the fact that Aximris XR is bioequivalent to OxyContin, thus establishing a scientific bridge to the Agency's prior finding of safety and efficacy of OxyContin.

#### 1.4 Public Health Perspective

The total number of opioid deaths in the United States (US) is increasing, primarily due to overdose deaths from heroin and synthetic opioids like fentanyl (CDC, 2016). While the number of opioid-related deaths due to natural and semi-synthetic opioids like oxycodone have plateaued since 2011, they remain at historically high levels.

Preventing injection with prescription opioids has been one of the primary public health goals of abuse-deterrent formulations (ADFs), because IV abuse is associated with more severe health consequences. Data from the RADARS Poison Center Program suggest that the relative risk of death or a major adverse effect (e.g., overdose) for the IV route is 2.6 times greater than abuse by the oral route (RADARS, 2016). Furthermore, IV abuse was also associated with 9% of new human immunodeficiency virus (HIV) diagnoses and 13% of all new acquired immunodeficiency syndrome (AIDS) diagnoses in the US in 2016 (CDC, 2016).

OxyContin was reformulated in 2010 with properties intended to make injection and other forms of manipulated abuse (e.g., crushing for oral or intranasal abuse) more difficult. While the rate of injection of OxyContin has decreased since reformulation, among those individuals who reported experience abusing both the pre-abuse-deterrent and the reformulated OxyContin, 34% reported successfully defeating the abuse-deterrent properties and continuing injection or snorting (Cicero and Ellis, 2015). There has also been published instructions on drug abuse online forum, on how to prepare OxyContin for abuse (bluelight.org, 2017).

As such, there is room for incremental improvement in the abuse-deterrent features of OxyContin, particularly to address the danger associated with the IV route of abuse.

## 1.5 Clinical Pharmacology Studies Supporting the Proposed Aximris XR Indication

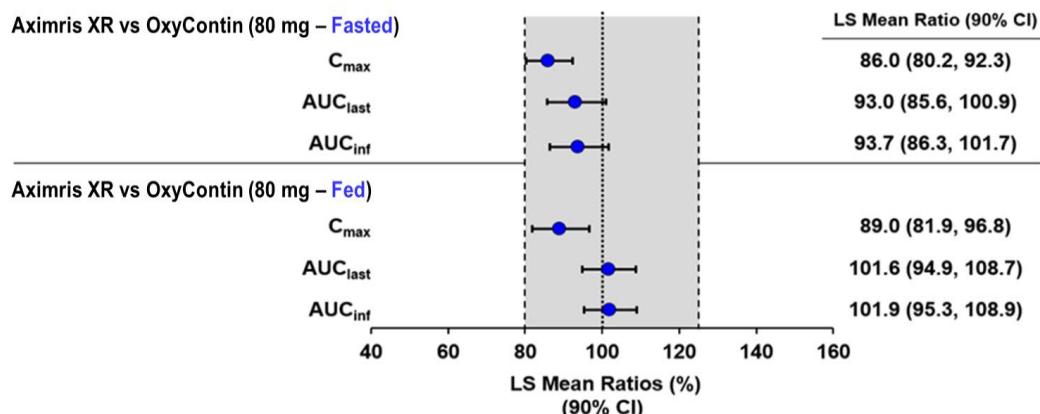
Aximris XR was developed using the 505(b)(2) regulatory pathway. For this NDA, approval is based, in part, on bioequivalence to the LD, OxyContin.

It is important to note that all the clinical pharmacology studies supporting the Aximris XR NDA were performed with the pre-change Aximris XR formulation (containing blue dye). However, the results from these studies are valid for the current post-change formulation (blue dye removed), because (as the Agency agreed in Intellipharmaceutics' Type A Post-action meeting) removal of the blue dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997).

### 1.5.1 Bioequivalence of Aximris XR to OxyContin

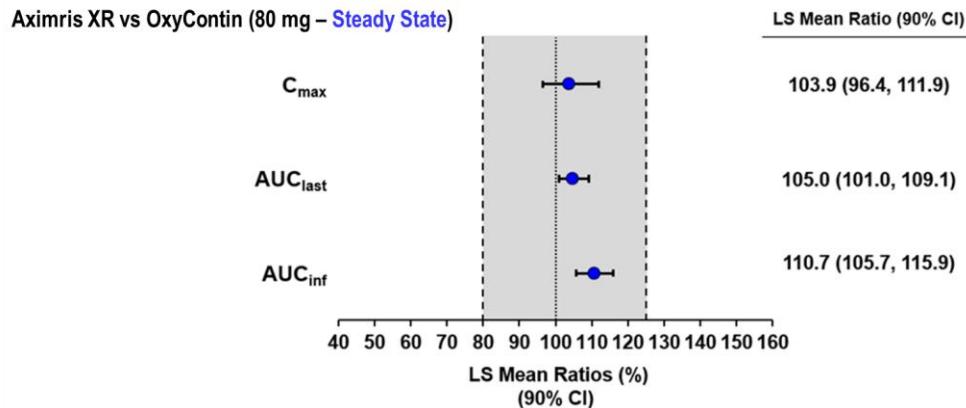
Clinical PK single-dose fasting and single-dose fed studies have demonstrated that Aximris XR is bioequivalent to OxyContin at both the lowest (10 mg) and highest (80 mg) dosage strengths (see [Figure 3](#) for example with highest dosage strength). A clinical PK multiple dose study under fasting conditions also demonstrated that Aximris XR 80 mg is bioequivalent to OxyContin 80 mg ([Figure 4](#)).

**Figure 3: Bioequivalence Results for 80 mg Dosage Strengths of Aximris XR and OxyContin Under Fasted (Study 656-15) and Fed Conditions (Study 655-15)**



Note: gray shaded area reflects bioequivalence range of 80% to 125%.

**Figure 4: Bioequivalence Results for Multiple Dose Studies for Aximris XR 80 mg vs OxyContin 80mg (Study 80-184)**

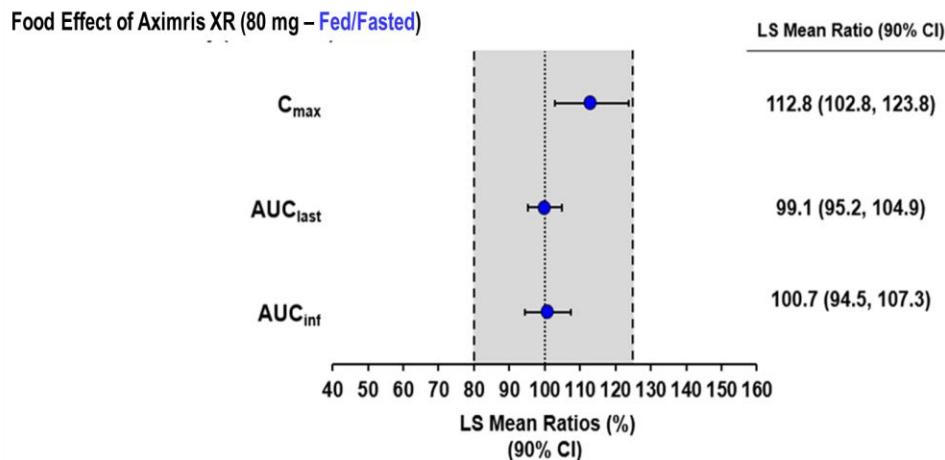


Note: gray shaded area reflects bioequivalence range of 80% to 125%.

### 1.5.2 Dose Proportionality of Aximris XR Dosage Strengths

Another clinical PK study demonstrated that Aximris XR dosage strengths are dose proportional, which provides support for the approval of all dosage strengths. Furthermore, a clinical PK food effect study has demonstrated that Aximris XR is bioequivalent in the fed and fasted states, so patients can take Aximris XR without regard to meals ([Figure 5](#)).

**Figure 5: Bioequivalence Results for Food Effect Studies for Aximris XR 80 mg Fed vs Fasted State (Study 80-186)**



Note: gray shaded area reflects bioequivalence range of 80% to 125%.

## 1.6 Evaluations of Abuse-deterrent Properties of Aximris XR

The current abuse-deterrent program for Aximris XR includes a comprehensive set of Category 1 (in vitro) abuse-deterrence studies, as well as Category 2 (pharmacokinetic) and Category 3 (clinical abuse potential) studies. Based on the similar dissolution profiles of pre- and post-change Aximris XR (which were submitted to the Division and in the Type A Post-action meeting minutes, February 28, 2019), the FDA stated that the Category I pre-change testing did not have to be repeated prior to NDA resubmission. The Agency did, however, request several additional syringeability studies be conducted on manipulated Aximris XR tablets (post-change formulation) after convection heat pre-treatment prior to conducting small volume extractions with four solvents. Additionally, in response to Agency feedback, toxicological risk assessments (including hemolytic studies and in vivo toxicology studies in rabbit) were performed to assess the exposure of Aximris XR excipients (or degradation products thereof) if the product is manipulated for abuse via the oral, intranasal, vaping, or intravenous routes.

### 1.6.1 Category 1 (In Vitro) Studies

A comprehensive set of Category 1 in vitro physical manipulation and chemical extraction studies evaluated the abuse-deterrent properties of Aximris XR compared to OxyContin. In accordance with FDA guidance, all studies were performed with the highest dosage strength (80 mg) of Aximris XR and OxyContin. Notably, most of the previous abuse-deterrent products reviewed by these Advisory Committees have used non-abuse-deterrent comparators in their Category 1 studies to demonstrate the products' abuse-deterrent properties. In contrast, the Category 1 studies for Aximris XR were designed to compare its abuse deterrence properties to those of OxyContin, an ER oxycodone HCl product with label claims for deterrence of the nasal and IV routes of abuse.

Category 1 studies included evaluation of resistance to physical manipulation (cutting, crushing, milling, and grinding tablets), dissolution of manipulated tablets (simulated oral ingestion), small volume (2mL, 5mL and 10mL) to large volume (20mL, 30mL and 50mL) IV extraction (syringeability/injectability, simulated intranasal), very large volume (100mL and 200mL) chemical extraction, alcohol dose dumping, complex extraction, smoking/vaporization (simulated insufflation), and more complex multi-step chemical extractions. These studies were designed in consultation with FDA and experts in the evaluation and development of ADFs. Overall, the results of these studies support the proposed IV abuse-deterrent claims for the Aximris XR label in accordance with the FDA Guidance "*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*" (CDER, 2015).

A brief description of the findings from these studies is provided below.

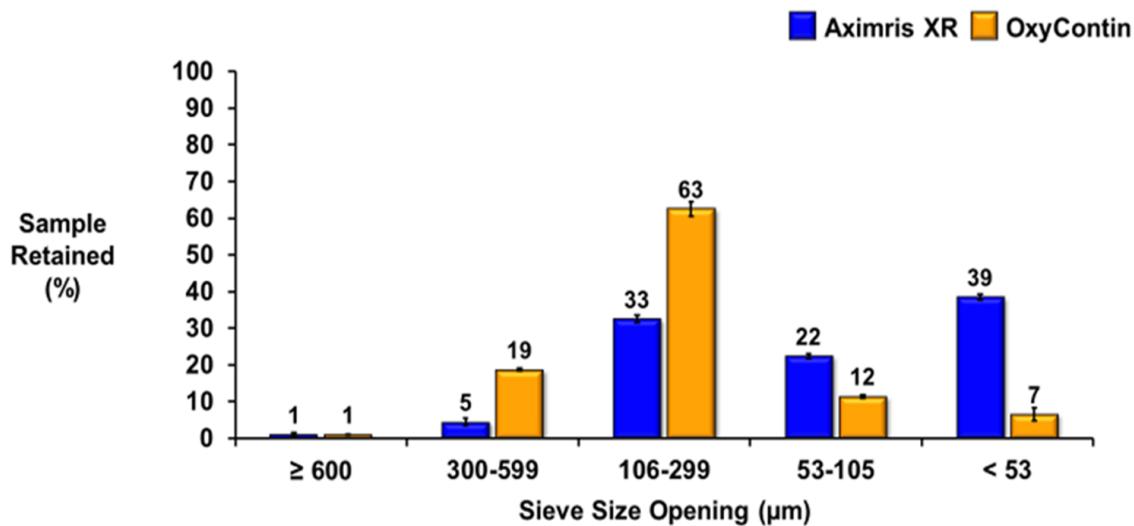
#### 1.6.1.1 Particle Size Reduction

In order to defeat the controlled-release mechanism of ADFs, opioid abusers typically crush the tablet formulation into fine particle size to defeat its controlled release mechanism in order to obtain a quick release of drug from the product. Thus, many ADFs, such as OxyContin, rely on the property of physical hardness as a way of presenting a barrier to particle size reduction and a means to deter abuse. However, there are continued reports of "recipes" on drug-user internet forums indicating that abusers are becoming more inventive in their attempts to defeat ADFs

(McNaughton et al., 2014; bluelight.org, 2017). Aximris XR is not dependent on physical hardness alone as its primary abuse-deterrent features. Rather, Aximris XR exploits the fact that there is an increase in surface area that accompanies particle size reduction when a tablet is crushed or ground.

Aximris XR and OxyContin were evaluated for their resistance to physical manipulation using 10 household tools representative of the different mechanisms used by abusers to crush, cut, grate, or grind solid oral dosage forms by mechanical or electrical means. Given that tablet hardness is not the primary abuse-deterrent feature of Aximris XR, it yielded a higher percentage of small particles across the various tools in comparison to OxyContin. Note that Aximris XR tablets have specifically been formulated to deter abuse with enhanced viscosity and hypercoagulability properties when its particle size is reduced or its surface area is increased. Although Aximris XR yielded finer particles than OxyContin, the smaller particles actually increased coagulation and viscosity and did not increase drug release or extraction.

The optimized particle size reduction method involved using an advanced kitchen appliance for an optimum number of tablets over an optimum period. Using this optimized procedure, both products had a particle size distribution with 99% of particles < 600 microns (see **Figure 6**). This procedure was used as the method of physical manipulation for all subsequent Category 1 studies and the resulting sample is referred to as ground tablet. The advanced kitchen appliance was necessary as a comminution method for OxyContin and Aximris XR because one of the tenets of the FDA Guidance is to test the abuse-deterrent properties of a formulation to failure to understand the limits of the physical and chemical barriers. Under these conditions, both products offered some resistance to physical manipulation, but OxyContin was more resistant to manipulation than Aximris XR. However, when Aximris XR and OxyContin underwent physical reduction to smaller particles and were brought in contact with aqueous environment, Aximris XR formed a more viscous material and coagulated more rapidly than OxyContin. This resulted in Aximris XR demonstrating more resistance to manipulation compared to OxyContin, as less drug was extractable in injectable volumes for abuse.

**Figure 6: Particle Size Distribution: Optimal Procedure Using Advanced Kitchen Appliance**


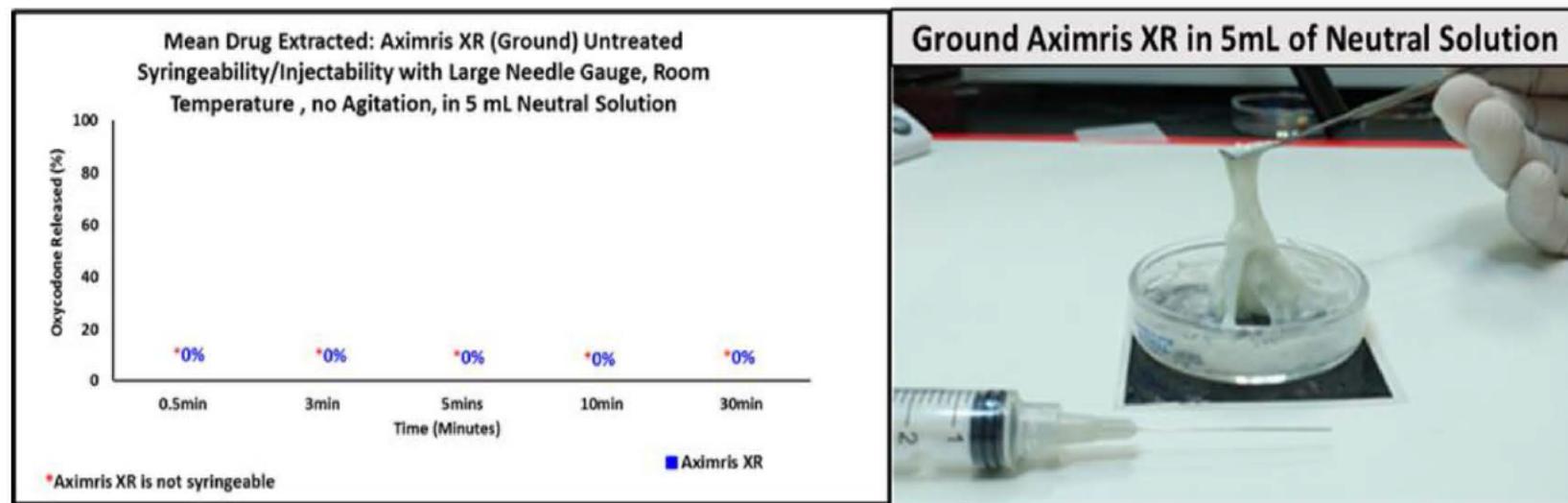
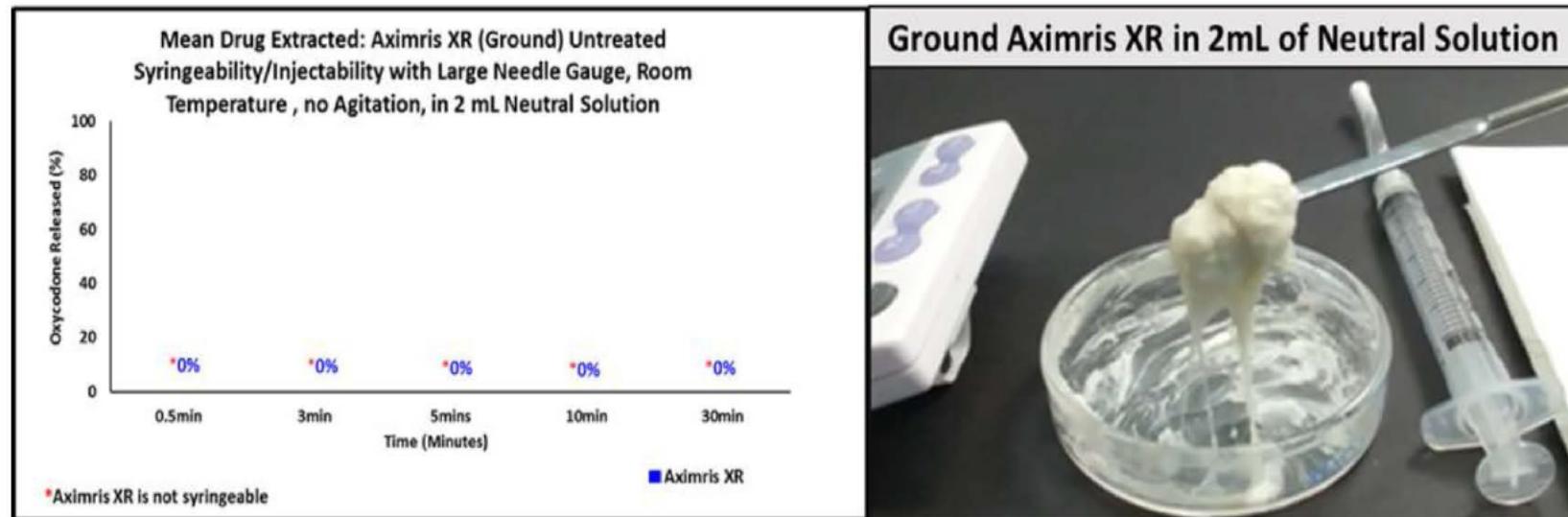
### 1.6.1.2 Extractability/Syringeability/Injectability

Most ADFs are designed to resist common methods for IV abuse. Both Aximris XR and OxyContin are formulated with properties intended to make IV abuse difficult by producing a highly viscous material and coagulating rapidly, entrapping drug when subjected to an aqueous environment. Unlike OxyContin, Aximris XR is formulated with excipients to enhance viscosity/hypercoagulability and drug entrapment even if subjected to high temperatures and considerable extraction volume in ingestible solvents. The *in vitro* IV abuse studies for Aximris XR evaluated simple methods for preparing opioid products for injection as well as “recipes” referenced on drug abuser websites to overcome the gelling properties of ADFs such as OxyContin. Aximris XR was also tested against advanced methods for defeating abuse deterrent formulations suggested by the FDA.

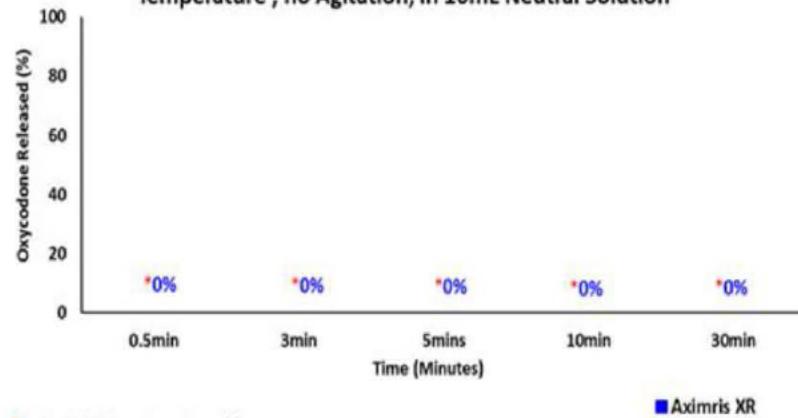
#### 1.6.1.2.1 Standard/Common Syringeability/Injectability

For standard or common syringeability/injectability assessments, samples of untreated ground Aximris XR or untreated ground OxyContin were added into various volumes ranging from small (2mL, 5mL, and 10mL as shown in **Figure 7**) to large volumes (20mL and 50mL) of a neutral or isotonic solution and incubated for up to 30 minutes with no agitation or with high agitation, at room or elevated temperatures.

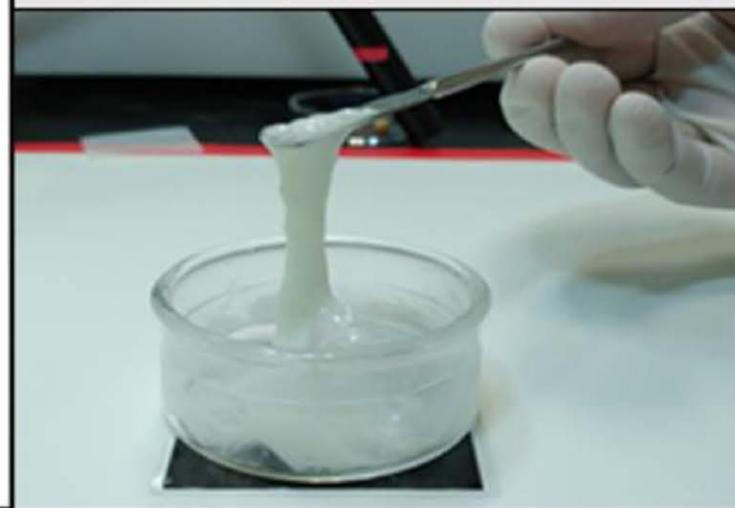
**Figure 7: Untreated Ground Aximiris XR displays high viscosity and hypercoagulability: not extractable, not syringeable and not injectable using standard or common manipulation methods with increasing small volumes of neutral solution**



Mean Drug Extracted: Aximris XR (Ground) Untreated  
Syringeability/Injectability with Large Needle Gauge, Room  
Temperature , no Agitation, in 10mL Neutral Solution



### Ground Aximris XR in 10mL of Neutral Solution



A similar study was performed using untreated intact tablet of Aximris XR or untreated intact tablet of OxyContin in large volume of isotonic solution, incubated for 5, 10, and 30 minutes with high agitation at room or elevated temperatures. No oxycodone was extracted at room temperature, while less than 10% was recovered at elevated temperature.

None of the conditions yielded a suitable amount of injectable oxycodone for either Aximris XR or OxyContin, which supports that both Aximris XR and OxyContin have abuse-deterrent properties for the IV route under these standard or common conditions.

#### ***1.6.1.2.2 Extractability/Syringeability/Injectability of Ground Aximris XR and OxyContin Tablets After Convection Heat Pre-treatment Using Neutral Solution, Isotonic Solution or Ingestible Alcoholic Solution***

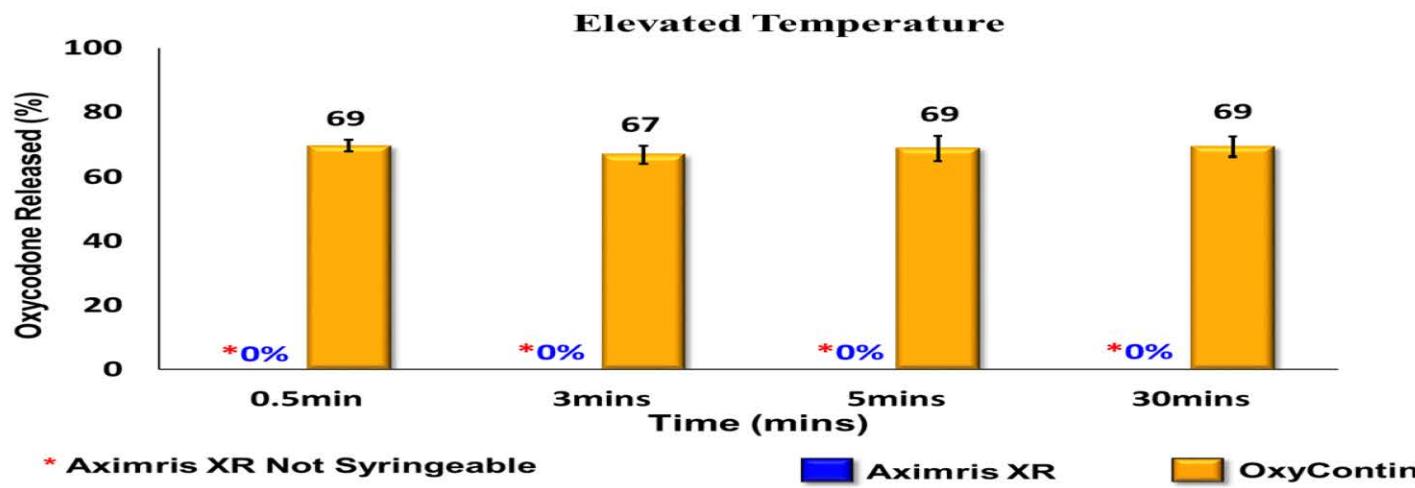
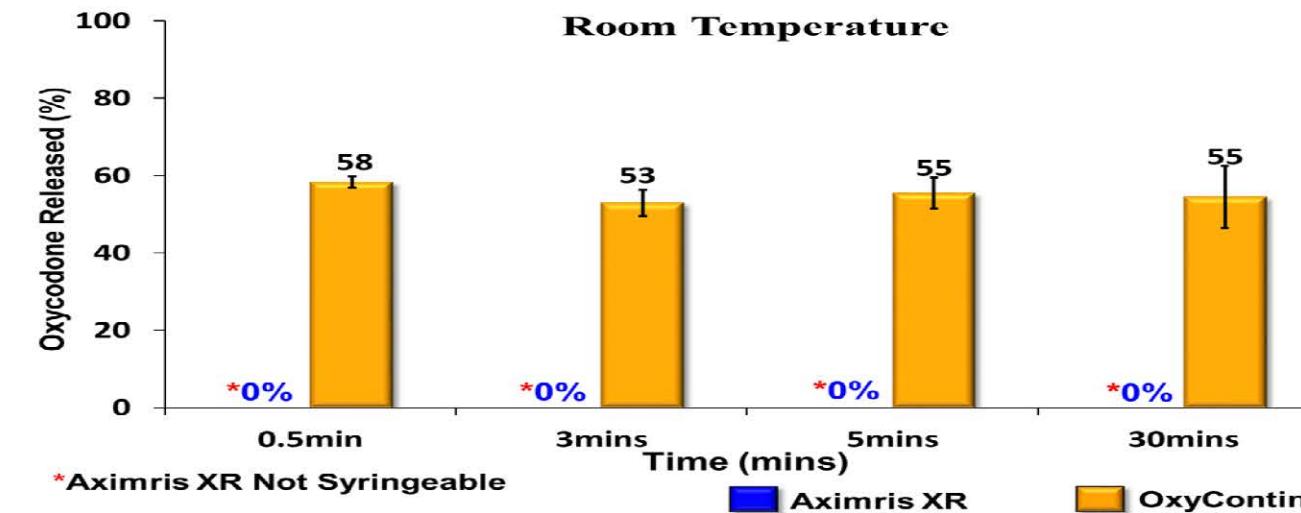
The Agency recommended (during the Type A Post Action meeting held February 2018) that Intellipharmaceutics perform studies on the syringeability of Aximris XR when manipulated using convection heat pre-treatment.

Both Aximris XR and OxyContin were challenged by subjecting the products to convection heat pre-treatment in order to determine if their extended release properties can be defeated to allow drug to be extracted in quantities that could be used for IV injection and be rewarding to an abuser.

The results showed that drug cannot be easily extracted in sufficient amount for IV injection from manipulated ground Aximris XR Tablet even after subjecting it to convection heat pre-treatment. This is in contrast with the comparator, ground OxyContin Tablet. Significantly high yield of oxycodone hydrochloride suitable for IV injection was obtained from OxyContin under the conditions studied.

These results support that Aximris XR is significantly more resistant to drug extraction for IV injection than OxyContin across the range of conditions and ingestible solvents investigated. This is exemplified in the figures below (details in **section 5.3.4**).

**Figure 8: Drug Extraction From Ground Aximiris XR or Ground OxyContin Tablets After Convection Heat Pre-treatment, Using 2mL of Ingestible Alcoholic Solution at Room or Elevated Temperatures Under Various Conditions**



#### **1.6.1.2.3 Extractability/Syringeability/Injectability From Intact Aximris XR and OxyContin Tablets, After Convection Heat Pre-treatment, Using Neutral Solution, Isotonic Solution or Ingestible Alcoholic Solution**

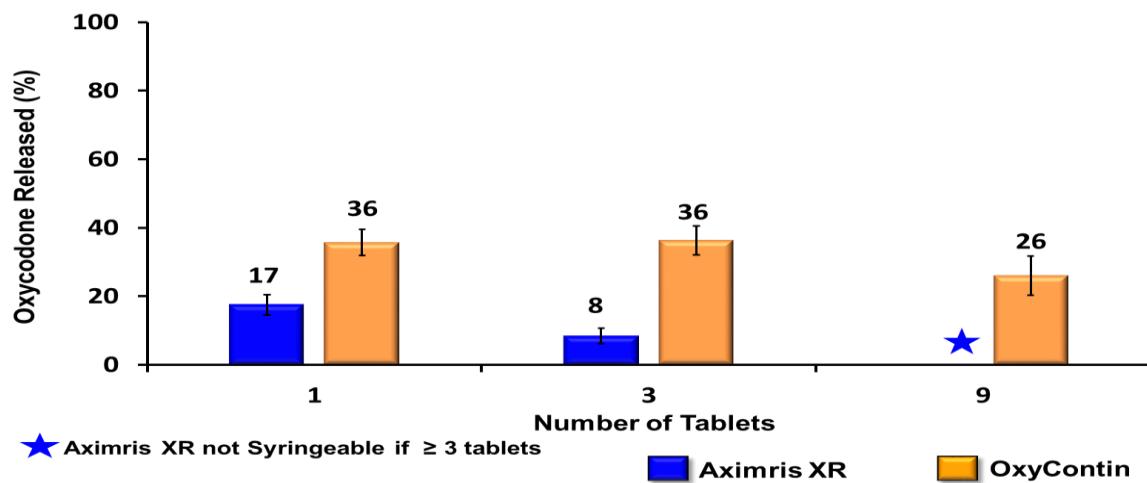
Insignificant amount of drug was extracted from intact Aximris XR and OxyContin Tablet. The amount of oxycodone extracted from both Aximris XR and the comparator, OxyContin were generally too low in all solvents. Incubation in 2mL, 5mL and 10mL of neutral solution at various time points (0.5 min to 30 min) showed Aximris XR 80 mg recovery of oxycodone ranging from < 1% to 6% of label claim across all platforms; while the comparator (OxyContin) was about 2 – 11% of label claim across the same platforms.

#### **1.6.1.2.4 Extractability/Syringeability/Injectability of Multiple Tablets of Ground Aximris XR and OxyContin After Convection Heat Pre-treatment Using Neutral or Hypertonic Solution**

In addition to studies on the syringeability of manipulated single tablet of Aximris XR after convection heat pre-treatment using neutral, isotonic or alcoholic solutions, the Agency also recommended that Intellipharmaceutics investigate the extractability/syringeability/injectability starting with a single pre-treated tablet and increasing the number of pre-treated tablets in subsequent steps until the solution is no longer syringeable. Multiple tablets of ground Aximris XR or OxyContin were manipulated using convection heat pre-treatment and then tested for extractability/syringeability/injectability, using 30mL of neutral or hypertonic solution at elevated temperature with high agitation.

The results indicate that at elevated temperature, the amount of drug that can be extracted from Aximris XR and OxyContin® decreased as the number of tablets were increased. Overall less drug could be extracted from Aximris XR compared to OxyContin as shown in the figure below.

**Figure 9: Drug Extraction From Multiple Tablets of Ground Aximris XR and OxyContin After Convection Heat Pre-treatment, Using 30mL of Neutral Solution at Elevated Temperature and High Agitation for 30 Minutes Under Various Conditions**



#### ***1.6.1.2.5 Extractability/Syringeability/Injectability After Using “Recipe” from Drug Abuse Websites (Radiant Heat Pre-treatment): Aximris XR vs OxyContin.***

One of the most common methods cited on drug abuse websites (e.g., bluelight.org) to defeat the IV abuse deterrence property of OxyContin is to perform radiant heat pre-treatment prior to drug extraction. Therefore, radiant heat pre-treatment was applied to ground Aximris XR or ground OxyContin Tablets followed by extraction in 2mL, 5mL, and 10mL of neutral solution and incubation for up to 5 minutes with no agitation at room or elevated temperatures using very small gauge needle to large gauge needle. The results obtained using radiant heat pre-treated Ground Tablet, without agitation at 0.5 minutes in neutral solution and large gauge needle can be summarized as follows;

##### ***2mL at room temperature***

The mean oxycodone drug recovered from Aximris XR was 15.0% while that for OxyContin was 73.0%. 2mL at elevated temperature

##### ***2mL at elevated temperature***

The mean oxycodone drug recovered from Aximris XR was 43.6% (small gauge needle yielded 15.4%) while that for OxyContin was 57.2% (small gauge needle yielded 65.0%).

##### ***5mL at room temperature***

The mean oxycodone drug recovered from Aximris XR was 20% while that for OxyContin was 85.0%.

##### ***5mL at elevated temperature***

The mean oxycodone drug recovered from Aximris XR was 51.8% (small gauge needle yielded 22.8%) while that for OxyContin was 47.8% (small gauge needle yielded 44.2%).

##### ***10mL at room temperature***

The mean oxycodone drug recovered from Aximris XR was 33.7% (small gauge needle yielded 28.3%) while that for OxyContin was 43.1% (small gauge needle yielded 36.0%).

##### ***10mL at elevated temperature***

The mean oxycodone drug recovered from Aximris XR was 18.5% (small gauge needle yielded 24.3%) while that for OxyContin was 25.6% (small gauge needle yielded 28.1%).

Overall, drug could be extracted from both Aximris and OxyContin. However, Aximris displayed greater resistance to extraction compared to OxyContin.

#### ***1.6.1.2.6 Extractability/Syringeability/Injectability Using Three-dose Equivalents After Using Recipe” from Drug Abuse Websites (Radiant Heat Pre-treatment): Aximris XR vs OxyContin***

Multiple tablets syringeability assessments were carried out for three-dose equivalents of untreated and radiant heat pre-treated ground Aximris XR and ground OxyContin Tablets.

For untreated tablets, none of the conditions yielded a suitable amount of injectable oxycodone for either Aximris XR or OxyContin.

For ground tablets of Aximris XR that underwent radiant heat pre-treatment, no suitable amount of injectable oxycodone was obtained with 10mL and 20mL of neutral solution at room temperature, while 56% and 26% were obtained from ground Oxycontin Tablets under the same conditions. Additionally, at elevated temperature ground Aximris XR Tablets could not be syringed to obtain suitable amount of injectable oxycodone at 10mL of neutral solution while the comparator ground OxyContin Tablets yielded 63% of oxycodone. In 20mL of neutral solution, at elevated temperature, ground Aximris XR Tablets yielded 30% while the comparator ground OxyContin Tablets yielded 60%. Note that 20mL is not a suitable volume that abusers typically use.

#### ***1.6.1.2.7 Gel-blob Syringeability: Aximris XR vs OxyContin***

An alternate method for IV abuse involves attempting to overcome the gelling effect of abuse-deterrant products with longer incubation times (i.e., gel-blob syringeability). For this study, ground Aximris XR and OxyContin Tablets were added to 5mL of neutral solution and incubated for 4 and 24 hours at room or elevated temperatures. At room temperature, it was not possible to extract drug from Aximris XR and OxyContin. While at elevated temperature smaller amount of drug was extracted from Aximris XR compared to OxyContin.

#### ***1.6.1.3 Very Large Volume Extraction***

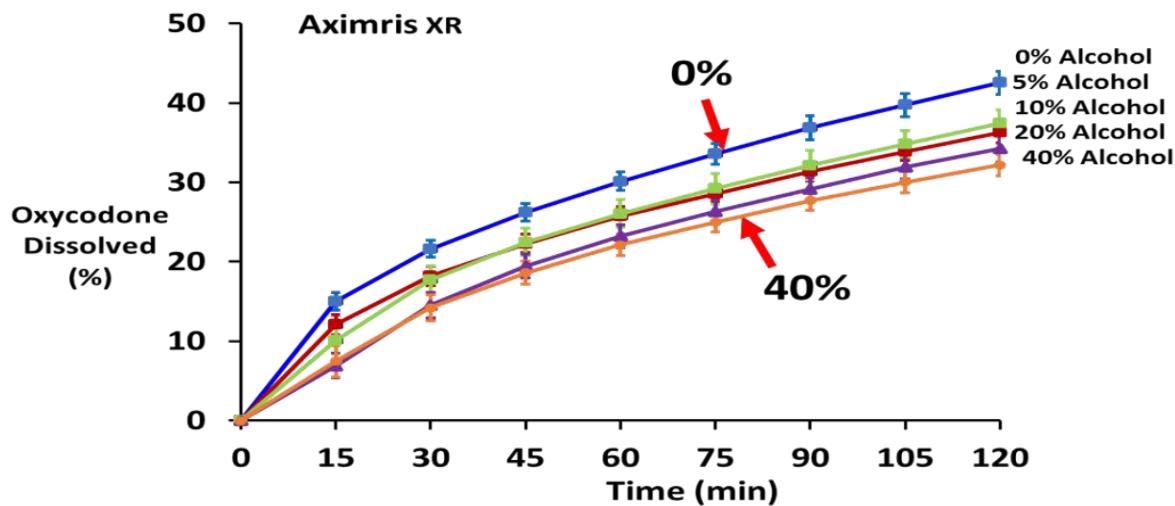
The resistance to extraction of manipulated Aximris XR and OxyContin 80 mg tablet equivalents in large volumes was evaluated in 20 common and advanced solvents, including under stress conditions with modifications to temperature and agitation. Overall, the resistance to very large volume (100mL and 200mL) extraction was similar for both products, for the most common ingestible solvents and non-ingestible solvents.

#### ***1.6.1.4 Alcohol Dose Dumping***

One common concern with ER opioid products is rapid release of the drug in the presence of alcohol (i.e., alcohol dose dumping). The potential for alcohol dose dumping with Aximris XR and OxyContin was evaluated using an in vitro model with acidic and basic dissolution media having different concentrations of alcohol. Results support that Aximris XR does not dose dump in the presence of alcohol (see **Figure 10**). The release of oxycodone from Aximris XR decreased with increasing concentrations of alcohol, just like for OxyContin. Despite the lack of

dose dumping with alcohol, Aximris XR, like all opioid products, should not be co-ingested with alcohol.

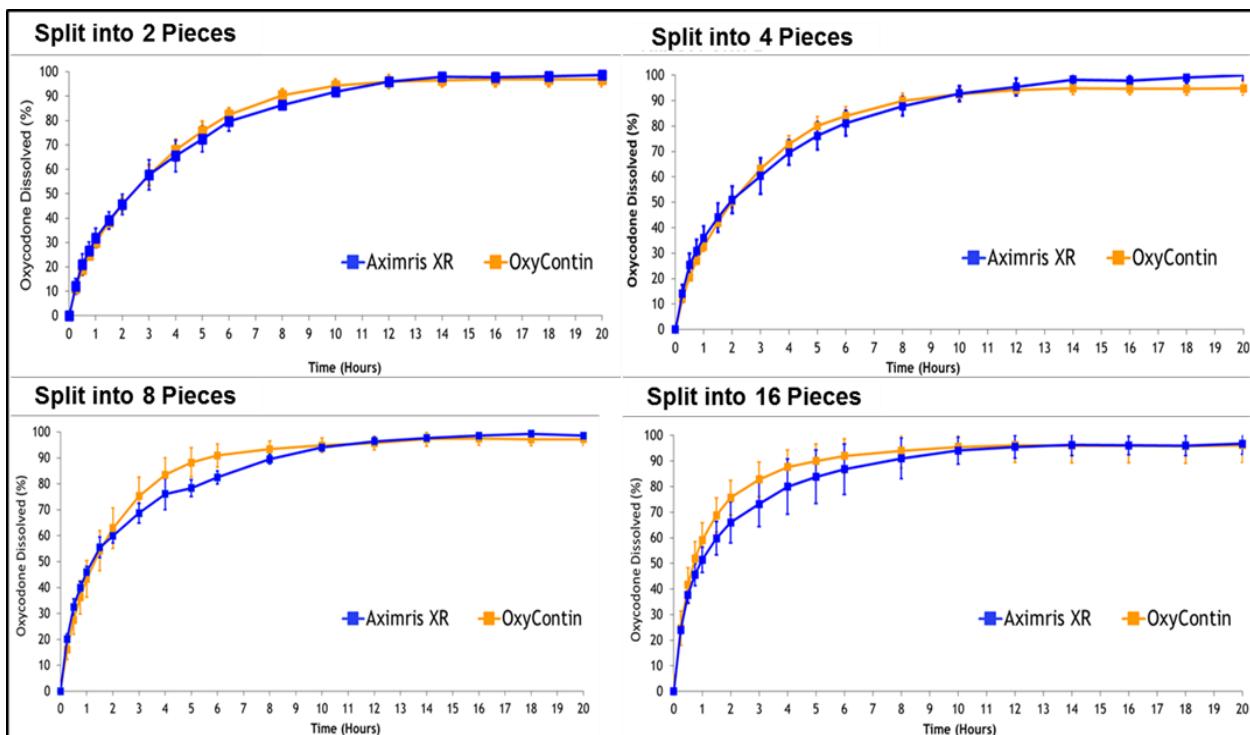
**Figure 10: Percent Oxycodone Dissolved From Intact Tablet of Aximris XR in Varying Concentrations of Alcohol in Acidic Dissolution Media**



#### 1.6.1.5 Ability to Defeat ER Properties When Intact Aximris XR Tablet is Manipulated and Split into 2, 4, 8 and 16 Pieces

Abusers have attempted to defeat the extended release properties of ADFs by splitting them into 2, 4, 8 and 16 pieces etc., and ingesting them. Dissolution of Aximris XR and OxyContin tablets when split into 2, 4, 8 and 16 pieces using acidic and basic dissolution media showed Aximris XR and OxyContin maintained extended release properties with Aximris XR demonstrating more resilience as the number of split units increased. (see [Figure 11](#)).

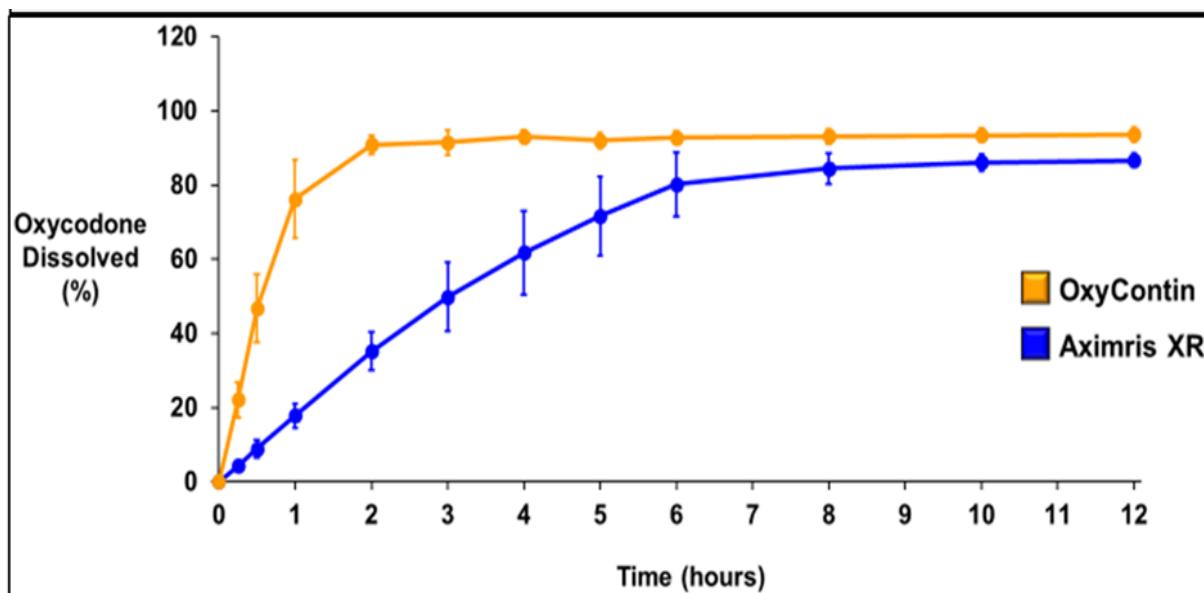
**Figure 11: Comparative Dissolution Profiles of Aximris XR vs OxyContin When Split Into 2, 4, 8 and 16 pieces in Acidic or Basic Dissolution Media**



#### 1.6.1.6 Ability to Defeat ER Properties of Intact Tablet Aximris XR and OxyContin Using Radiant Heat Pre-treatment With or Without Rotation

Radiant heat pre-treatment with or without rotation are common methods used to defeat abuse deterrent properties in order to release drug for abuse, as cited on drug abuser websites. Aximris XR and OxyContin were subjected to radiant heat pre-treatment with or without rotation; the release of oxycodone in neutral dissolution media was considerably lower for Aximris XR than for OxyContin, especially in the first five hours. For example, using radiant heat pre-treatment with rotation, less than 20% of drug was released in one hour for Aximris XR compared to over 75% drug released for OxyContin (Figure 12). Similar results were observed for radiant heat pre-treatment without rotation.

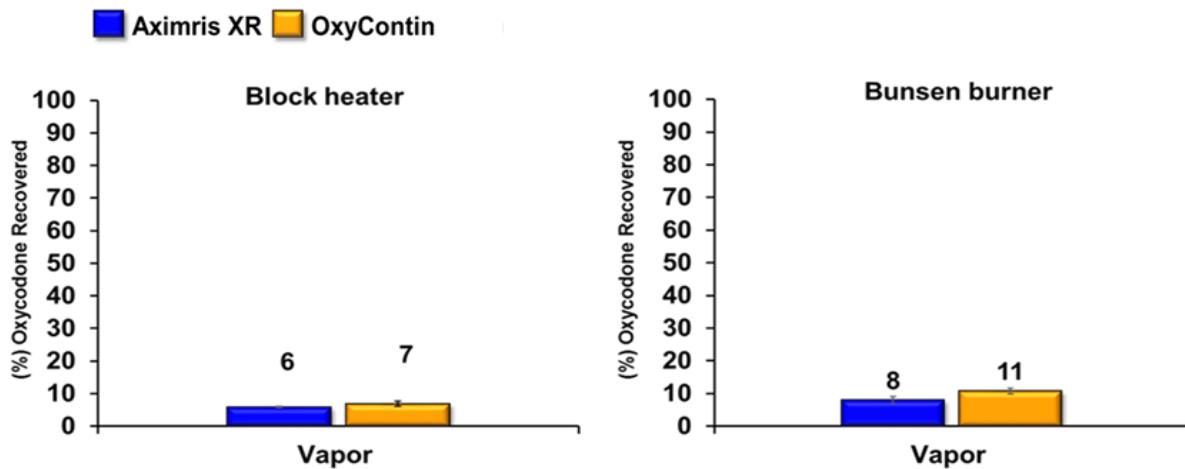
**Figure 12: Dissolution Profile of Intact Aximris XR and OxyContin Tablets Following Radiant Heat Pre-treatment With Rotation in Neutral Dissolution Media**



#### **1.6.1.7 Simulated Smoking/Vaporization Studies (Simulated Intranasal Insufflation)**

Vaporization may be attempted by abusers for the smoking route of administration. Vaporization of Aximris XR and OxyContin using optimal conditions with a block heater produced approximately 6% and 7% oxycodone in vapor (Figure 13). Applying direct heat with a Bunsen burner yielded 8% oxycodone recovery from Aximris XR and 11% from OxyContin. Neither method would be considered an efficient route of abuse for Aximris XR or OxyContin.

**Figure 13: Vaporization of Aximris XR and OxyContin Using Optimal Conditions With a Block Heater and Bunsen Burner**



## 1.6.2 Category 2 (Pharmacokinetic) and Category 3 (Clinical Abuse Potential) Studies

In response to the Agency's feedback from the CRL, Category 2 (pharmacokinetic) and Category 3 (clinical abuse potential) investigations on potential intranasal and oral routes of abuse of Aximris XR compared to OxyContin and oxycodone IR have been performed in two studies. A brief description of the findings of these studies is included below.

FDA Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry of April 2015 suggest that "if there are similar approved products with abuse-deterrent properties described in labeling, the appropriate comparator should be one of those abuse-deterrent products".

Thus, it was important to compare Aximris XR to OxyContin, especially since reductions in abuse, including reductions in oral and non-oral abuse, have been demonstrated in real-world studies for OxyContin, and shown to be consistent across various data sources and surveillance systems, some up to 5 years after the introduction of reformulated OxyContin (Coplan et al., 2016; Severtson et al., 2016; Cassidy et al., 2017; Dart et al., 2017).

### 1.6.2.1 Intranasal HAL study (Category 2 and 3)

In this randomized, double-blind, active- and placebo-controlled, 5-way crossover study, 33 non-dependent, recreational opioid users received intranasally administered active and placebo drug treatments. The five treatment arms were Aximris XR 30 mg tablets ground, OxyContin 30 mg tablets ground (an approved abuse-deterrent formulation with label for intranasal abuse deterrence), Oxycodone IR 30 mg crushed, placebo matched to Aximris XR tablet ground; and placebo to match oxycodone IR tablets crushed or OxyContin 30 mg tablets ground. A total of 33 subjects were randomized into the Treatment phase, and 30 subjects completed the planned treatments. Based on the co-primary and secondary pharmacodynamic (PD) endpoints, the abuse potential of both Aximris XR and OxyContin (an approved abuse-deterrent formulation), when ground and administered via the intranasal route are similar, and did not significantly differ from those of oxycodone IR, crushed, in non-dependent, recreational opioid users. The results also showed that there is no statistically significant difference between Aximris XR and OxyContin.

The pharmacokinetic results show that mean peak concentrations were achieved rapidly following intranasal administration of oxycodone IR, crushed, Aximris XR and OxyContin, ground. Although  $C_{max}$  and partial AUCs were significantly higher for Aximris XR, the overall exposure was similar for all the active test products. Peak and early exposure to oxycodone were significantly higher for Aximris XR, ground, compared with oxycodone IR crushed. Similarly, OxyContin ground was no better than oxycodone IR; it had same peak and early exposure to oxycodone compared to immediate release oxycodone crushed.

It is important to note that Aximris XR, unlike OxyContin and Oxycodone IR, displayed properties that could make its intranasal abuse more unpleasant to abusers. Aximris was rated to be more difficult to insufflate compared with the other active treatments (ground OxyContin and crushed oxycodone IR). Aximris XR, ground, had more local irritating effects and was rated to be more difficult to insufflate compared to OxyContin and Oxycodone IR. Aximris XR, ground, was also associated with a higher incidence of Treatment-emergent Adverse Events (TEAEs) of nausea and dizziness compared with oxycodone IR, crushed. For detailed descriptive statistics of

ease of snorting VAS and subject-rated assessment of intranasal irritation (SRAII) see [sections 6.1.3](#) and [6.1.4](#) respectively. These properties, combined, will make abuse of Aximris XR difficult and unattractive to potential abusers.

The main PD results indicate that Drug Liking E<sub>max</sub> and Take Drug Again E<sub>max</sub> were similar for both Aximris XR and OxyContin, ground, while both products did not significantly differ from oxycodone IR, crushed. Nonetheless, Aximris XR had numerically better Take Drug Again VAS E<sub>max</sub>.

Furthermore, mean and median Drug Liking Visual Analog Scale (VAS) E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> values were similar for Aximris XR, ground, OxyContin, ground and oxycodone IR, crushed ([Table 1](#)).

It is also important to note that both Aximris XR and OxyContin were ground and manipulated using a comminution method (advanced kitchen appliance) that was selected to give the worst case scenario based on Category 1 studies. Thus, it can be said that the results observed for Aximris XR and OxyContin could be due to the method of comminution (grinding) employed in this study. The advanced kitchen appliance was necessary as a comminution method for OxyContin and Aximris XR because one of the tenets of the FDA Guidance is to test the abuse-deterrent properties of a formulation to failure to understand the limits of the physical and chemical barriers.

**Table 1: Selected Descriptive Statistics of Drug Liking VAS Emax and Take Drug Again VAS Emax (Completers Population) – Intranasal Study**

Statistic	AXIMRIS XR 30 mg, Ground (N=30)	OxyContin 30 mg, Ground (N=30)	Oxycodone IR 30 mg, Crushed (N=30)	Placebo (Aximris XR) (N=30)	Placebo (Oxycodone IR/Aximris XR) (N=30)
<b>Drug Liking VAS</b>					
Mean (SD)	87 (13)	86 (14)	86	51 (4)	53 (7)
Median	88.0	89.0	87.5	50.0	50.0
Range	50 – 100	50 – 100	50 - 100	50 – 69	50 – 81
<b>Take Drug Again VAS</b>					
Mean (SD)	78 (24)	81 (24)	85 (18)	49 (8)	51 (6)
Median	89.5	90.5	92	50.0	50.0
Range	0 – 100	1 – 100	41 - 100	8 – 63	50 – 83

E<sub>max</sub>=maximum effect; ER=extended-release; IR=immediate-release; range=minimum – maximum; SD=standard deviation; VAS=visual analog scale

### 1.6.2.2 Oral HAL study (Category 2 and 3)

This study was a randomized, double-blind, placebo- and active-controlled crossover study to evaluate the oral abuse potential and pharmacokinetics of manipulated Aximris XR compared with Aximris XR (intact), manipulated OxyContin tablets, manipulated oxycodone IR tablets, and placebo in non-dependent recreational opioid users.

FDA Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry of April 2015 suggest that “if there are similar approved products with abuse-deterrent properties described in

labeling, the appropriate comparator should be one of those abuse-deterrent products”. Thus, it was important to compare Aximris XR to OxyContin, for which reductions in abuse, including reductions in oral and non-oral abuse, have been demonstrated in real-world studies, and shown to be consistent across various data sources and surveillance systems, including some up to 5 years after the introduction of reformulated OxyContin (Coplan et al., 2016; Severtson et al., 2016; Cassidy et al., 2017; Dart et al., 2017).

Based on the co-primary and secondary PD endpoints, the abuse potential of both Aximris XR and OxyContin, when milled and administered via oral solution, are not statistically different and both did not significantly differ from those of oxycodone IR in non-dependent, recreational opioid users. However, Aximris XR caused local irritating effects (**Table 2**).

Both Aximris XR and OxyContin were milled and manipulated using a comminution method that was selected to give the worst-case scenario based on Category 1 studies.

**Table 2: Selected Descriptive Statistics of Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> (Completer Population) – Oral Study**

Statistic	AXIMRIS XR 40 mg, Milled in Solution (N=40)	OxyContin 40 mg, Milled in Solution (N=40)	Oxycodone IR 40 mg, Crushed in Solution (N=40)	AXIMRIS XR 40 mg, Intact (N=40)	Placebo (N=40)
<b>Drug Liking VAS</b>					
Mean (SD)	90.4 (9.79)	89.8 (10.11)	89.7 (10.71)	73.5 (17.05)	52.5 (5.80)
Median	91.0	93.0	93.0	75.0	50.0
Range	60 – 100	68 - 100	65 – 100	50 – 100	50 – 72
<b>Take Drug Again VAS</b>					
Mean (SD)	85.8 (18.71)	83.0 (18.55)	81.0 (22.71)	69.7 (23.47)	51.9 (8.42)
Median	92.0	88.5	88.0	67.5	50.0
Range	24 – 100	22 - 100	22 – 100	0 – 100	41 – 100

E<sub>max</sub>=maximum effect; IR=immediate-release; range=minimum – maximum; SD=standard deviation; VAS=visual analog scale

Results from these human abuse liability studies suggest that, while Aximris XR has abuse potential via the intranasal and oral routes similar to that of OxyContin, abusers of Aximris XR may experience difficulty in snorting and local irritation that could act as an additional level of abuse deterrence for Aximris XR.

### 1.6.3 Toxicological Risk Assessments

To further assess safety of the product if abused and based on FDA feedback in the CRL and Type A Post Action meeting, several toxicological risk assessments were performed on the chemical components of Aximris XR following manipulation for abuse. These risk assessments were performed to assess the safety of Aximris XR excipients (or degradation products thereof) if abused by the oral, intranasal, vaping, or intravenous routes. These assessments are summarized below.

### ***1.6.3.1 Excipient exposure risk assessment of the oral, intranasal, and vaping routes of abuse***

In an assessment evaluating exposure risk of individual excipients if Aximris XR is abused by the oral, intranasal, and vaping routes, it was determined that taking Aximris XR orally at the maximum tolerable daily dose carries a low risk of toxicity. Insufficient information was available to determine the risk of excipient exposure if Aximris XR is abused intranasally or by vaping.

### ***1.6.3.2 Excipient exposure risk assessment of the intravenous route of abuse***

In this evaluation, the exposure risk of individual excipients if Aximris XR is abused intravenously was assessed. It was determined that manipulating a single 80 mg Aximris XR tablet for injection (once or repeatedly) carries a low risk of toxicity.

Further evaluations were also carried out to look at the potential safety risks of IV Injection of Aximris XR extracts which contain oxycodone and various excipients through general toxicology studies. The major findings from these studies are given below.

#### ***1.6.3.2.1 In Vitro hemocompatibility, plasma compatibility and flocculation studies***

The hemocompatibility of syringed solutions extracted from pretreated Aximris XR Tablets, which contain oxycodone and various excipients, using 0.9% NaCl solution (Test Item 1) and Tap Water (Test Item 2) were investigated with the following results:

- Test Items are compatible with human blood
- Test Items are non-hemolytic in human blood
- Test Items do not cause flocculation
- Aximris XR extracts are hemocompatible

#### ***1.6.3.2.2 In Vivo repeat-dose IV toxicity study in Rabbit***

In vivo assessment of toxicity of syringed solutions extracted from pretreated ground Aximris XR, which contain oxycodone and various excipients, using 10 mL tap water (G2) and 10 mL of 0.9% normal saline (G3) were conducted to evaluate the potential for local effects, hematological effects, thrombotic microangiopathy, overt toxicity, and tissue damage. Normal saline alone (G1) was used as vehicle control.

- There was no mortality and/or morbidity in the study, and all rabbits survived until the end of experimental period.
- Based on the gross and histopathology evaluation, there was no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retinal damage, or acute kidney injury
- Mild, procedure-related injection site reactions were observed in all the groups.

- No treatment related changes were noticed in the coagulation parameters (Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) for all groups, except for slight but significant ( $p<0.05$ ) increase in APTT seen in G3 group.
- In terms of microscopic findings, mononuclear cell (MNC)/polymorphonuclear leukocyte (PMN) infiltration was observed for liver, kidney, heart, and injection sites with similar severity found across the groups including control.

Furthermore, based on overall observations and under the circumstances of the study, the Test Items, when administered as slow intravenous bolus injection in marginal ear vein of New Zealand white rabbits for 3 consecutive days, were well tolerated and did not produce any local (injection site) or systemic effects in any organ/system.

Overall, the minimal to slight changes observed in these animals are not considered to be adverse in the context of the study findings.

#### **1.6.3.3 Aluminum exposure risk assessment**

In an assessment of the potential risk of Aximris XR to cause toxicity due to systemic aluminum exposure if abused via the oral, intranasal, and intravenous routes, it was determined that the potential toxicity risk is low.

### **1.7 Risk/Benefit Assessment**

As described in the June 2019 FDA Draft Guidance for Industry *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework* (CDER, 2019), FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, FDA also considers the broader public health effect. This involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others. As described below, the efficacy and safety evaluations of Aximris XR provide evidence that supports a positive benefit/risk ratio for the product.

#### **1.7.1 Risks**

As Aximris XR contains oxycodone, a Schedule II controlled substance, it has a high potential for abuse and is subject to misuse, addiction, and criminal diversion. Abuse of Aximris XR poses a risk of overdose and death. This risk is increased with concurrent use of Aximris XR with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved Aximris XR enhances drug release and increases the risk of overdose and death. Aximris XR can produce unpleasant effects, such as irritation of the nasal mucosa, if ground and snorted.

As with other oxycodone-containing controlled-release products, with parenteral abuse, the inactive ingredients in Aximris XR can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse

have been reported. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

### 1.7.2 Benefits

Aximris XR has demonstrated bioequivalence to OxyContin. Therefore, Aximris XR can be beneficial to patients, in that it represents an alternate ADF of controlled-release oxycodone for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

While many controlled-release opioid formulations, such as OxyContin, have deterred opioid abuse to a certain extent (Butler et al., 2013; Havens et al., 2014), abusers can still defeat the ADF properties (Cicero and Ellis, 2015). In the case of OxyContin, despite its reformulation with abuse-deterrent properties, epidemiologic and survey data show that some abusers are able to overcome its gelling features to enable extraction and injection of oxycodone. It is recognized that no ADF is abuse-proof, but until there are adequate alternatives to opioid-containing products for managing pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, there is a need for incremental improvement and innovation in abuse-deterrent opioid formulations.

An important benefit of Aximris XR is that it represents an important improvement in abuse-deterrent technology for the IV route of abuse for ER oxycodone products. This is demonstrated by the following results from Intellipharmaceutics' Category 1, 2, and 3 abuse-deterrent program for Aximris XR:

- When Aximris XR tablet is crushed or ground into smaller particles, its surface area is increased, lending it the ability to rapidly form a highly viscous semisolid material on contact with moisture.
- Aximris XR and OxyContin can both resist extraction and syringeability/injectability using simple and common methods to prepare an opioid tablet formulation for injection using intact or manipulated tablets.
- “Recipes” or Advanced methods to overcome the gelling feature of ADFs for IV abuse or otherwise, found on drug abuser websites, were able to defeat the abuse-deterrent properties of OxyContin. These methods could result in relatively high yields of injectable oxycodone. In contrast, Aximris XR showed more resistance to being prepared for injection under the conditions that defeated OxyContin, representing a significant improvement over OxyContin.
- Aximris XR shows similar resistance to OxyContin against chemical extraction in large volumes of various solvents an abuser might use for oral abuse.
- Aximris XR did not dose dump in the presence of alcohol.
- Aximris XR and OxyContin have similar release profiles after physical manipulation, suggesting that there is not an increased risk of Aximris XR for manipulated routes of abuse compared to OxyContin.
- Aximris XR and OxyContin were not efficiently smoked or vaporized.

- When ground and administered via the intranasal route, Aximris XR had more local irritating effects and was rated to be more difficult to insufflate compared with the other active treatments (ground OxyContin and crushed oxycodone IR).
- When milled and administered via oral solution, Aximris XR caused local irritating effects.
- Toxicological risk assessments of excipient exposure from Aximris XR abused via the oral, intranasal, vaping, or intravenous routes, determined that taking Aximris XR orally at the maximum tolerable daily dose or manipulating a single 80 mg tablet for injection (once or repeatedly) carries a low risk of toxicity. Insufficient information was available to determine the risk of excipient exposure if Aximris XR is abused intranasally or by vaping.
- Based on hemocompatibility studies, Aximris XR is compatible with human blood, as it is non-hemolytic and does not cause flocculation.
- Based on in vivo rabbit toxicology assessments, syringeable material from Aximris XR when administered as slow intravenous bolus injection in marginal ear vein of New Zealand white rabbits for 3 consecutive days was well tolerated and did not produce any local (injection site) or systemic effects in any organ/system. Furthermore, the syringeable materials were not associated with signs or symptoms of thrombotic microangiopathy, overt toxicity, or tissue damage that was previously reported with a particular type of high molecular weight (HMW) polyethylene oxide that is not present in Aximris XR. However, it is important to emphasize that it is not safe to administer extract from any solid dosage form due, to the risk for overdose and the inclusion of excipients to facilitate the intended oral route of administration, which are not intended for IV use.
- An additional toxicological risk assessment determined that the potential risk of Aximris XR to cause toxicity due to systemic aluminum exposure is low if abused by the oral, inhalation, or intravenous routes.

## 1.8 Abuse-deterrence Labeling Claims

At this time, Intellipharmaceutics is requesting abuse-deterrent labeling only for the IV route of abuse. However, based on results from the Sponsor's Category 2 and 3 studies on oral and intranasal abuse, Aximris XR may also present potential abuse deterrence for the oral and intranasal routes. This is due to the incidence of TEAEs, such as "nasal congestion" and "throat irritation," that are observed when the product (or its vehicle control) is administered intranasally, as well as TEAEs such as "pruritus" and "headache" when the product is ground and administered in oral solution. Furthermore, Aximris XR was rated more difficult to snort or insufflate.

## 1.9 Conclusions

### Clinical Pharmacology

Two PK studies for Aximris XR have demonstrated that Aximris XR is bioequivalent to OxyContin under fasted and fed conditions, establishing a scientific bridge to FDA's prior findings of safety and efficacy for OxyContin. Another PK study demonstrated that the proposed dosage strengths of Aximris XR are dose proportional, providing support for the safety and efficacy of all dosage strengths. Furthermore, a clinical PK study demonstrated that there is no significant effect of food on the bioavailability of oxycodone with Aximris XR; therefore, Aximris XR may be taken without regard to meals. Additionally, it was observed from the clinical PK study that the  $T_{max}$  values under fed conditions for Aximris XR and OxyContin are similar (see **Table 4**). While these studies were all performed on Intellipharmaceutics' original Aximris XR formulation (containing blue dye), because the removal of the blue dye constitutes a Level 1 change as per the SUPAC-MR guidelines (CDER, 1997), the results of these studies are valid for the current Aximris XR formulation (no blue dye). Therefore, Aximris XR can be expected to provide effective analgesia for the intended patient population, for whom alternative non-opioid therapies are inadequate.

### Abuse-deterrent Properties

The current abuse-deterrent program for Aximris XR includes a comprehensive set of Category 1 (*in vitro*) abuse-deterrence studies, as well as Category 2 (pharmacokinetic) and Category 3 (clinical abuse potential) studies. Additionally, in response to Agency feedback, risk assessments were performed to assess the exposure of Aximris XR excipients (or degradation products thereof) if the product is manipulated for abuse via the oral, intranasal, vaping, or intravenous routes.

#### Category 1 (*in vitro*) Studies

The Category 1 *in vitro* abuse-deterrent studies for Aximris XR demonstrated comparable features with OxyContin, associated with an expectation to deter IV abuse. While IV abuse of OxyContin has decreased since its reformulation, epidemiologic data demonstrate that the reformulated OxyContin is still abused via the IV route. Studies evaluating Aximris XR and OxyContin using usual volumes and methods chosen by abusers used to prepare OxyContin for injection indicate that Aximris XR has superior abuse-deterrent properties for the IV route. Specific internet recipes (Butler et al., 2013; Havens et al., 2014; Cicero and Ellis, 2015) and advanced methods used to overcome gelling properties of ADFs cited on drug abuser websites yielded appreciable amounts of injectable oxycodone from OxyContin, but little to none from Aximris XR.

In addition, Category 1 studies demonstrated that Aximris XR has similar resistance to extraction in large volumes of ingestible and non-ingestible solvents compared to OxyContin and does not dose dump in alcohol. Simulated oral ingestion studies confirm that manipulation of Aximris XR by splitting tablets into 2, 4, 8 and 16 pieces did not result in an immediate release of oxycodone (<30% of oxycodone released in 30 minutes). Furthermore, the dissolution profile from simulated oral ingestion study shows that particle size reduction with Aximris XR does not increase the rate of oxycodone release relative to OxyContin.

## Category 2 (Pharmacokinetic) and Category 3 (Clinical Abuse Potential) Studies

The Category 2 (pharmacokinetic) and Category 3 (clinical abuse potential) studies demonstrated that, when ground and administered via the intranasal route, or milled and administered vial oral solution, Aximris XR and OxyContin (an approved abuse-deterrent formulation) have similar abuse potential. The abuse potential for both products did not significantly differ from that of manipulated oxycodone IR, a non-abuse-deterrent formulation, in non-dependent, recreational opioid users. However, when manipulated for intranasal abuse, Aximris XR had more local irritating effects and was rated to be more difficult to insufflate compared with the other active treatments (crushed oxycodone IR and ground OxyContin). Additionally, when milled and administered via oral solution, Aximris XR also caused local irritating effects. Taken together, the results from these human abuse liability studies suggest that while Aximris XR has abuse potential via the intranasal and oral routes similar to that of OxyContin, abusers of Aximris XR will experience local irritation and difficulty snorting that would act as an additional level of abuse deterrence for the product.

## Toxicological Risk Assessments

Toxicological risk assessments of the excipients of Aximris XR when manipulated for oral, intranasal, vaping, or intravenous routes determined that taking Aximris XR orally at the maximum tolerable daily dose (MTDD) or manipulating a single 80 mg tablet for injection (once or repeatedly) carries a low risk of toxicity. Insufficient information was available to determine the risk of excipient exposure if Aximris XR is abused intranasally or by vaping. Additionally, the potential risk of Aximris XR to cause toxicity due to systemic aluminum exposure is low if abused by the oral, inhalation, or intravenous routes.

## Overall Conclusion

Overall, these results demonstrate that Aximris XR would be an effective ER opioid analgesic with important improvements in abuse deterrence for the IV route, which is the most dangerous route of opioid abuse. The intrinsic properties of Aximris XR may make its abuse by the intranasal route difficult and unpleasant.

## 2 PUBLIC HEALTH NEED FOR ABUSE-DETERRENT ER OPIOID ANALGESICS

### Summary

- IV abuse of opioid products is a major public health concern. According to the CDC, in 2016, IV abuse was associated with 9% of new HIV diagnoses and 13% of all new AIDS diagnoses in the US.
- Injecting drug use puts the abuser at risk for blood-borne infections such as Hepatitis C and endocarditis as well as blood clots and other problems.
- The reduction of IV abuse is one of the primary goals of abuse-deterrent opioid formulations because it is the most dangerous. Data from the RADARS Poison Center Program suggest that the relative risk of a death or major adverse effect (e.g., overdose) is 2.6 times greater for the IV route than the oral route.
- OxyContin was reformulated in 2010 with abuse-deterrent properties, in part, to make abuse via injection more difficult. Epidemiologic data indicate that IV abuse of OxyContin decreased following its reformulation, but there are continued reports of abuse via the IV route. For example, in 2016 approximately 15% of individuals entering substance abuse treatment who recently abused ER oxycodone reported abuse via the IV route.
- “Recipes” on drug abuse websites provide information on how to overcome the abuse-deterrent gelling features of OxyContin in order to successfully prepare it for insufflation or injection. An alternative product that can be more resistant to these “recipes” is desirable.
- FDA has anticipated “iterative improvements in products with abuse-deterrent properties”. Incremental improvement in abuse deterrence, particularly for the dangerous IV route, is a worthwhile public health goal.

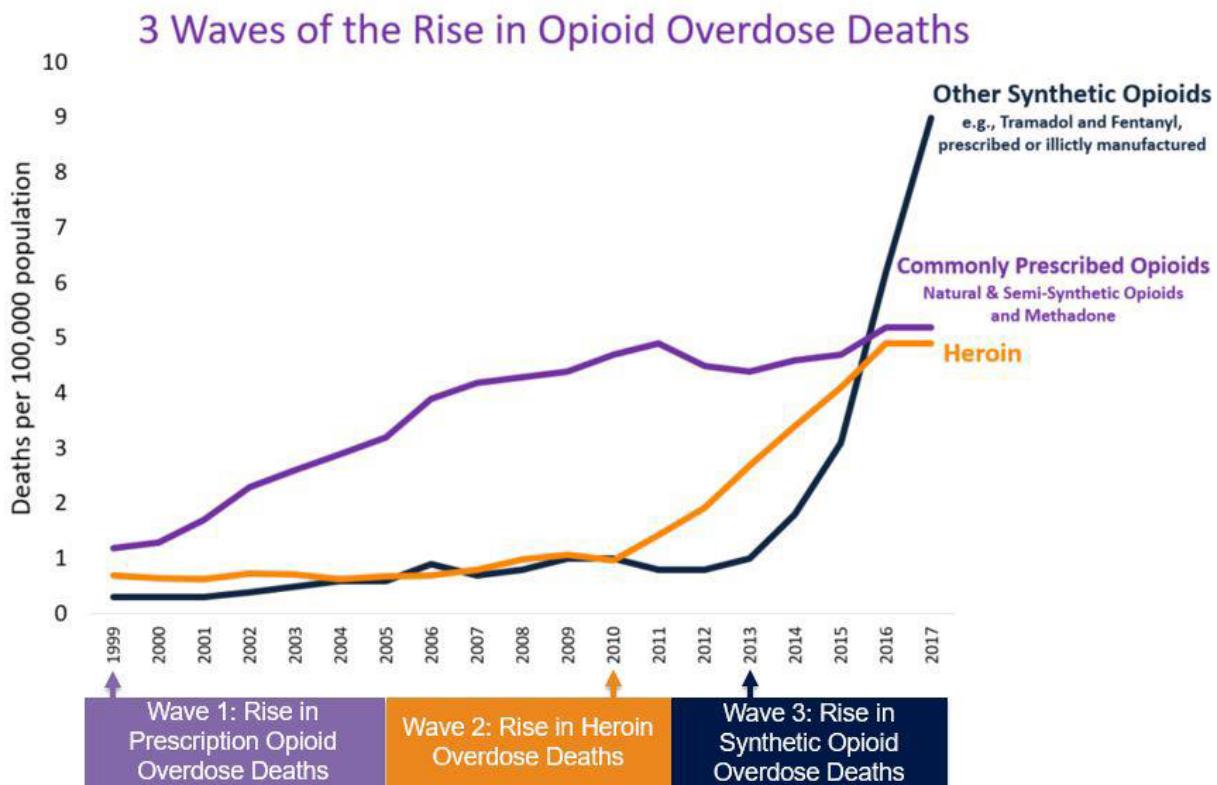
### 2.1 Background on Opioid Abuse

Immediate-release (IR) and ER opioid products remain an important treatment option for acute and chronic pain. However, both IR and ER opioid products are associated with high abuse potential and are subject to abuse, misuse, and diversion.

The total number of deaths in the US attributable to opioids continues to increase. Between 2001 and 2016, the number of opioid-related deaths in the US increased by 345%, from 9,489 to 42,245 deaths (33.3 to 130.7 deaths per million population) (Gomes et al., 2018). In 2016 alone, 66.4% (42,249 of 63,632) of overdose-related deaths in the US involved an opioid (Seth et al., 2018). The numbers increased further in 2017, with opioids accounting for 67.8% (47,600 of 70,237) of overdose-related deaths (Scholl et al., 2018). This continuing rise in deaths is worsened by increases in overdose deaths from heroin and synthetic opioids, such as fentanyl ([Figure 14](#)). The number of opioid-related deaths attributable to natural and semi-synthetic

opioids such as oxycodone, hydrocodone, and oxymorphone appears to have plateaued since 2011; however, the frequency remains at historically high levels.

**Figure 14: Number of Deaths in the US Attributable to Opioids: 3 Distinct Waves**



Source: National Vital Statistics System Mortality File (CDC/NCHS, 2018)

## 2.2 Epidemiology of ER Oxycodone Abuse via the IV Route

Some drug abusers prefer the IV route of administration for opioid products because of the enhanced potency and rapidity of onset of effects compared to oral or intranasal use. Preventing injection of prescription solid oral dosage forms of opioids has been one of the primary public health goals of ADFs, because IV use is associated with the most severe health consequences.

In terms of direct opioid-related effects (e.g., respiratory depression), a single instance of IV opioid abuse is associated with 2.6 times greater risk for death or a major, life-threatening adverse effect, such as an overdose, compared to a single instance of oral abuse (Researched Abuse, Diversion and Addiction-Related Surveillance [RADARS®] Poison Center Program, Data on File).

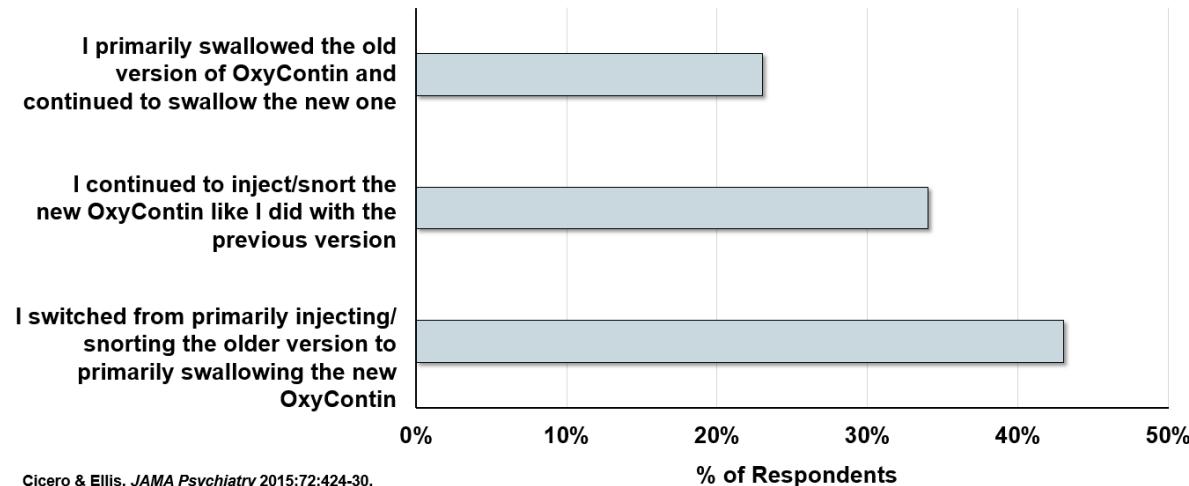
In addition to the risks of opioid abuse, like respiratory depression and overdose, the IV route carries additional risks due to the hazards of injection. According to the CDC, 9% of new HIV diagnoses and 13% of AIDS diagnoses in 2016 were attributable to injection drug use (CDC,

2016). Furthermore, IV drug abuse is associated with increased risks for acquisition of Hepatitis C (Nelson et al., 2011; Bruneau et al., 2012; Suryaprasad et al., 2014), infective endocarditis (Wurcel et al., 2016; Weir et al., 2019), and thrombosis (Pieper et al., 2007).

In an effort to reduce abuse of OxyContin, including IV abuse, the product was reformulated in 2010 with properties intended to deter abuse, including crush-resistance and gelling when exposed to an aqueous environment. The impact of the OxyContin reformulation in reducing abuse, misuse, and diversion has been well documented across various epidemiologic data sources (Havens et al., 2014; Coplan et al., 2016). Additionally, evaluations of internet forums for drug user reactions to OxyContin's reformulation indicated reduction in discussions and drop in the proportion of reported abuse of reformulated OxyContin via recipes, particularly by injecting or snorting routes (McNaughton et al., 2014).

The effect of OxyContin's reformulation on changes in its abuse patterns has been evaluated in the Survey of Key Informants' Patients (SKIP) program, which is part of the RADARS system. A subset of these patients were interviewed to evaluate their changes in abuse pattern (Cicero and Ellis, 2015). Individuals included in the survey had a diagnosis of opioid use disorder and entered into substance abuse treatment at one of the 150 participating drug treatment programs in 48 states. Among those individuals who reported experience abusing both the pre-abuse-deterrent and the reformulated OxyContin, 34% reported successfully defeating the abuse-deterrent properties and continuing injection or snorting (**Figure 15**).

**Figure 15: Change in OxyContin Abuse Patterns Following Reformulation with Abuse-Deterrent Properties**

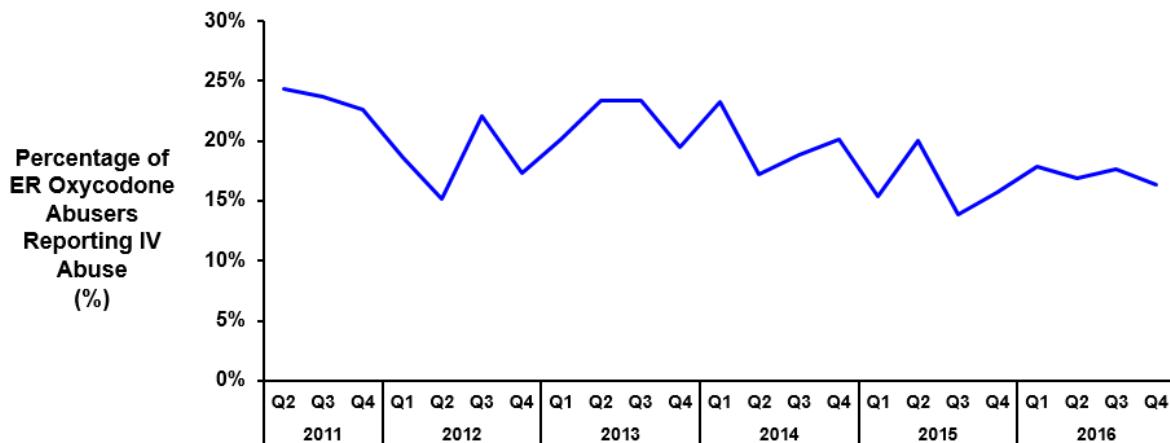


Source: (Cicero and Ellis, 2015)

While OxyContin is resistant to many common methods for preparation for IV abuse, “recipes” for overcoming the gelling features of the formulation can be readily found on drug abuse websites (e.g., bluelight.org). The residual IV abuse of abuse-deterrent ER oxycodone is also evident in data from the RADARS Treatment Center Program. This program interviews

individuals being evaluated for substance abuse treatment regarding their drugs of abuse and routes of abuse for each drug. Among those who reported abuse of OxyContin in the last 30 days, over 15% reported abuse via the IV route across the four quarters of data in 2016 ([Figure 16](#)).

**Figure 16: Percentage of Individuals Entering Substance Abuse Treatment in RADARS Treatment Center Program Reporting Abuse of ER Oxycodone Abusing via IV Route**



Source: (RADARS, 2016)

### 2.3 Improvement in IV Abuse Deterrence

Given the continued abuse of OxyContin via the IV route despite its reformulation with abuse-deterrent properties, there is room for incremental improvement in technology to deter abuse via this route. In fact, the 2015 FDA Guidance for Industry on Evaluation and Labeling of Abuse-deterrent Opioids (CDER, 2015) acknowledges that “FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties.” Aximris XR was developed to address the public health need for improvement in abuse-deterrent technology, particularly for the IV route, which is the most dangerous route of abuse.

### 3 AXIMRIS XR DEVELOPMENT AND FORMULATION

#### Summary

- Aximris XR is a single-entity, extended-release oxycodone HCl tablet formulation with a proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- Aximris XR was developed in accordance with the 505(b)(2) regulatory pathway where approval relies on some information from an approved product, the listed drug (LD). The LD for Aximris XR is OxyContin, an approved abuse-deterrent ER oxycodone product.
- A waiver for Phase III studies was granted by FDA based on demonstrated bioequivalence to OxyContin. Since Aximris XR is bioequivalent to the LD, OxyContin, an adequate and well-controlled efficacy study is not required to support approval. Bioequivalence studies were conducted on the lowest and highest strengths according to FDA guidance. Although these studies were conducted on the original Aximris XR formulation (containing blue dye), the Agency agreed that removal of the blue dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997), and therefore, the results of any studies conducted with the original formulation are still valid.
- The  $T_{max}$  values for Aximris XR and OxyContin under fed conditions are similar.
- Intellipharmaceutics has conducted food effect and dose proportionality studies to further characterize Aximris XR. Aximris XR has no food effect and it is dosage strength proportional.
- Aximris XR is formulated with physical and chemical barriers to deter various forms of tampering commonly used by abusers.
- Intellipharmaceutics has performed a comprehensive set of Category 1 in vitro physical manipulation and chemical extraction studies to evaluate the abuse-deterrent properties of Aximris XR. These studies were designed in consultation with FDA as well as experts in the evaluation and development of ADFs.
- Intellipharmaceutics has performed Category 2 and Category 3 studies to assess the pharmacokinetics and clinical abuse potential of Aximris XR if manipulated for oral or intranasal abuse. These studies were designed in consultation with FDA to address deficiencies in the original 2016 Aximris XR NDA.
- As recommended by FDA, Intellipharmaceutics has conducted toxicological risk assessments to assess the exposure of Aximris XR excipients (or degradation products thereof) if the product is manipulated for abuse via the oral, intranasal, vaping, or intravenous routes.
- To further investigate the potential toxicity of the syringeable material from ground Aximris XR, Intellipharmaceutics has measured the hemocompatibility of manipulated Aximris XR using human plasma, serum, and whole blood and conducted an in vivo rabbit toxicology study.
- At this time, Intellipharmaceutics is requesting abuse-deterrent labeling for the IV route based on Category 1 findings compared to OxyContin.

### 3.1 Formulation

Aximris XR is an ER, single-entity, oxycodone HCl tablet with a proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The proposed indication is for adults and opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent, which is the same as the LD, OxyContin.

Aximris XR has seven proposed dosage strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. These are the same currently marketed dosage strengths as OxyContin. The excipients and structure of the tablet formulation are the same for all Intellipharmaceutics strengths with the exception of the coloring agents on the outer layer of the tablets.

### 3.2 Aximris XR Abuse-Deterrent Technology

Aximris XR is formulated to offer resistance to chemical extraction in a variety of solvents, resistance to dose dumping when co-ingested with alcohol, and properties to form a viscous material and coagulate when subjected to an aqueous environment to deter syringing, injecting, and snorting. This viscous coagulant is made of polyethylene oxide (PEO), an inactive ingredient in Aximris XR, which swells upon contact with liquid. Additionally, Aximris XR contain known respiratory irritants in humans such as sodium lauryl sulfate (SLS), magnesium stearate, Opadry II White, stearic acid, and talc. Notably, in Intellipharmaceutics' current clinical program evaluating human abuse potential of Aximris XR, various forms of local irritation were observed when the product was manipulated for both intranasal and oral abuse.

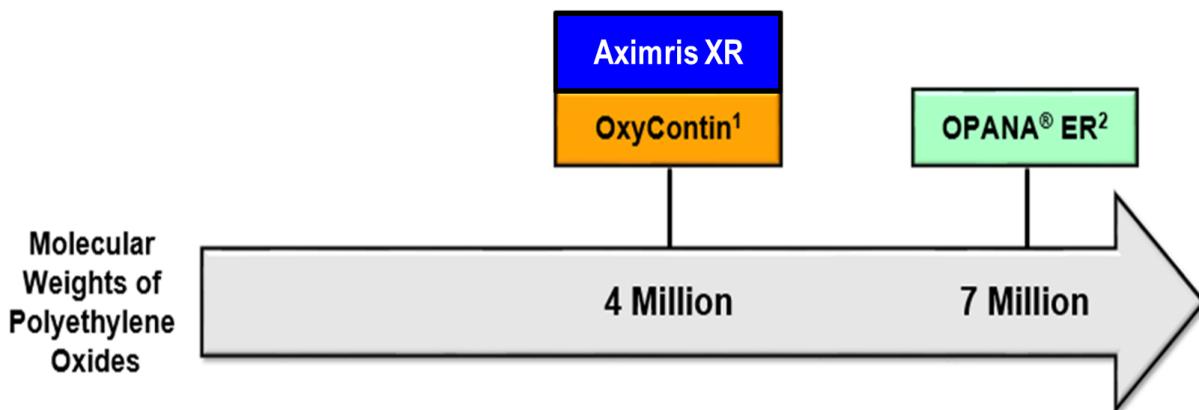
### 3.3 Safety Risks of IV Abuse With Polyethylene Oxide-containing Products

In March 2017, joint Advisory Committees reviewed epidemiologic and pre-clinical data suggesting that the high molecular weight polyethylene oxide (HMW PEO) in Opana<sup>®</sup> ER led to cases of thrombotic thrombocytopenic purpura (TTP)-like illness (FDA, 2017; Hunt et al., 2017). Pre-clinical data suggest that the incidence of TTP-like illness observed with Opana ER was due to its relatively high molecular weight (~7 million) as compared with other abuse-deterrent products like OxyContin, with a PEO with a molecular weight of approximately 4 million ([Figure 17](#)).

Aximris XR uses PEO with the same molecular weight as that of OxyContin, so it is not anticipated that IV abuse of Aximris XR would be associated with additional risk for TTP-like illness compared to OxyContin. This potential safety risk is further mitigated by the fact that “recipes” to overcome the gelling features of OxyContin for injection are less successful with Aximris XR. Additionally, hemocompatibility studies and in vivo rabbit toxicity studies on manipulated Aximris XR have shown that manipulated Aximris XR is non-hemolytic. Furthermore, tests show that, when administered as slow intravenous bolus injection in marginal ear vein of New Zealand white rabbits for 3 consecutive days, it was well tolerated and did not

produce any local (injection site) or systemic effects in any organ/system that could be associated with signs or symptoms of thrombotic microangiopathy, overt toxicity, or tissue damage.

**Figure 17: Molecular Weights of Polyethylene Oxides in Aximris XR, OxyContin, and Opana ER**



1. Purdue -FDA Advisory Committee on Reformulated OxyContin, Public session September 24, 2009
2. Hunt et al. *Blood* 2017;129:896-905.

Source: (FDA, 2017; Hunt et al., 2017)

### 3.4 Overview of Aximris XR Development Program

Intellipharmaceutics developed Aximris XR using the 505(b)(2) regulatory pathway with OxyContin as the LD. In the original NDA for Aximris XR (submitted in November 2016), the product was formulated with blue dye (FD&C Blue No. 1 Aluminum Lake) to impart a blue color to the drug product. In September 2017, Intellipharmaceutics received a complete response letter (CRL). In February 2018, Intellipharmaceutics engaged with the Agency in a Type A Post-action meeting to discuss and gain agreement on Intellipharmaceutics plans to address deficiencies in the NDA. In February 2019, Intellipharmaceutics submitted an amendment to the NDA, addressing deficiencies identified in the CRL based on advice from the Agency. It is important to note that, in response to FDA's comments in the CRL, Intellipharmaceutics changed the Aximris XR formulation to remove FD&C Blue No. 1 Aluminum Lake prior to submission of the February 2019 NDA amendment. The function of this excipient was solely to impart color; the material did not have any release controlling property and did not impact the quality attributes of the product. There was no change in the manufacturing process, critical material attributes, or the controls of the manufacturing process when this excipient was removed. In the Type A Post-action meeting, the Agency agreed that the removal of the FD&C Blue No. 1 Aluminum Lake dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997). Therefore, in the current Aximris XR NDA, Intellipharmaceutics is relying upon data from studies (including PK bioequivalence studies and Category 1, 2, and 3 abuse deterrence studies) conducted with the product both pre-change (containing blue dye) and post-change (blue dye removed). Importantly, Intellipharmaceutics clinical pharmacology studies demonstrated bioequivalence to OxyContin, as well as Aximris XR dose proportionality, and the waiver

granted for Phase III studies by FDA for the original NDA still applies to the current formulation (as the formulation change was a Level 1 change).

The proposed IV abuse-deterrent labeling is supported by a series of Category 1 in vitro studies. As requested by the Agency in the CRL, the human abuse potential of Aximris XR was further evaluated in Category 2 (PK) and 3 (clinical abuse potential) studies, and the safety of excipients if Aximris XR is abused was studied in several toxicological risk assessments. FDA and experts in abuse-deterrent products provided input and feedback into the design of the development program and the study protocols.

### 3.5 Clinical Pharmacokinetic Studies and Effect of Food

All of the clinical pharmacology studies conducted for Aximris XR used the original Aximris XR formulation (containing blue dye). As the Agency agreed in Intellipharmaceutics Type A Post-action meeting that the removal of the FD&C Blue No. 1 Aluminum Lake dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997), the results of these studies are valid for the current Aximris XR formulation (blue dye removed).

Randomized, open-label, crossover studies in healthy volunteers were conducted to evaluate the relative bioavailability of Aximris XR to OxyContin at both 10 mg and 80 mg dosage strengths, the dose proportionality of Aximris XR at all proposed dosage strengths, and the effect of food on bioavailability of Aximris XR ([Table 3](#)). All studies were conducted under naltrexone blockade.

**Table 3: Overview of Clinical Pharmacokinetic Studies in Healthy Volunteers**

Study	Purpose	Subjects Analyzed	Treatment Arms (Food Condition)
1878	Fasted bioequivalence study at 10 mg dose	31	10 mg Aximris XR (fasted) 10 mg OxyContin (fasted)
1879	Fed bioequivalence study at 10 mg dose	29	10 mg Aximris XR (fed) 10 mg OxyContin (fed)
656-15	Fasted bioequivalence study at 80 mg dose	30	80 mg Aximris XR (fasted) 80 mg OxyContin (fasted)
655-15	Fed bioequivalence study at 80 mg dose	29	80 mg Aximris XR (fed) 80 mg OxyContin (fed)
80-184	Steady state study at 80 mg dose (6 consecutive doses every 12 hours)	24	80 mg Aximris XR 80 mg OxyContin
80-185	Dose proportionality study	22	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg Aximris XR (fasted)
80-186	Food effect study at 80 mg dose	25	80 mg Aximris XR (fasted and fed)

### 3.6 Category 1 Studies

In consultation with the FDA and experts in the field of abuse deterrence, Intellipharmaceutics conducted a comprehensive set of Category 1 in vitro physical manipulation and extraction studies as defined by the 2015 FDA Guidance on the Evaluation and Labeling of Abuse-Deterrent Opioids. These studies included evaluation of particle size reduction, syringeability/injectability, small volume extraction (including multiple tablet extraction), large volume extraction, alcohol dose dumping, complex extraction and isolation of oxycodone base, and simulated smoking/vaporization.

### 3.7 Category 2 and 3 Studies

Category 2 (pharmacokinetic) and Category 3 (clinical abuse potential) investigations on potential intranasal and oral routes of abuse of Aximris XR have been performed in two studies. The design of these studies is in accordance with the 2015 FDA Guidance on abuse deterrent opioids (CDER, 2015) and was further agreed upon with the Agency in the February 2018 Type A Post-action meeting.

### 3.8 Rationale for Approval and IV Abuse-Deterrent Labeling

In light of the significant improvement in IV abuse deterrence (described in detail in [Section 5.3](#)), Intellipharmaceutics is requesting approval of Aximris XR with IV abuse-deterrent labeling. Intellipharmaceutics contends that it is reasonable to approve Aximris XR given its bioequivalence to OxyContin, similarity in Human Abuse Potential between Aximris XR and OxyContin (described in detail in [Sections 6.1](#) and [6.2](#)) and its demonstration of superior IV abuse deterrence. Intellipharmaceutics has met all of the requirements and recommendations of the Agency detailed in the CRL and discussed in the Type A Post-action meeting with respect to conducting a comprehensive set of Category 1, 2, and 3 studies and risk assessments to adequately characterize the abuse potential and safety profile of Aximris XR.

## 4 CLINICAL PHARMACOLOGY

### Summary

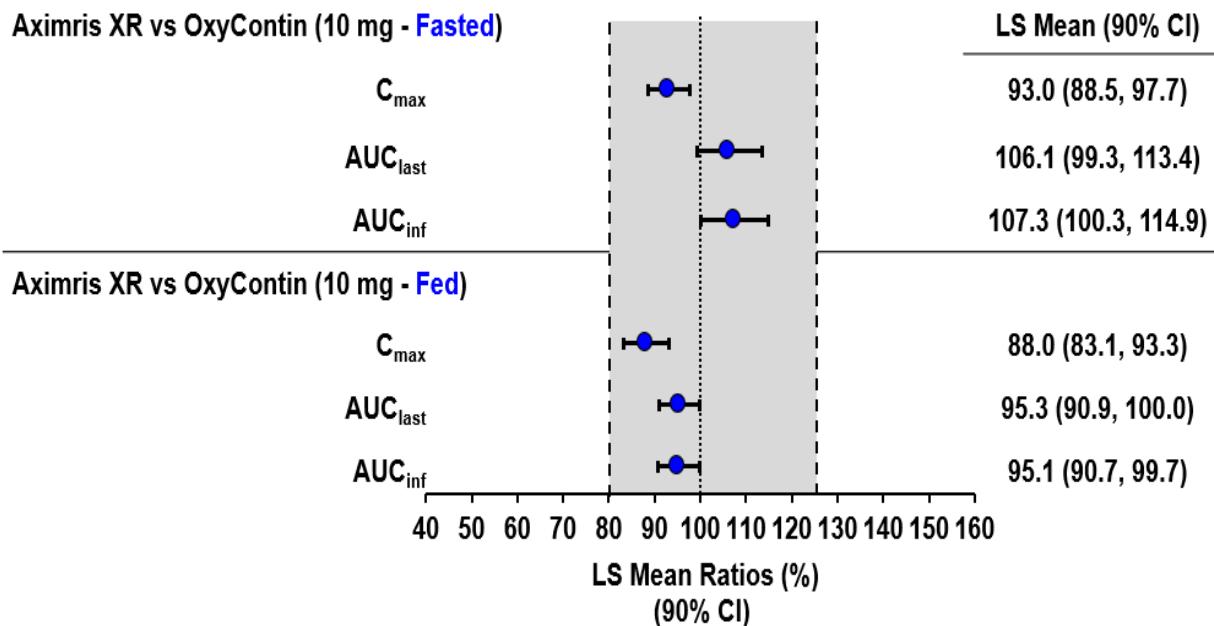
- All clinical pharmacology studies were conducted with the original Aximris XR formulation (containing blue dye); the formulation of Aximris XR was subsequently revised to remove the blue dye. The Agency agreed that the removal of the FD&C Blue No. 1 Aluminum Lake dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997), and therefore the results of studies using the pre-change product (containing blue dye) are also valid for the post-change product (blue dye removed).
- In single-dose clinical PK studies, Aximris XR demonstrated bioequivalence to OxyContin at the lowest and highest dosage strengths in the fed and fasted states, supporting the scientific bridge to prior findings of efficacy and safety of OxyContin.
- A multiple-dose clinical PK study demonstrated bioequivalence of Aximris XR to OxyContin at steady state.
- Aximris XR demonstrated dose proportionality of all proposed dosage strengths, which provides support of approval for all dosage strengths.
- A clinical food effect study demonstrated that there is no clinically significant effect of food on the bioavailability of oxycodone with Aximris XR, so Aximris XR may be taken without regard to meals. Additionally, the  $T_{max}$  values for Aximris XR and OxyContin under fed conditions were found to be similar.

### 4.1 Single-dose Bioequivalence of Aximris XR to OxyContin

Study 1878 and Study 1879 evaluated the relative bioavailability of the lowest (10 mg) dosage strengths of Aximris XR and OxyContin in the fasted and fed states, respectively. Both studies were designed as open-label, single-dose, randomized, 2-period, crossover studies in healthy adult subjects. A 7-day washout period was used between dosing in order to avoid carry-over effects of the preceding treatment. All subjects had their study treatment administered under naltrexone blockade to block the pharmacodynamic effects of oxycodone.

**Figure 18** provides a summary of the key study results, which demonstrated that Aximris XR 10 mg and OxyContin 10 mg were bioequivalent in the fasted and fed states. The criteria for bioequivalence is based on 90% confidence interval (CI) for the least squares (LS) mean ratio of  $C_{max}$  and area under the curve (AUC) parameters falling between 80% and 125%.

**Figure 18: Single-Dose Bioequivalence Results of 10 mg Dosage Strengths of Aximris XR and OxyContin Under Fasted (Study 1878) (N=31) and Fed Conditions (Study 1879) (N=29)**

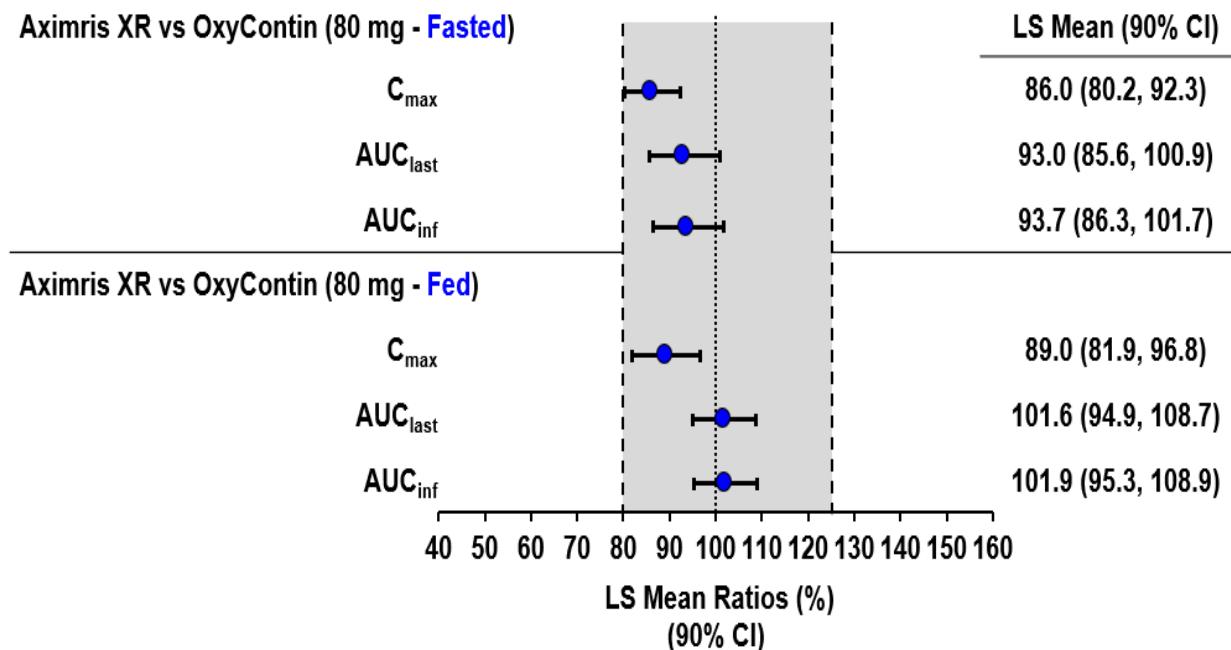


Note: gray shaded area reflects bioequivalence range of 80% to 125%.

Study 656-15 and Study 655-15 evaluated the relative bioavailability of the highest (80 mg) dosage strengths of Aximris XR and OxyContin in the fasted and fed states, respectively. Both studies were designed as open-label, single-dose, randomized, 2-period, crossover studies in healthy adult subjects. A 7-day washout period was used between dosing in order to avoid carry-over effects of the preceding treatment. All subjects had their study treatment administered under naltrexone blockade to block the pharmacodynamic effects of oxycodone. In the fed condition, a standard high fat/high calorie breakfast was administered.

**Figure 19** provides a summary of the key study results, which demonstrated that Aximris XR 80 mg and OxyContin 80 mg were bioequivalent in the fasted and fed states, as illustrated with all 90% CIs for all parameters falling within the pre-defined bioequivalence limits.

**Figure 19: Single-Dose Bioequivalence Results of 80 mg Dosage Strengths of Aximris XR and OxyContin under Fasted (Study 656-15) (N=30) and Fed Conditions (Study 655-15) (N=29)**



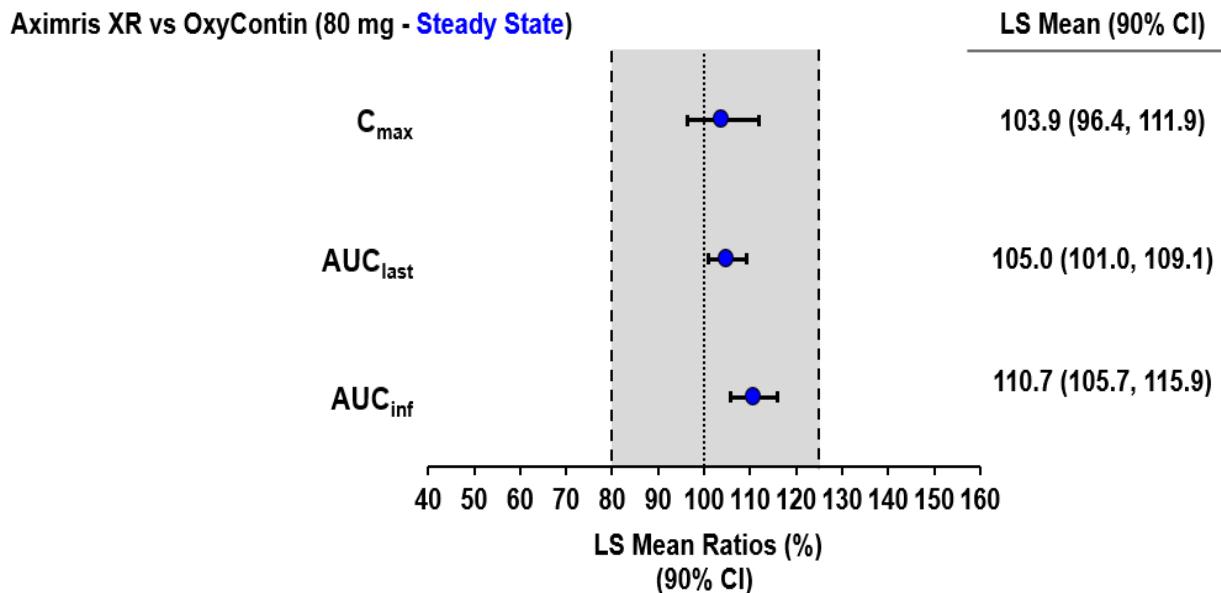
Note: gray shaded area reflects bioequivalence range of 80% to 125%.

#### 4.2 Multiple-Dose Bioequivalence of Aximris XR to OxyContin

Study 80-184 evaluated the relative bioavailability of Aximris XR and OxyContin at the highest dosage strength at steady state (steady state for OxyContin can be achieved within 36 hours). The multiple-dose study was an open-label, randomized, 2-period crossover study in healthy adult subjects. In each period, subjects were administered 1 tablet of 80 mg product every 12 hours (twice daily) for 3 days. A 12-day washout period was used between dosing in order to avoid carry-over effects of the preceding treatment. All subjects were administered under naltrexone blockade to block the pharmacodynamic effects of oxycodone.

**Figure 20** illustrates the primary results of the study, which demonstrated that Aximris XR 80 mg and OxyContin 80 mg were bioequivalent at steady state. All steady state parameters fell within the pre-defined bioequivalence limits of 80% to 125%.

**Figure 20: Multiple-dose Bioequivalence Results of 80 mg Dosage Strengths of Aximris XR and OxyContin (Study 80-184)**

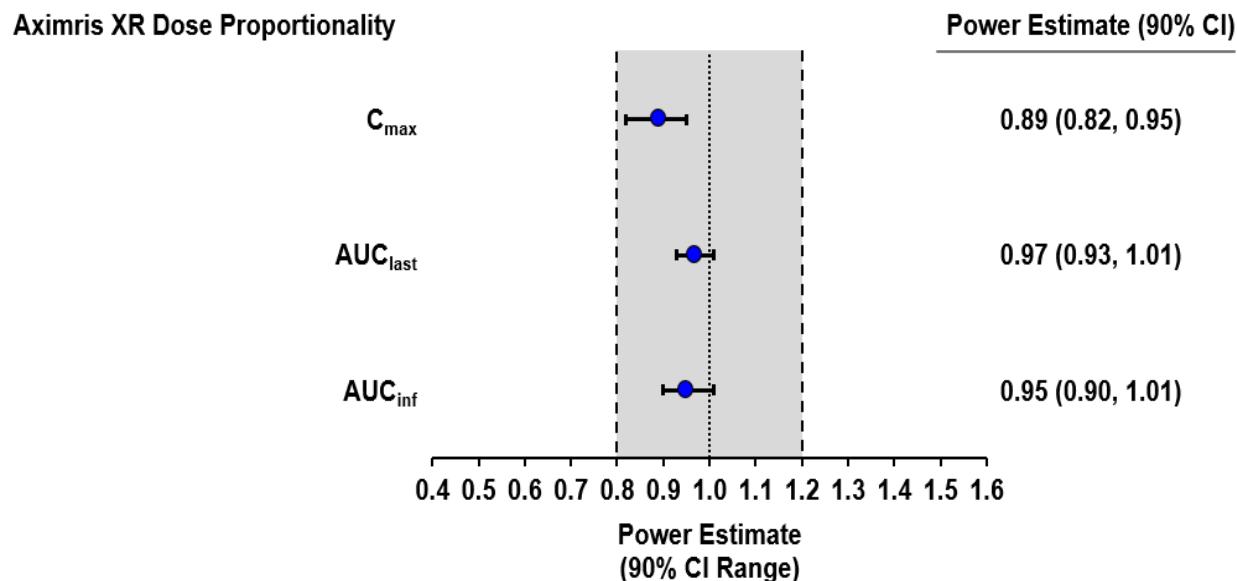


Note: gray shaded area reflects bioequivalence range of 80% to 125%.

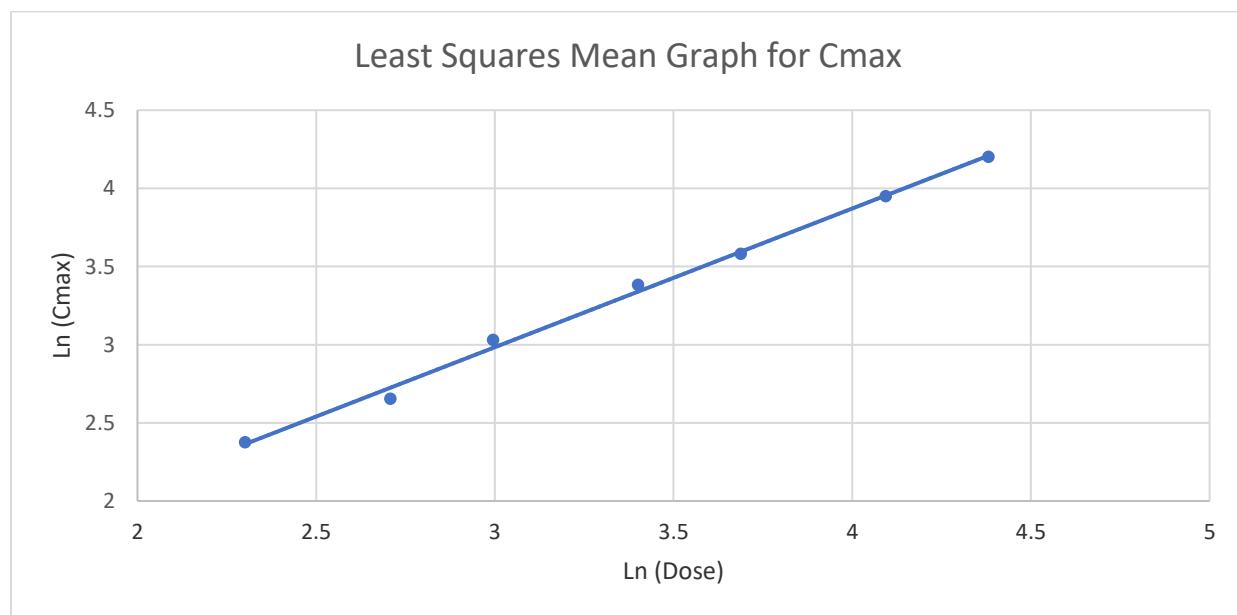
#### 4.3 Dose Proportionality

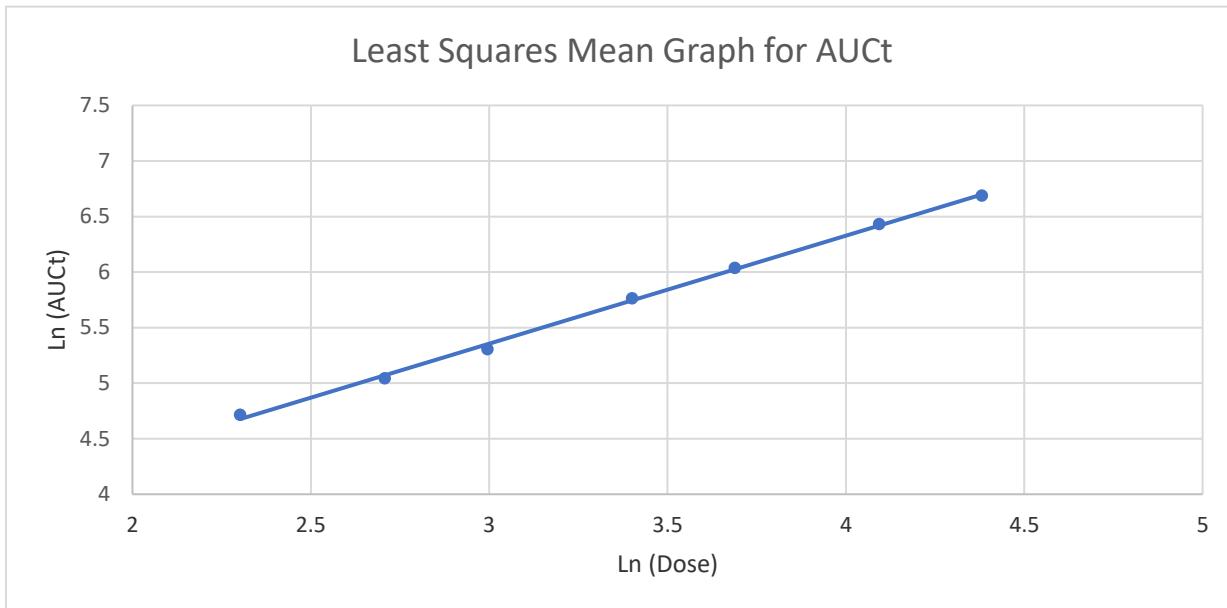
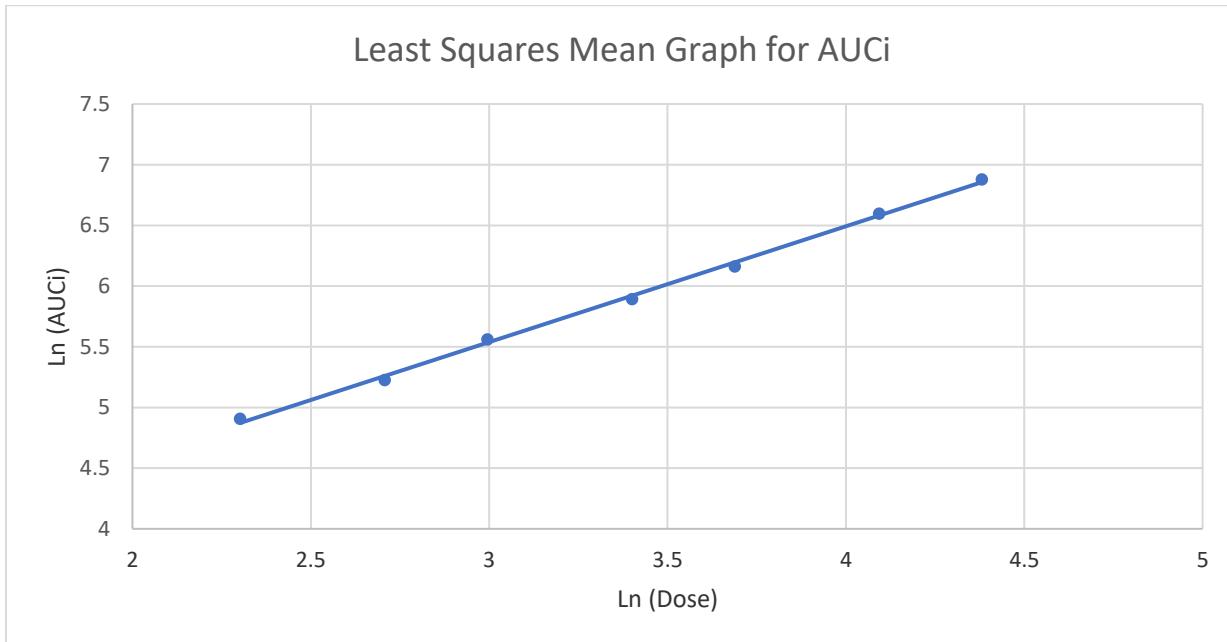
Study 80-185 evaluated the dose proportionality of all 7 proposed dosage strengths of Aximris XR in the fasted state. The dose proportionality study was an open-label, randomized, 7-period, single-dose crossover study in healthy adult subjects. In each period, subjects were administered a single dosage strength of Aximris XR in a randomized order. A 7-day washout period was used between dosing in order to avoid carry-over effects. All subjects had their study treatment administered under naltrexone blockade to block the pharmacodynamic effects of oxycodone.

**Figure 21** demonstrates that the power estimates for all relevant PK parameters fell within the pre-defined limits for dose proportionality (i.e., all 90% CIs fall within 0.8 to 1.2). This provides support that all dosage strengths will provide the expected oxycodone levels relative to the dose.

**Figure 21: Dose Proportionality Results for Aximris XR\* (Study 80-185) (N=22)**


**Figure 22**, **Figure 23**, and **Figure 24** provide the least-squares means for the ln-transformed pharmacokinetic parameters for each dose. In these analyses, in addition to Subject and Period effects, Dose was also considered as a classification variable. Plots of these least-squares means illustrate the dose proportional responses obtained in this study.

**Figure 22: Least Squares Mean Graph for  $C_{\max}$  (Dose Proportionality Study 80-185) (N=22)**


**Figure 23: Least Squares Mean Graph for  $AUC_{0-t}$  (Dose Proportionality Study 80-185) (N=22)****Figure 24: Least Squares Mean Graph for  $AUC_{0-\infty}$  (Dose Proportionality Study 80-185) (N=22)**

#### 4.4 Effect of Food on Bioavailability

Study 80-186 evaluated the effect of food on bioavailability of Aximris XR at the 80 mg dose. The study was an open-label, randomized, two-period crossover study in healthy adult subjects. A 7-day washout period was used between dosing in order to avoid carry-over effects. All subjects had their study treatment administered under naltrexone blockade to block the pharmacodynamic effects of oxycodone. A similar study (Study 1879) evaluated the effect of food on bioavailability of Aximris XR at the 10 mg dose. In both of these studies, the bioavailability of OxyContin was also measured.

In these studies, the median  $T_{max}$  values for Aximris XR under fed and fasted conditions are similar for both the 80 mg and 10 mg doses ([Table 4](#)).

[Figure 25](#) illustrates the mean oxycodone plasma concentration curves in the fed and fasted states of Aximris XR 80 mg.

[Figure 26](#) summarizes the primary study results demonstrating that Aximris XR 80 mg is bioequivalent in the fed and fasted states.

Based on these data, the product may be taken without regard to meals.

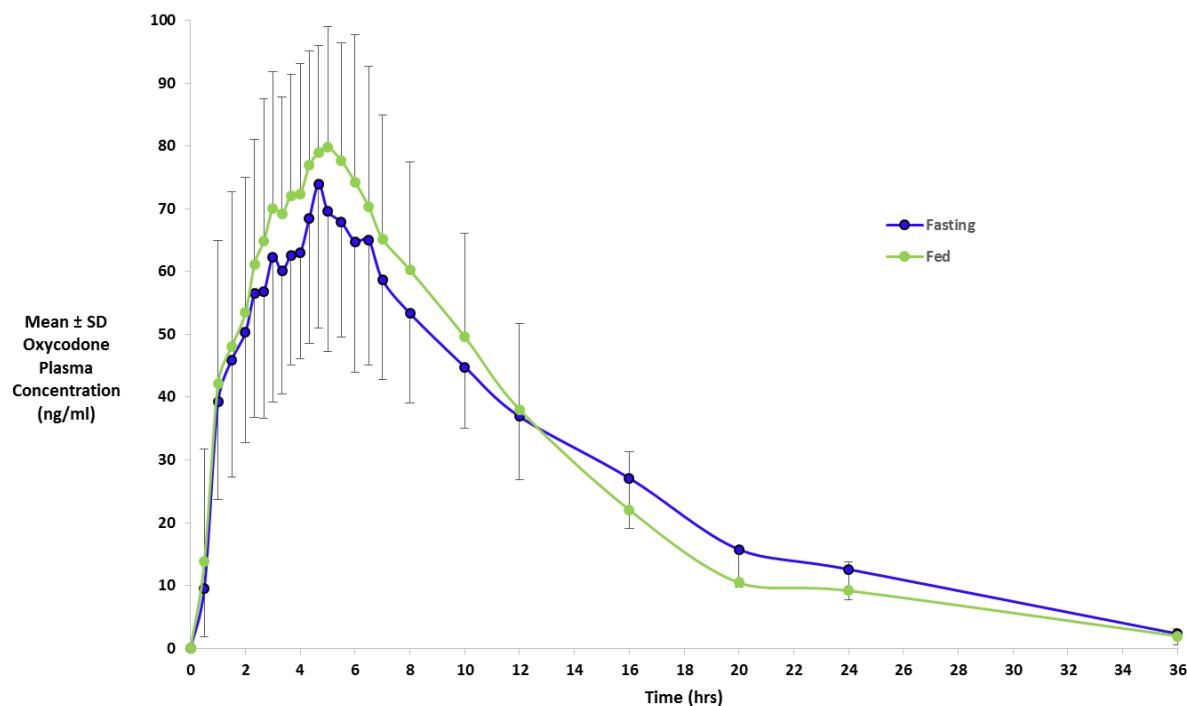
**Table 4: Pharmacokinetic Parameters of Aximris XR and OxyContin (10 mg and 80 mg) Under Fasted and Fed Conditions**

			C <sub>max</sub> (ng/mL)	T <sub>max</sub> * (hr)	AUC <sub>0-t</sub> (ng·h/mL)	AUC <sub>0-inf</sub> (ng·h/mL)	T <sub>½**</sub> (hr)	K <sub>el**</sub> (1/h)
Aximris XR	10 mg Mean±SD	Fasted (n = 31)	10.04 (30.43)	5.50 (1.00 - 10.00)	115.92 (32.61)	121.98 (30.76)	5.19 (26.51)	0.1440 (31.32)
		Fed (n = 29)	13.94 (22.77)	5.50 (1.50 - 10.00)	143.74 (28.35)	147.71 (27.91)	4.02 (15.69)	0.1765 (14.99)
OxyContin	10 mg Mean±SD	Fasted (n = 31)	10.58 (26.95)	5.00 (2.00 - 6.00)	107.56 (27.54)	112.45 (26.81)	4.61 (23.36)	0.1576 (21.62)
		Fed (n = 29)	16.04 (26.48)	5.00 (3.00 - 10.00)	152.40 (30.82)	156.70 (30.06)	4.18 (16.38)	0.1699 (15.50)
Aximris XR	80 mg Mean±SD	Fasted (n = 30)	72.88 (23.90)	4.834 (1.00 - 10.00)	851.66 (283.44)	870.44 (294.55)	4.89 (1.25)	0.149 (0.032)
		Fed (n = 29)	106.47 (26.39)	5.000 (1.00 - 12.00)	1053.29 (311.46)	1068.04 (314.54)	4.24 (0.79)	0.168 (0.025)
OxyContin	80 mg Mean±SD	Fasted (n = 30)	86.03 (30.35)	4.850 (2.00 - 6.12)	921.68 (298.81)	933.66 (300.47)	4.68 (0.80)	0.152 (0.025)
		Fed (n = 29)	119.09 (33.17)	5.500 (1.50 - 10.02)	1034.23 (320.57)	1045.43 (323.70)	4.10 (0.68)	0.174 (0.028)

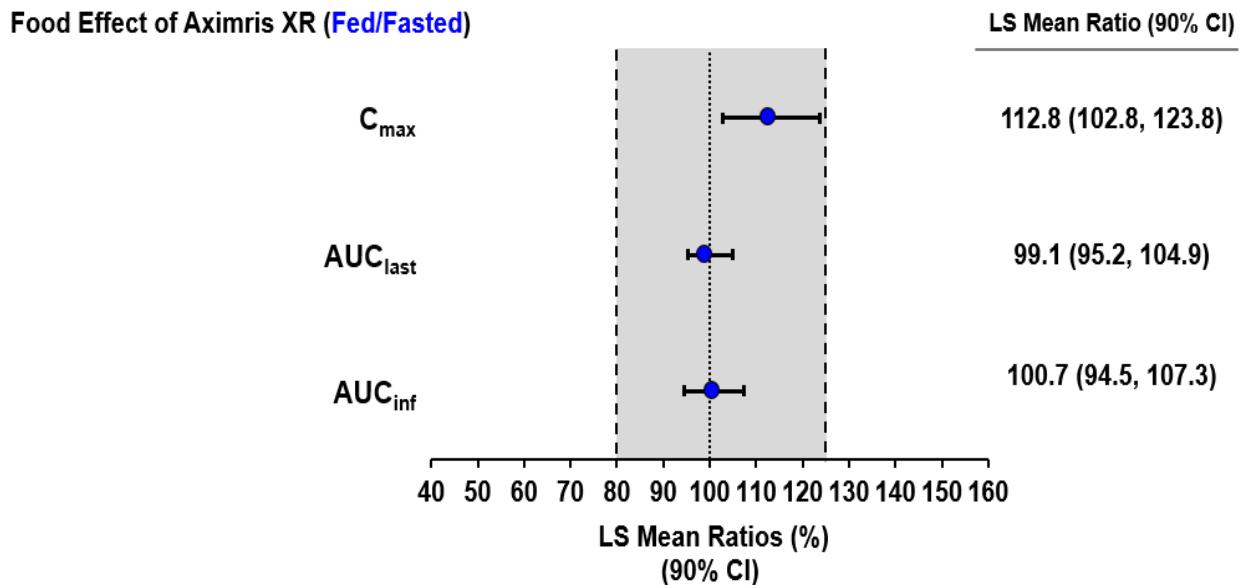
\* Presented as median (min – max) value

\*\* Presented as arithmetic mean (CV %)

**Figure 25: Oxycodone Plasma Concentration Curves for Aximris XR 80 mg in the Fed and Fasted States (Study 80-186) (N=25)**



**Figure 26: Bioequivalence Results of Aximris XR 80 mg in the Fed and Fasted States (Study 80-186)**



## 5 CATEGORY 1 STUDIES

### Summary

- A comprehensive series of Category 1 in vitro abuse-deterrent studies were conducted in accordance with FDA Guidance and in consultation with FDA and experts in the evaluation of ADFs.
- One of the tenets of the FDA Guidance is to test the abuse-deterrent properties of a formulation to failure to understand the limits of the physical and chemical barriers. This informed the choice of the tool for preparing ground tablets for the studies.
- OxyContin offered greater resistance to particle size reduction than Aximris XR, which was expected given the goals of the formulations (i.e., Aximris XR is formulated to produce very high viscosity and coagulate more quickly with greater particle size reduction). Both products could be reduced to relatively fine particles.
- Aximris XR demonstrated greater viscosity when subjected to aqueous environment compared to OxyContin.
- Aximris XR and OxyContin both offered considerable resistance to the standard methods abusers use to prepare and inject solid oral opioid dosage forms.
- Using common “recipes” on drug abuse websites which are known to defeat ADFs (radiant heat pre-treatment) and advanced methods, several conditions were able to yield a significant amount of injectable oxycodone from OxyContin while Aximris XR was more resistant.
- Manipulated Aximris XR ground tablets that had undergone the most stringent condition (convection heat pre-treatment) present a stronger resistance to extraction compared to OxyContin under the same condition.
- Aximris XR and OxyContin demonstrated comparable resistance to extraction in very large volumes (100mL and 200mL) of various solvents that an abuser might use for oral abuse.
- Aximris XR, like OxyContin, did not dose dump in the presence of alcohol.
- In dissolution studies, the release of oxycodone from Aximris XR and OxyContin tablets that were split into 2, 4, 8 and 16 pieces were similar with Aximris XR showing more resilience as the number of split units increased, which suggests that there is not an increased risk with Aximris XR for manipulated routes of abuse (e.g., manipulated oral, intranasal) compared to OxyContin. Using radiant heat pre-treatment with and without rotation, a common method used by abusers to overcome abuse-deterrent and ER properties, Aximris XR was considerably more resistant to drug release in dissolution testing than OxyContin.
- Aximris XR and OxyContin were not efficiently smoked or vaporized (all conditions released  $\leq 8\%$  and  $\leq 11\%$  oxycodone in vapor for Aximris XR and OxyContin, respectively).

- Overall, Aximris XR demonstrated significant improvement in IV abuse deterrence over OxyContin with greater resistance to syringeability following the methods that abusers currently use to overcome abuse-deterrent properties of formulations like OxyContin.

## 5.1 Overview

In consultation with the FDA and abuse-deterrent experts, Intellipharmaceutics conducted a comprehensive series of Category 1, laboratory-based in vitro studies to evaluate the physical and chemical abuse-deterrent properties of Aximris XR. The studies were conducted in accordance with the 2015 FDA Guidance “*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*” (CDER, 2015).

Category 1 studies included general manipulations that are common for several routes of abuse (e.g., particle size reduction), as well as route-specific evaluations (e.g., syringeability/injectability, simulated smoking/vaporization). In all relevant studies, OxyContin was used as the abuse-deterrent comparator. Several studies evaluated multiple dosage strengths; however, for the purposes of this briefing document, only the highest dosage strength of 80 mg will be discussed. Results for the lower dosage strengths were consistent with those reported in this document for 80 mg.

The rationale for selection of tools, solvents, and other experimental conditions for Category 1 testing followed a systematic approach that typically started with an exploratory phase followed by a standardization phase. In the exploratory phase, consideration was given to the physicochemical characteristics of Aximris XR and OxyContin as well as the active pharmaceutical ingredient (API), how these products could be physically and chemically manipulated, and common practices employed by individuals engaged in abuse practices for different routes of abuse. The methods used attempted to be as representative as possible, though it should be acknowledged that no in vitro abuse-deterrent testing program battery can be completely exhaustive. Rather, after exploratory work, conditions were selected in an attempt to optimize procedures to create “worst-case” scenarios.

One of the tenets of the FDA Guidance is to test the abuse-deterrent properties of a formulation to failure to understand the limits of the physical and chemical barriers. This informed the choice of tool for preparing ground tablets for the studies. The FDA Guidance recognizes that ADFs are abuse-*deterrent*, not abuse-*proof*. Therefore, the range of experimental conditions in these studies encompass both common methods used by abusers as well as extreme laboratory manipulations that would be unlikely to be attempted by abusers in the real world, given the extensive time, resources, equipment, and chemistry knowledge involved. Toward this end, manipulations of Aximris XR were carried out using various combinations of 10 tools, 7 pre-treatment mechanisms (untreated, heat treated, cold treated, radiant heat pre-treatment, convection heat pre-treatment, radiant heat pre-treatment without rotation, radiant heat pre-treatment with rotation), 2 temperatures (room temperatures and elevated temperature), 4 needle gauges (very small, small, medium and large needle gauges), 27 solvents, 9 solvent volumes, 3 agitation conditions (no agitation, low agitation and high agitation), and 3 dissolution conditions (acidic, basic and neutral dissolution conditions).

## 5.2 Particle Size Reduction Studies

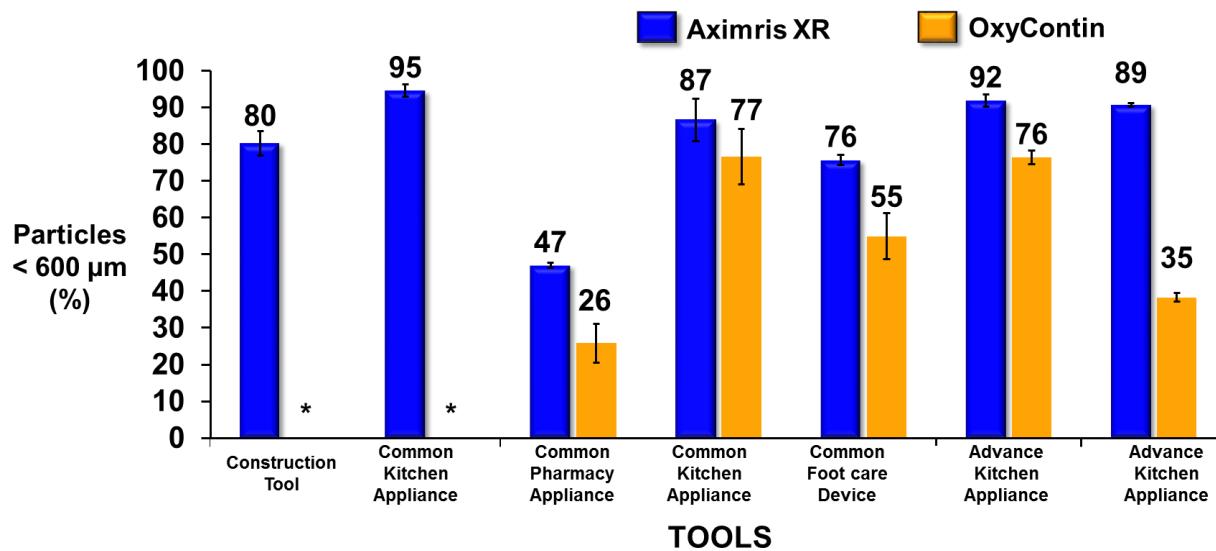
Physical manipulation (e.g., crushing, cutting, grinding, grating, and chewing) of a solid or semisolid oral dosage form of opioid formulations in order to reduce the formulations from one average particle size (e.g., tablet) to a smaller average particle size (e.g., powder) is commonly reported by individuals engaged in abuse of opioids. Reduction in particle size of a solid or semisolid oral dosage form of opioid formulations by physical manipulation often enable these individuals to defeat the controlled-release properties of an ER formulation and to abuse these products by using one or more of the following routes to administer the manipulated material.

- Oral route, such as by chewing, swallowing ground tablet (“parachuting”)
- Intranasal route, in which the manipulated material is snorted
- Intravenous route, in which the manipulated material is extracted or dissolved and injected
- Smoking route, in which the manipulated material is smoked or vaporized

Thus, particle size reduction of an ER opioid tablet formulation is often the first step for the potential abuser to attempt, because reducing a tablet to a powder allows immediate access to its opioid drug content by disrupting diffusion barriers and increasing the surface area of drug particles for more efficient drug extraction. For these reasons, Aximris XR tablets have specifically been formulated to deter abuse with enhanced swelling, viscosity, and coagulation properties when its particle size is reduced or its surface area is increased.

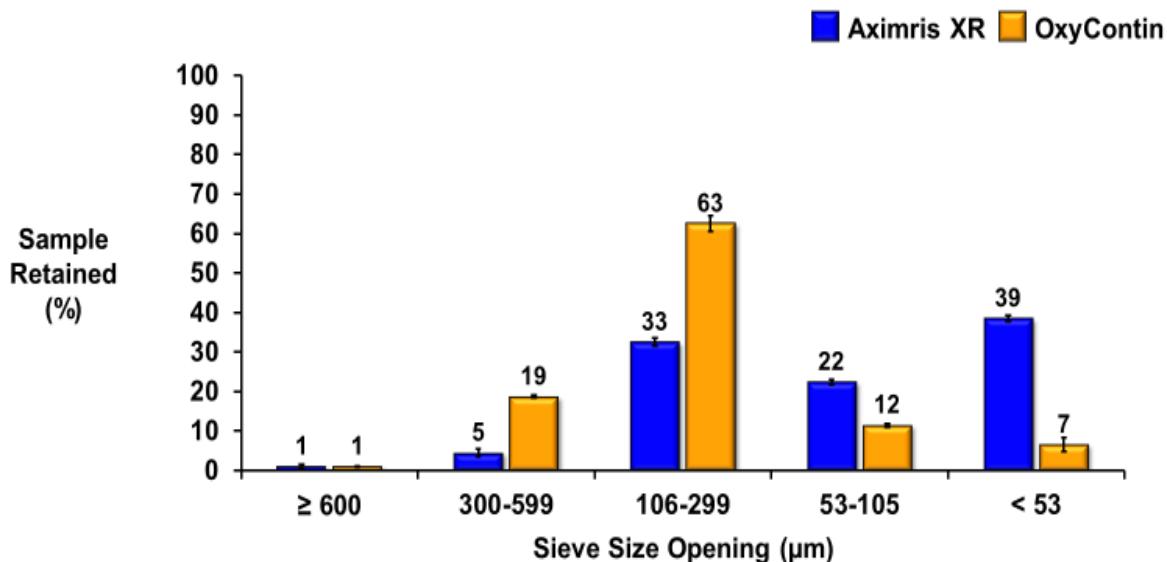
Using 10 household tools, Aximris XR and OxyContin were evaluated for their resistance to physical manipulation representative of the different mechanisms used by abusers to crush, cut, grate, or grind solid oral dosage forms with mechanical or electrical tools. Given that tablet hardness is not the primary abuse-deterrent feature of Aximris XR, it yielded a higher percentage of small particles across the various tools in comparison to OxyContin ([Figure 27](#)). OxyContin was more resistant to physical crushing, nonetheless it could still be ground to fine particles with tools that are easily available to an abuser.

**Figure 27: % Particles of Aximris XR and OxyContin with Size  $\leq 600 \mu\text{m}$  Following Particle Size Reduction Procedure Using Common and Advanced Tools**



An advanced kitchen appliance was further evaluated because it is known that adding additional tablets to this tool can produce smaller particle size output than a single tablet. The advanced kitchen appliance was applied for three different time intervals in an optimization procedure with multiple tablets. After iterative testing, the particle size reduction procedure that was optimal when manipulating several tablets at a specific time interval was chosen. The particle size distribution of ground Aximris XR and OxyContin tablets is shown in [Figure 28](#). While Aximris XR had a higher percentage of finer particles, both products had 99% of their particles reduced to less than 600 microns, which is a range suitable for snorting. Importantly, Aximris XR demonstrates high viscosity, rapid swelling, and hypercoagulability when its particle size is reduced and subjected to hydration with small volumes of aqueous solvents. Thus, although Aximris XR yielded finer particles than OxyContin, the smaller particles actually increased viscosity and coagulation and did not increase drug release or extraction, which is illustrated in the dissolution studies presented later in this document (see [Section 5.6](#)).

**Figure 28: Particle Size Distribution of Ground Aximris XR and OxyContin Tablets Following Optimal Particle Size Reduction Procedure**



### 5.3 Extractability/Syringeability/Injectability Studies

Some drug abusers prefer the IV route of administration for opioids because of the enhanced potency and rapidity of onset of effects compared to oral or intranasal use. Typically, these abusers crush a tablet with a spoon, add 1-2 mL of water or normal saline, and may apply heat to increase the speed and efficiency of drug dissolution. Some individuals may also stir the solution to enhance dissolution. Frequently, a piece of cotton or cigarette filter is added to the solution for filtration purposes to avoid solid undissolved matter clogging the needle or going into the syringe. Some individuals utilize micron filters for sterilization and removal of undissolved particles. Once prepared, the drug solution is drawn into a syringe through a needle and injected. The most frequently used injection equipment is an insulin syringe (1 cc) fitted with a 27 - 29 gauge needle. Some individuals may use larger syringes and needles with smaller gauges.

Most ADFs are designed to resist common or standard methods for IV abuse. Both Aximris XR and OxyContin are formulated with properties intended to deter IV abuse by producing a highly viscous material when subjected to an aqueous environment. Aximris XR is formulated with excipients to enhance this viscosity and leading to hypercoagulability even if subjected to a considerable extraction volume or heat pre-treatment. The in vitro IV abuse studies for Aximris XR evaluated simple methods for preparing opioid products for injection as well as “recipes” referenced on drug abuse websites to overcome the gelling properties of ADFs such as OxyContin. We also evaluated Aximris XR using advanced methods recommended by the FDA.

In general, following the small volume extraction procedure, trained laboratory technicians attempted to syringe the material through a small cotton filter starting with the large gauge needle. If the attempt was successful with the large needle gauge, the technicians tested smaller needles. Otherwise, the attempt was terminated.

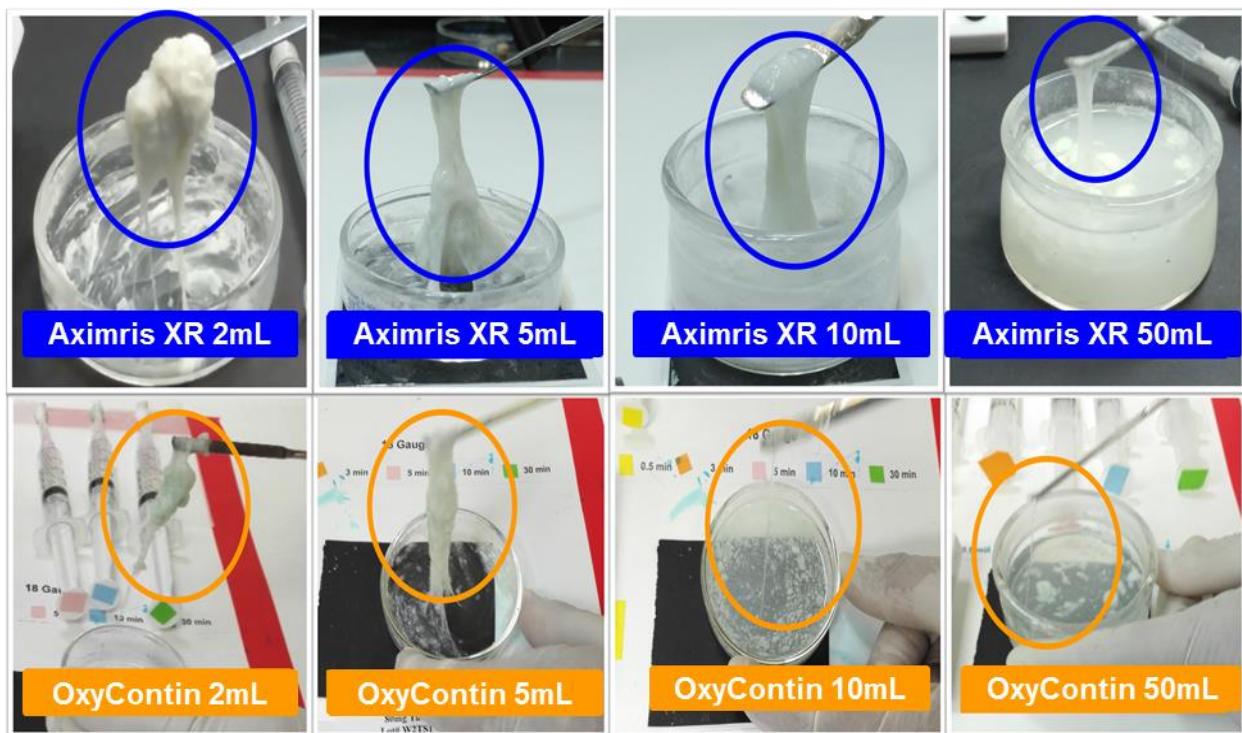
### 5.3.1 Standard Syringeability/Injectability and Extraction Studies

For standard syringeability/injectability assessments, samples of ground tablets of Aximris XR and OxyContin were added into various volumes ranging from 2mL, 5mL, 10mL, 20mL and 50mL of neutral solution or isotonic solution and incubated for up to 30 minutes with no agitation or with high agitation, at room or elevated temperatures. **Figure 29** illustrate the extreme viscosity and hypercoagulability properties of ground Aximris XR in various volumes of neutral solution, with no agitation and at room temperature. Additionally, it was found that the viscosity of Aximris XR is higher compared to OxyContin when manipulated using the same conditions (**Figure 30**, **Figure 31**, **Figure 32**).

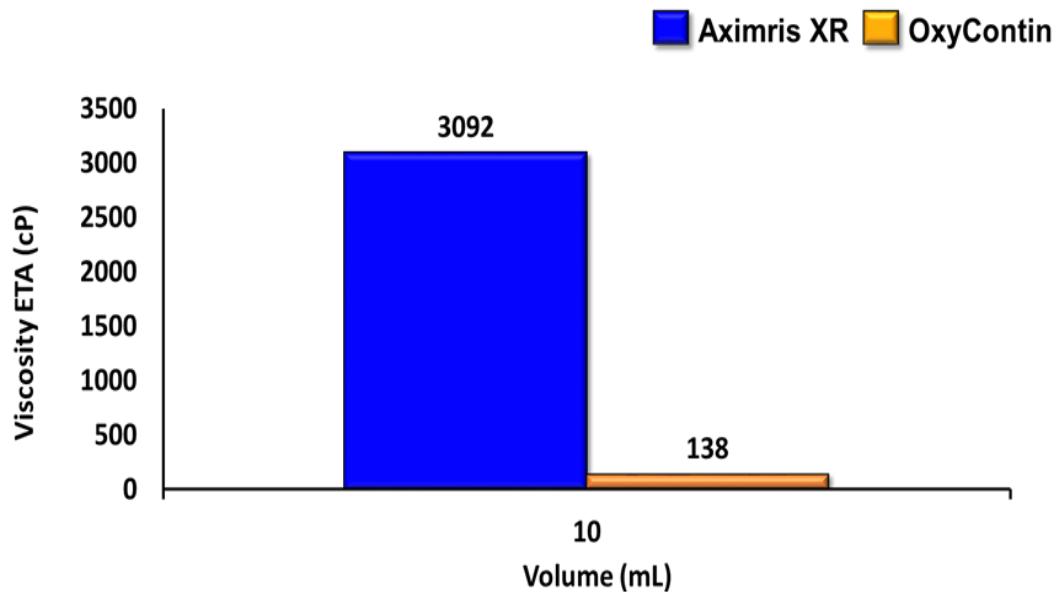
A similar study was performed using intact tablet in 50mL of isotonic solution, incubated for 5, 10, and 30 minutes with high agitation, at room and elevated temperature (No Oxycodone was extracted at room temperature, while less than 10% of drug was recovered at elevated temperature).

None of the conditions yielded an appreciable amount of injectable oxycodone for either Aximris XR or OxyContin, which supports that both Aximris XR and OxyContin have abuse-deterrent properties for the IV route under these common or standard conditions.

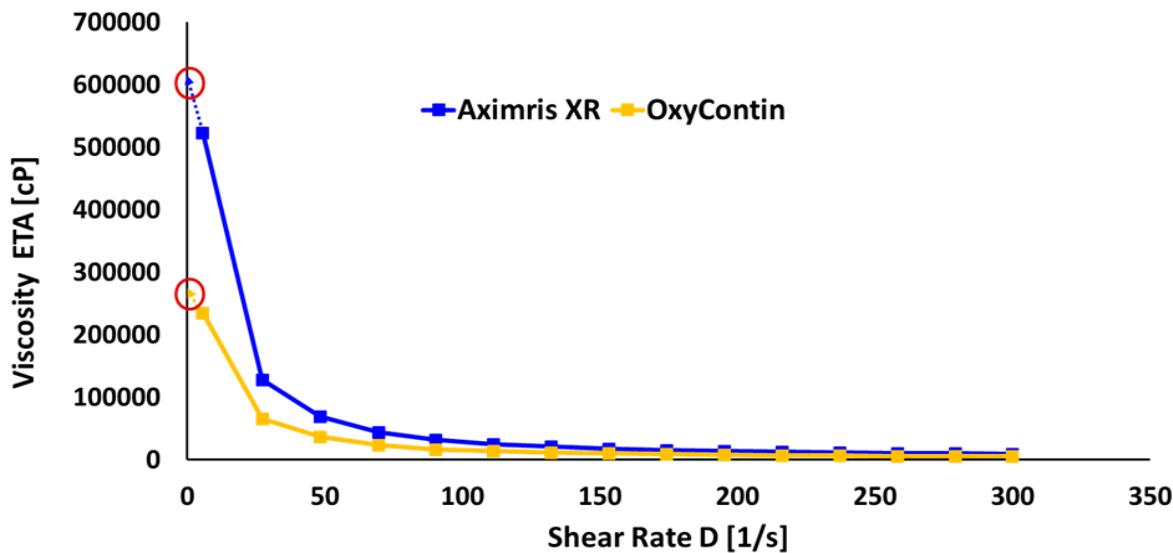
**Figure 29: Ground Aximris XR Is More Viscous and Coagulates Faster Than Ground OxyContin in Neutral Solution, with No Agitation at Room Temperature**



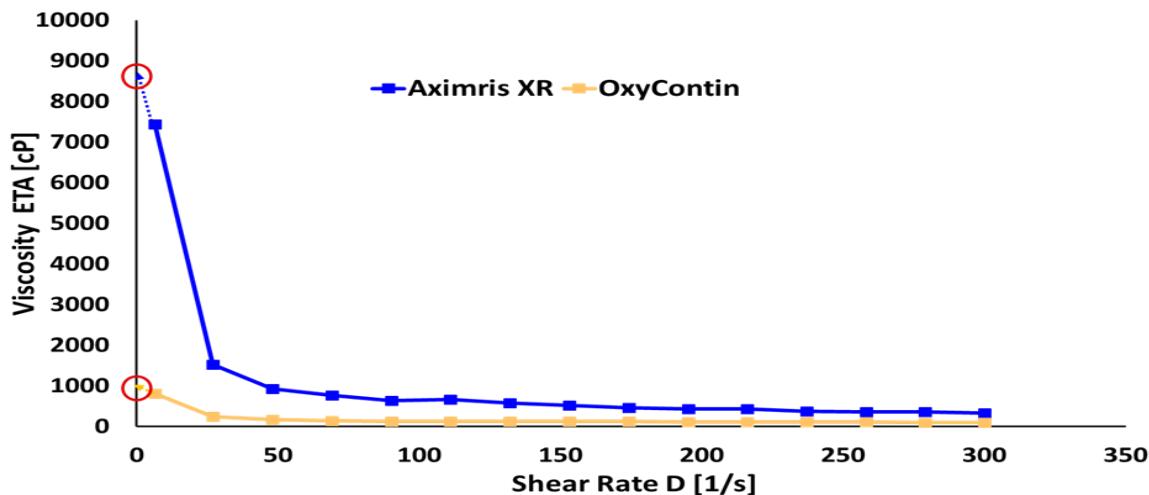
**Figure 30: Aximris XR Displays Significantly Greater Viscosity Than OxyContin – 10mL of Neutral Solution, Room Temperature using Brookfield Viscometer Model no. DV2T**



**Figure 31: Aximris XR Displays Significantly Greater Shear Rate Viscosity Than OxyContin – in 2mL Neutral Solution, Room Temperature using Brookfield Rheometer model no. RST-CPS**



**Figure 32: Aximris XR Displays Significantly Greater Shear Rate Viscosity Than OxyContin – in 10mL, Neutral Solution, Room Temperature using Brookfield rheometer model no. RST-CPS**



### **5.3.2 Extractability/Syringeability/Injectability of Ground Aximris XR and Ground OxyContin Tablets Using Advanced Methods (Convection Heat Pre-treatment) Recommended by the FDA, Using Neutral Solution, Isotonic Solution or Alcoholic Solution**

The Agency recommended that Intellipharmaceutics perform studies on the syringeability of Aximris XR when manipulated using advanced manipulation methods (convection heat pre-treatment).

In these studies, the syringeability of ground and whole tablets of Aximris XR and OxyContin were determined after the products were manipulated using convection heat pre-treatment. Following pre-treatment, the products were mixed vigorously in either 2mL, 5mL or 10mL of neutral solution, alcoholic solution or isotonic solution. A small rolled piece of cotton ("Q-tip" size) was securely attached to a very small, small, medium or large needle gauge, needle and attempts were made for up to 2 minutes to load the syringe with the solution from the glass container. All experiments were performed in triplicate.

#### Results obtained using 2mL of solution for extraction of ground tablets pre-treated with convection heat

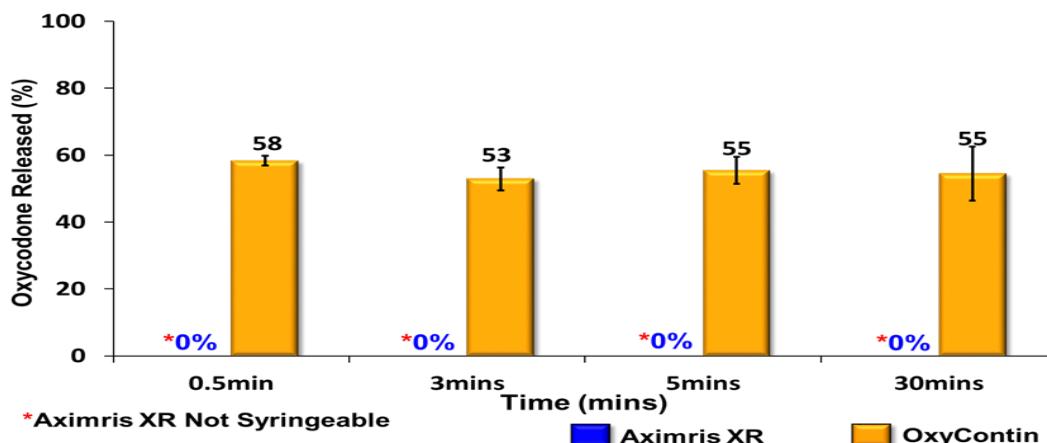
The amount of oxycodone extracted from ground Aximris XR ranged from 0% in solvents such as alcoholic solution (at room or elevated temperature) to about 10% in neutral solution (at elevated temperature) per label claim. Conversely, ground OxyContin was successfully syringed and high amounts of drug were successfully extracted using convection heat pre-treatment and incubated for 0.5 min, 3 min, 5 min or 30 min in 2mL of neutral solution, alcoholic solution and

isotonic solution, using the very small needle gauge. Analysis of the syringed solutions from OxyContin yielded injectable oxycodone ranging from 53% in alcoholic solution (at room temperature) to about 73% in isotonic solution (at elevated temperature) per label claim.

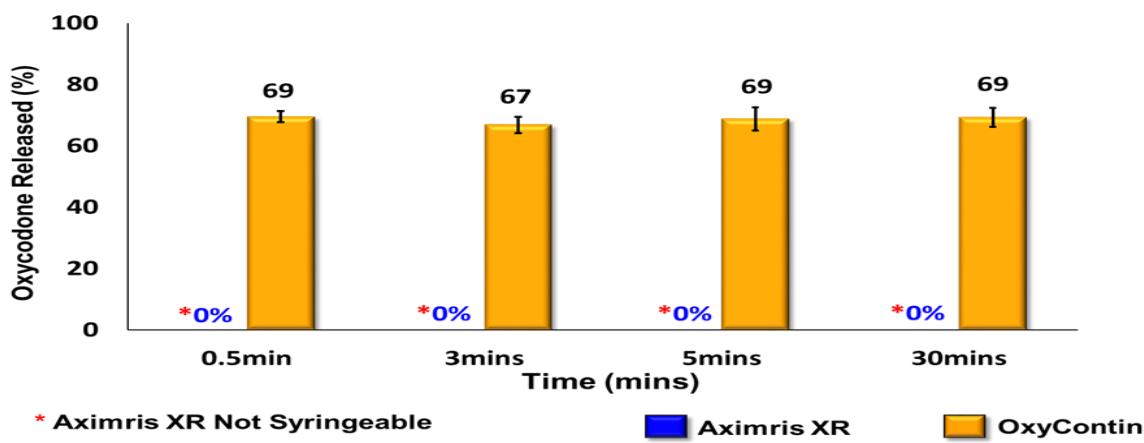
Overall, these studies showed that manipulated ground Aximris XR that had undergone the most stringent condition of convection heat pre-treatment will not be successfully syringed in a small volume of solvent (2mL) to yield oxycodone that will be enticing to an abuser. This is in contrast to ground OxyContin, which when similarly treated, was successfully syringed in a small volume (2mL) to give ranging from 53% to about 73% of oxycodone suitable for IV injection.

The results from experiments are presented graphically in the figures below (**Figures 33 - 38**).

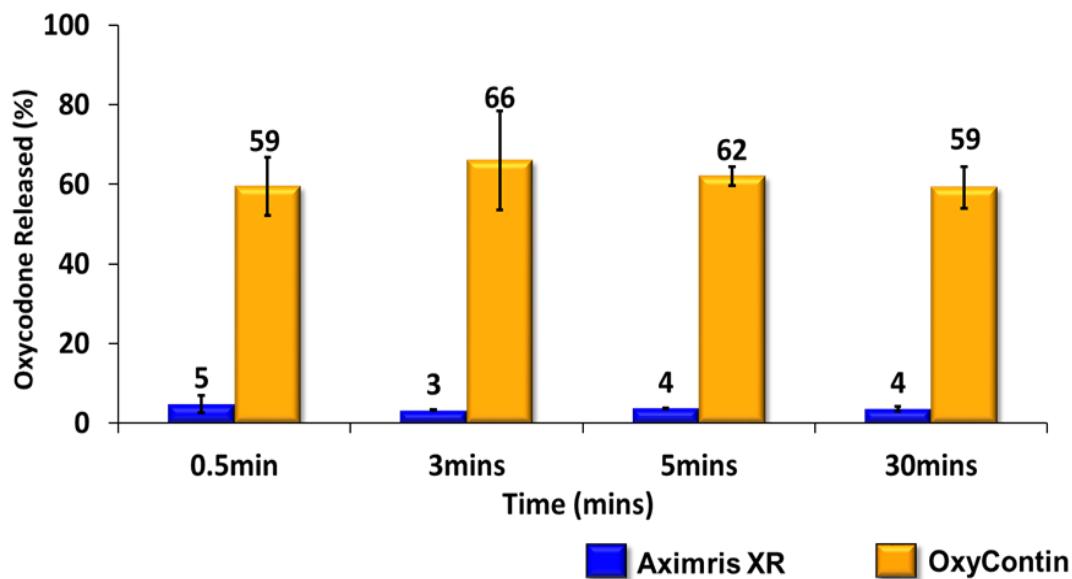
**Figure 33: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL, Alcoholic Solution at Room Temperature**



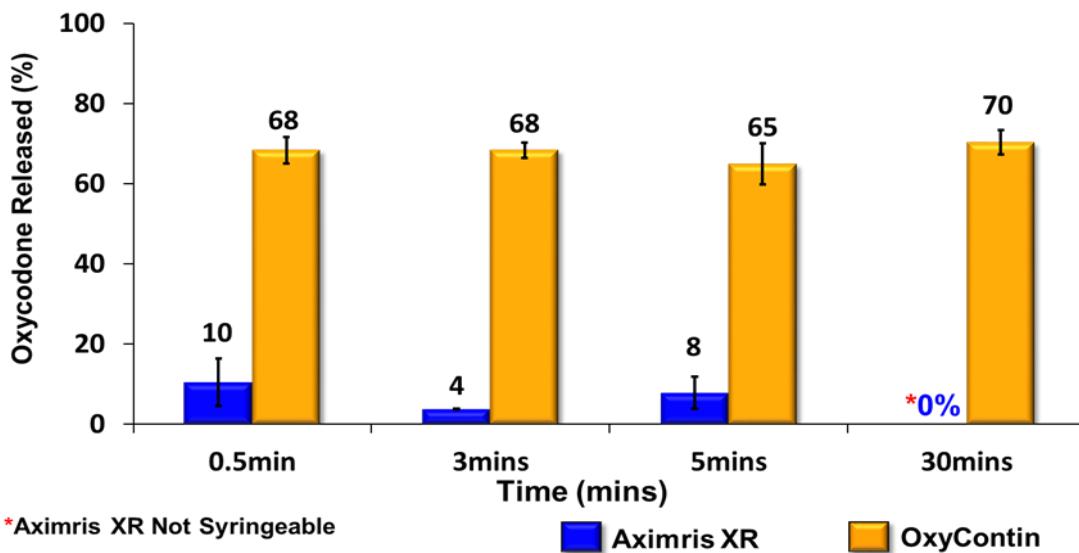
**Figure 34: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL of Alcoholic Solution at Elevated Temperature**



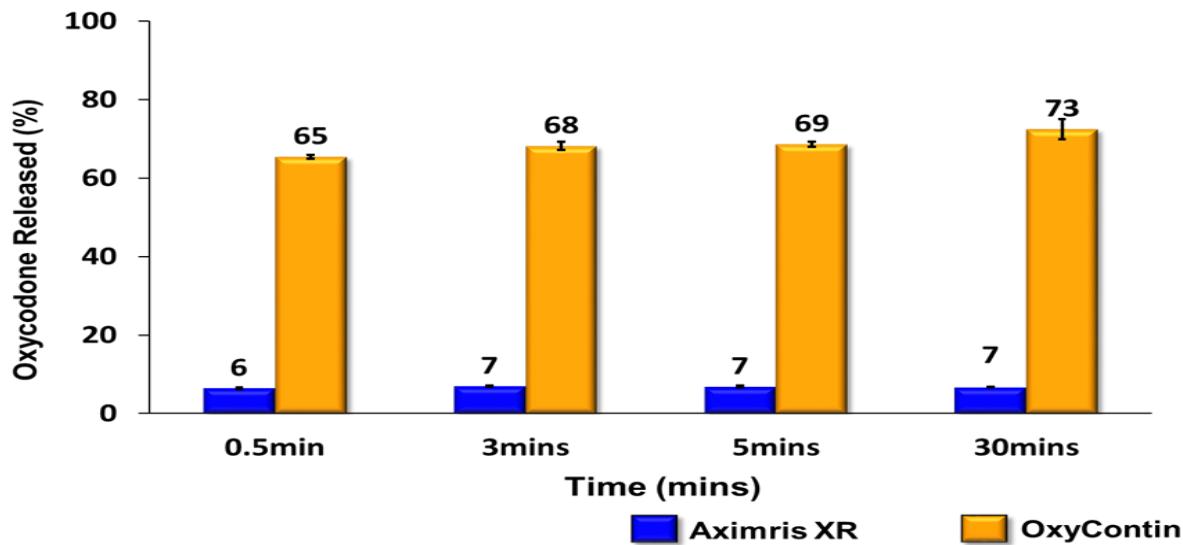
**Figure 35: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL of Neutral Solution at Room Temperature**



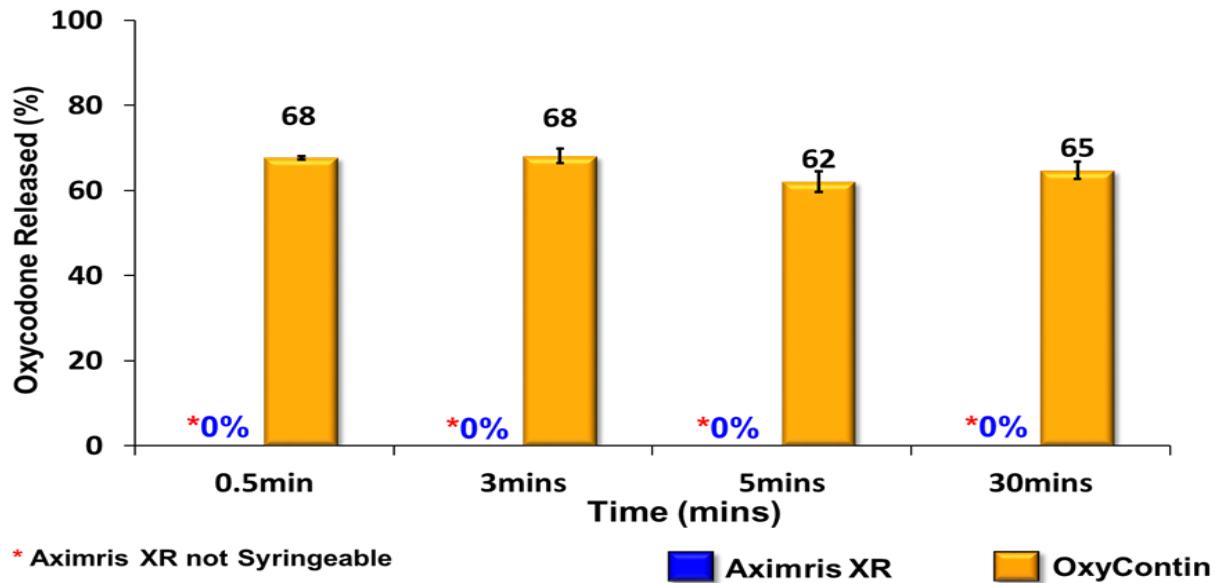
**Figure 36: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL of Neutral Solution at Elevated Temperature**



**Figure 37: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL of Isotonic Solution at Room Temperature**



**Figure 38: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 2mL of Isotonic Solution at Elevated Temperature**



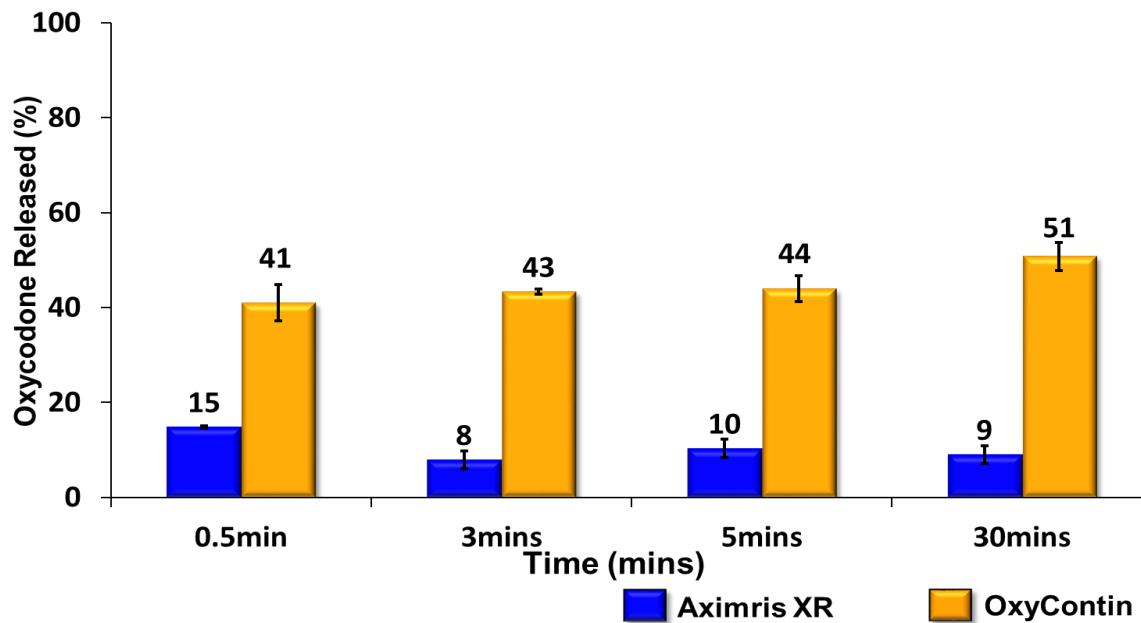
Results obtained using 5mL of solution for extraction of ground tablets pre-treated with convection heat

The amount of oxycodone extracted from ground Aximris XR ranged from 6% in alcoholic solution (at elevated temperature) to about 24% in neutral solution (at elevated temperature) per label claim. Conversely, for ground OxyContin, much higher amounts of drug suitable for IV injection were successfully extracted using convection heat pre-treatment and incubated for 0.5 min, 3 min, 5 min or 30 min in 5mL of neutral solution, alcoholic solution and isotonic solution, using the very small needle gauge. Analysis of the syringed solutions from OxyContin yielded injectable oxycodone ranging from 41% in alcoholic solution (at room temperature) to about 78% in both neutral and alcoholic solutions (at elevated temperature) per label claim.

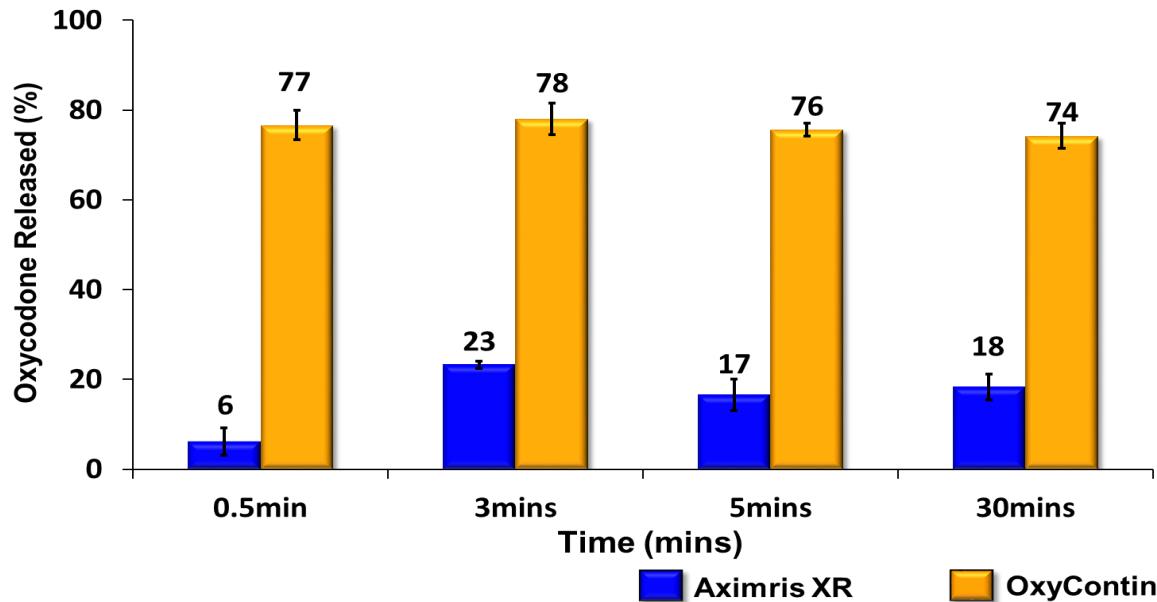
Overall, these studies showed that manipulated ground Aximris XR that had undergone the most stringent condition of convection heat pre-treatment will not be successfully syringed in a small volume of the solvent (5mL) to yield oxycodone that will be enticing to an abuser. This is in contrast to ground OxyContin, which when similarly treated, was successfully syringed in a small volume (5mL) to give ranging from 41% to about 78% of oxycodone suitable for IV injection.

The results are presented graphically in the figures below (**Figures 39 – 44**).

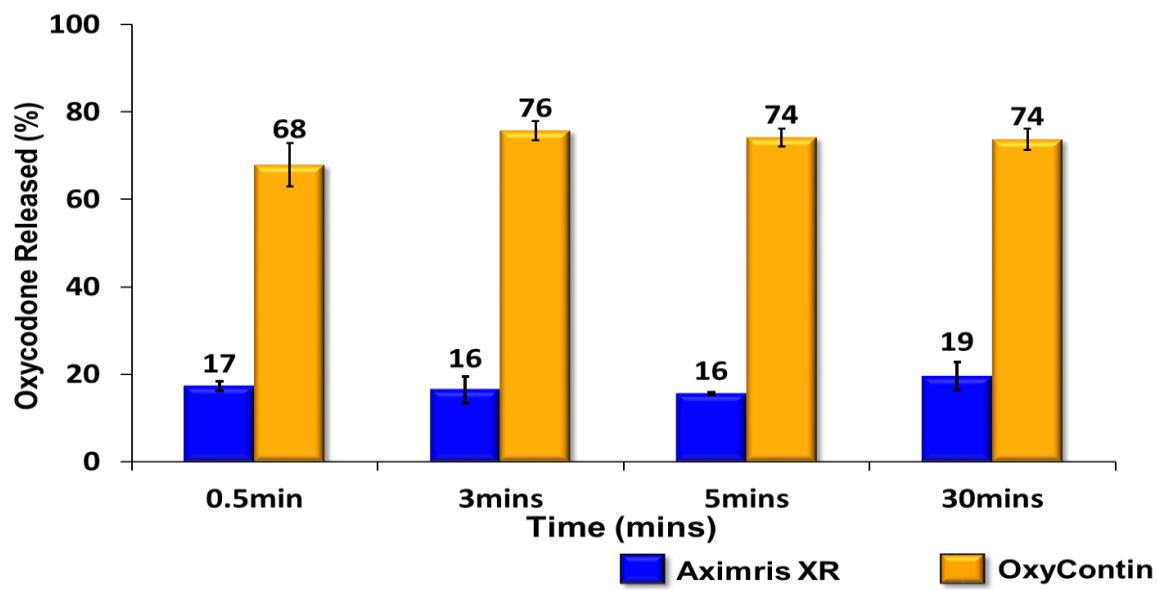
**Figure 39: Drug Extraction from Ground Aximris XR and Oxycontin Tablets Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 5mL of Alcoholic Solution at Room Temperature**



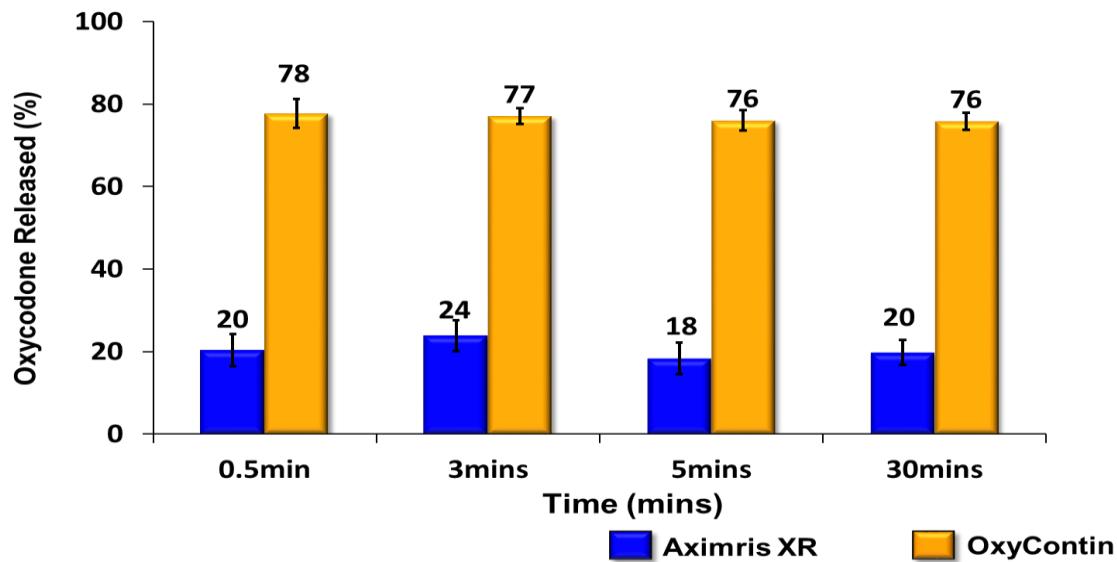
**Figure 40: Drug Extraction from Ground Aximris XR and Oxycontin Tablets Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 5mL of Alcoholic Solution at Elevated Temperature**



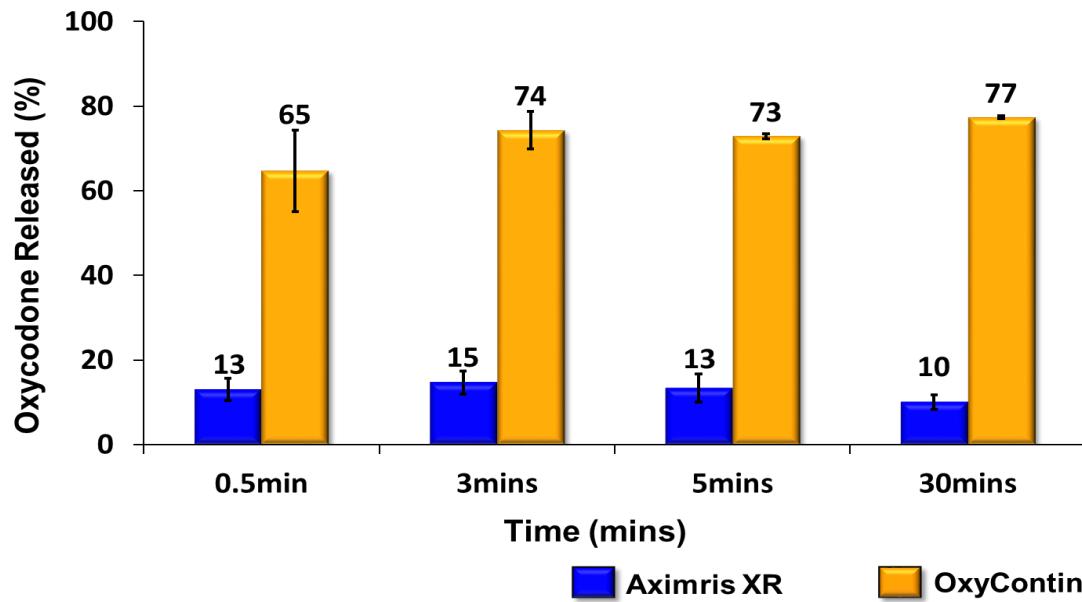
**Figure 41: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 5mL of Neutral Solution at Room Temperature**



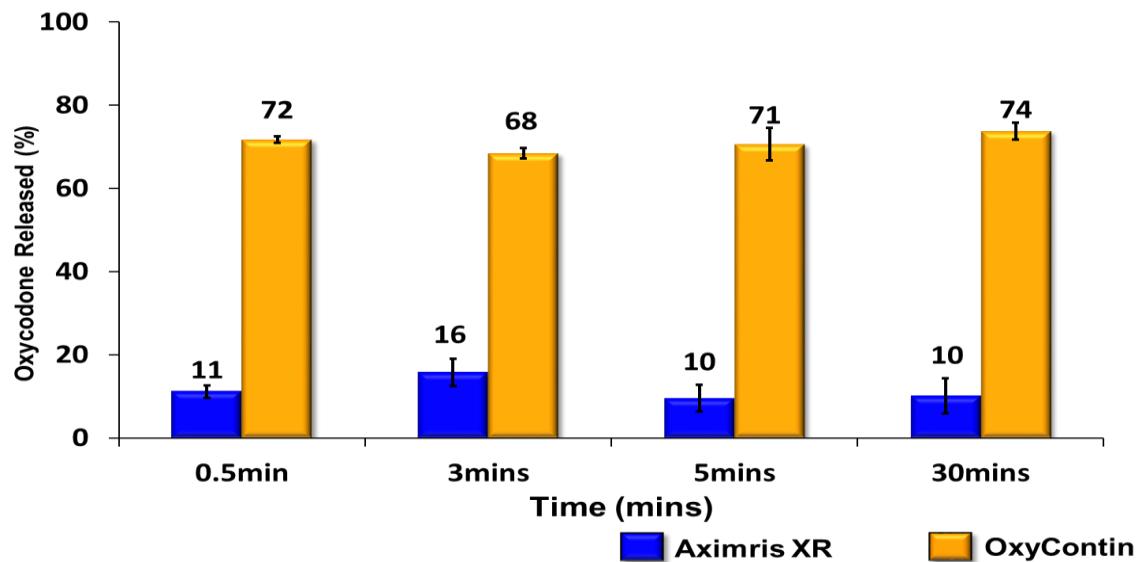
**Figure 42: Drug Extraction from Ground Aximiris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation 5mL of Neutral Solution at Elevated Temperature**



**Figure 43: Drug Extraction from Ground Aximiris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 5mL of Isotonic Solution at Room Temperature**



**Figure 44: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 5mL of Isotonic Solution at Elevated Temperature**



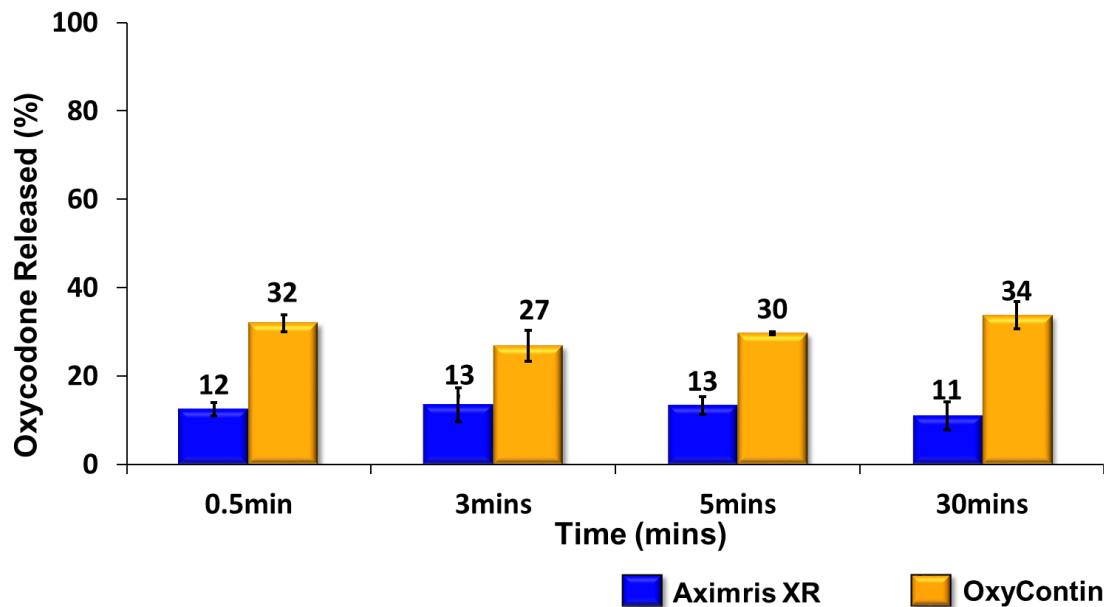
Results obtained using 10mL of solution for extraction of ground tablets pre-treated with convection heat

The amount of oxycodone extracted from ground Aximris XR ranged from 11% in alcoholic solution (at room temperature) to about 29% in neutral solution (at elevated temperature) per label claim. Conversely, for ground OxyContin, high amounts of drug suitable for IV injection were successfully extracted using convection heat pre-treatment and incubated for 0.5 min, 3 min, 5 min or 30 min in 10mL of neutral solution, alcoholic solution and isotonic solution, using the very small needle gauge. Analysis of the syringed solutions from OxyContin yielded injectable oxycodone ranging from 27% in alcoholic solution (at room temperature) to about 82% in neutral solution (at elevated temperature) per label claim.

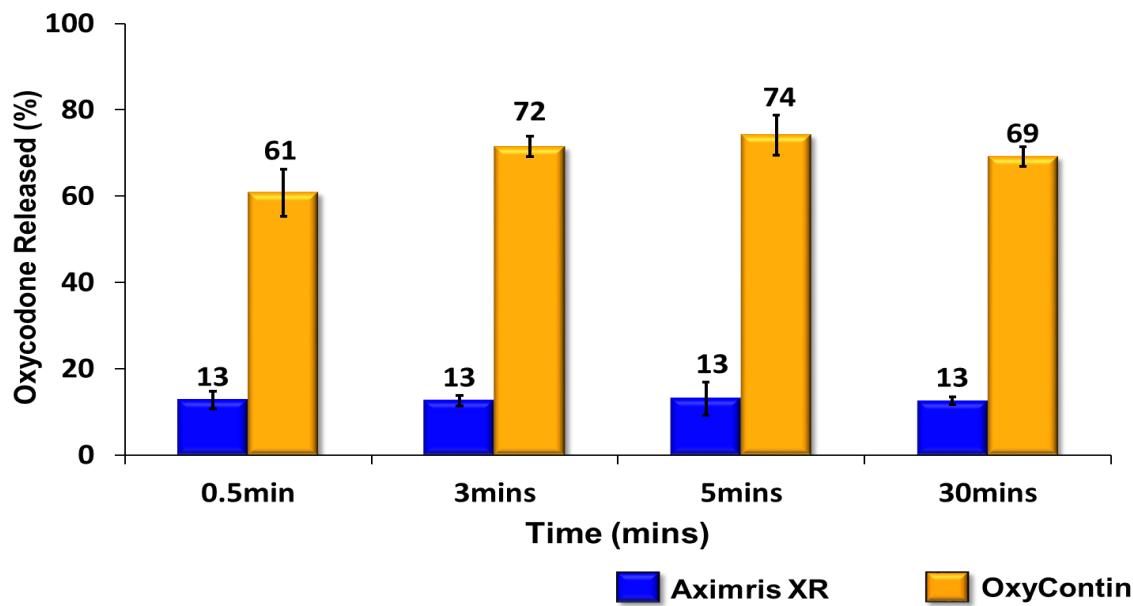
Overall, these studies showed that manipulated ground Aximris XR that had undergone the most stringent condition of convection heat pre-treatment will not be successfully syringed in a small volume of the solvent (10mL) to yield oxycodone that will be enticing to an abuser. This is in contrast to ground OxyContin, which when similarly treated, was successfully syringed in a small volume (10mL) to give ranging from 27% to about 82% of oxycodone suitable for IV injection.

The results are presented graphically in the figures below (**Figures 45 – 50**).

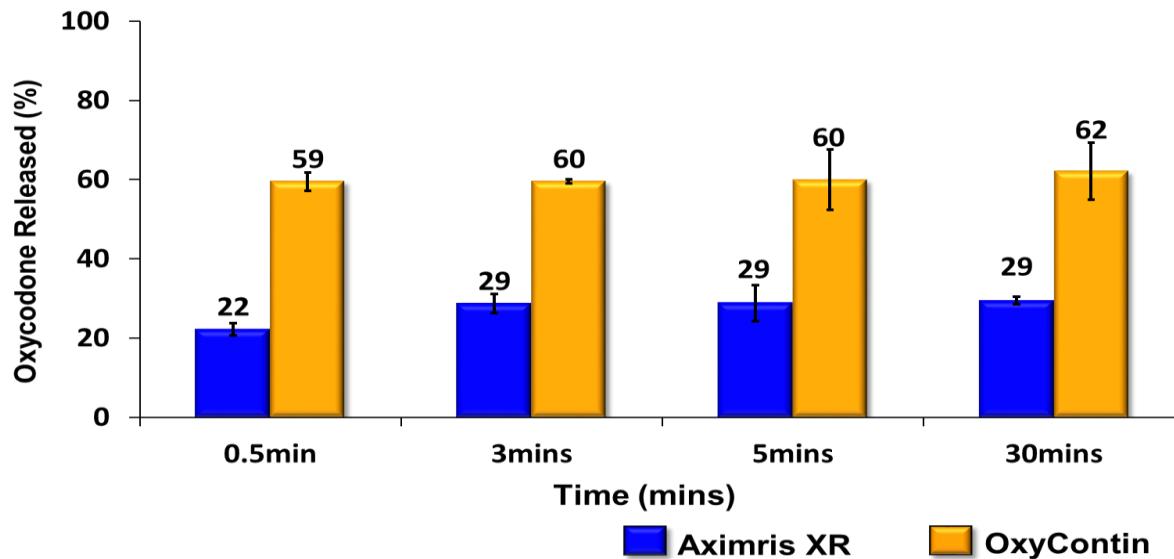
**Figure 45: Drug Extraction from Ground Aximris XR and Oxycontin Tablets Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mLof Alcoholic Solution at Room Temperature**



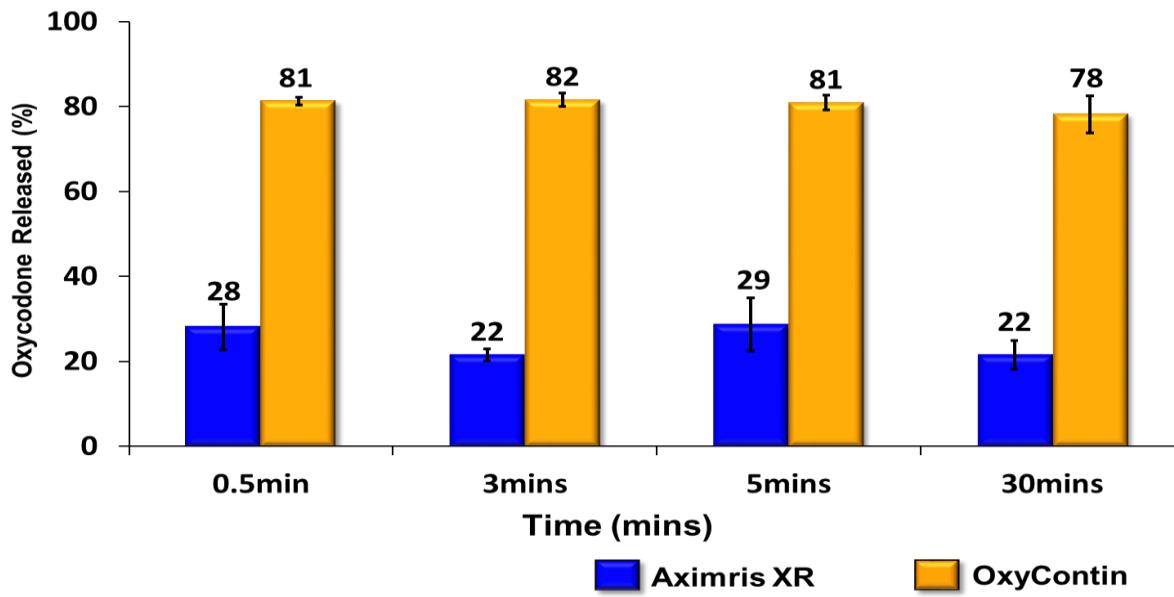
**Figure 46: Drug Extraction from Ground Aximris XR and Oxycontin Tablets Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mL of Alcoholic Solution at Elevated Temperature**



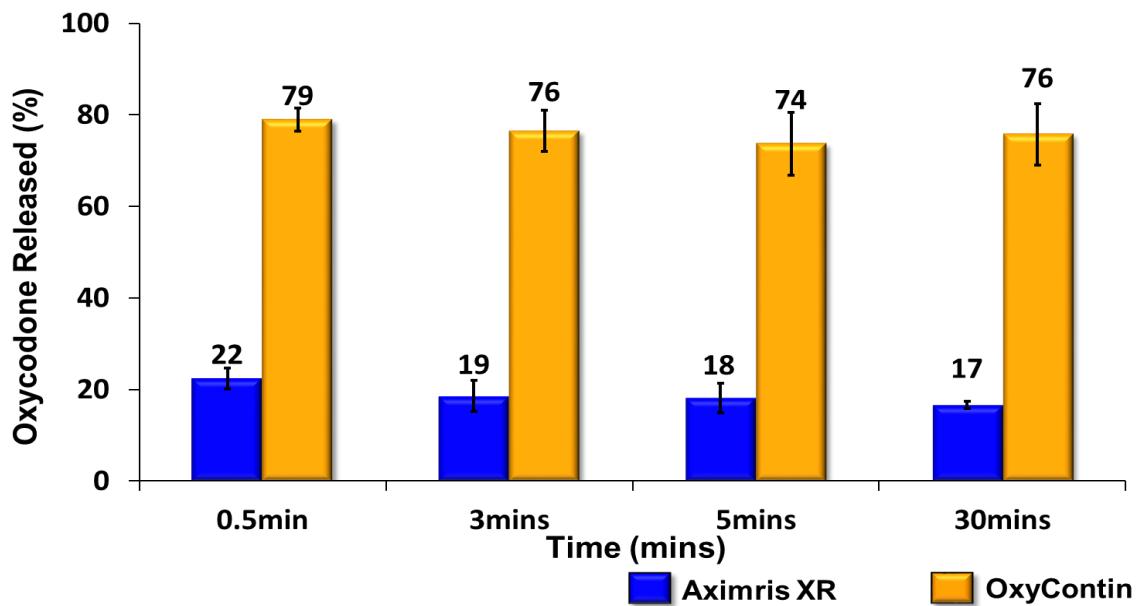
**Figure 47: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mL of Neutral Solution at Room Temperature**



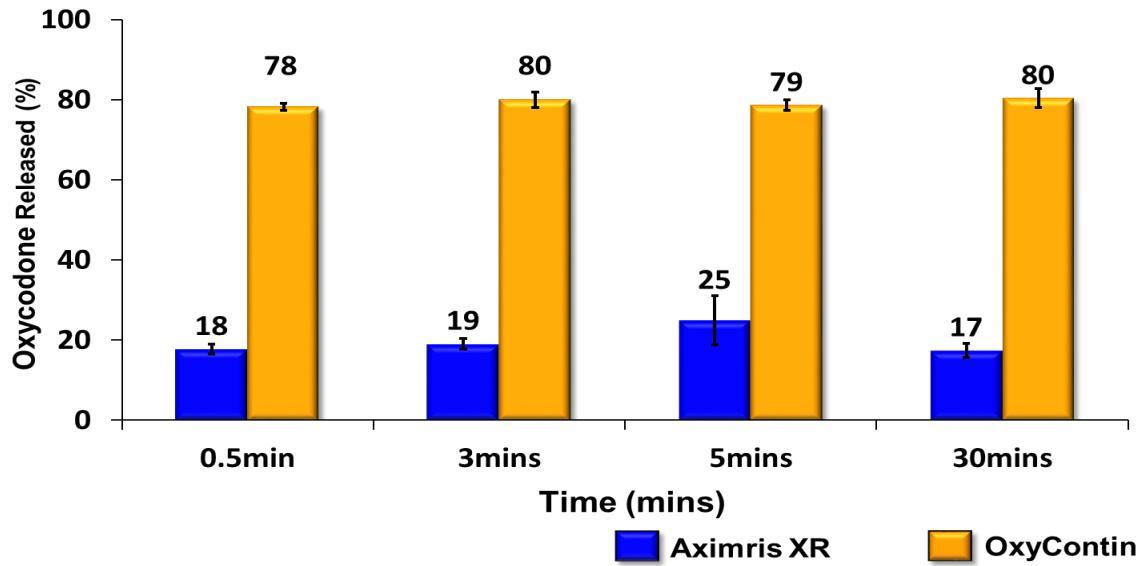
**Figure 48: Drug Extraction from Ground Aximris XR and OxyContin Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mL of Neutral Solution at Elevated Temperature**



**Figure 49: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mL of Isotonic Solution at Room Temperature**



**Figure 50: Drug Extraction from Ground Aximris XR and Oxycontin Tablets, Using Advanced Methods (Convection Heat Pre-treatment), No Agitation, 10mL of Isotonic Solution at Elevated Temperature**



Results obtained using 2mL, 5mL and 10mL of solution for extraction of intact tablets pre-treated with convection heat

When intact Aximris XR and intact OxyContin tablets were manipulated using convection heat pre-treatment, and incubated in neutral solution, alcoholic solution and isotonic solution for 0.5 min, 3 min, 5 min or 30 min and syringed, using the very small gauge needle, the amounts of oxycodone extracted from the intact tablets of Aximris XR and OxyContin were generally too low in all solvents. Incubation in 2mL, 5mL and 10mL of neutral solution (at various time points, 0.5 min to 30 min) showed recovery of oxycodone from intact tablet of Aximris XR ranging from <1% to 6% of the label claim across all platforms while intact tablet of OxyContin was about 2 – 11% of the label claim across the same platforms. The levels of oxycodone extracted using convection heat pre-treatment from intact tablets of Aximris XR and OxyContin are so low in the syringeable liquid such that it is not worth the effort and not likely to be attractive to abusers.

### **5.3.3 Extractability/Syringeability/Injectability From Multiple Tablets of Aximris XR and OxyContin After Convection Heat Pre-treatment, Using Neutral Solution and Hypertonic Solution**

In addition to studies on the syringeability of manipulated single tablet of Aximris XR using convection heat pre-treatment, the Agency recommended that Intellipharmaceutics perform studies on the syringeability/ injectability starting with a single pre-treated tablet and increasing the number of pre-treated tablets in subsequent steps until the solution is no longer syringeable.

Accordingly, the syringeability of multiple tablets of ground and intact tablets of Aximris XR and OxyContin were determined after the products were manipulated using convection heat pre-treatment. Following pre-treatment, the products were mixed with 30mL of either neutral solution or hypertonic solution and subjected to high agitation at elevated temperature for 30 minutes.

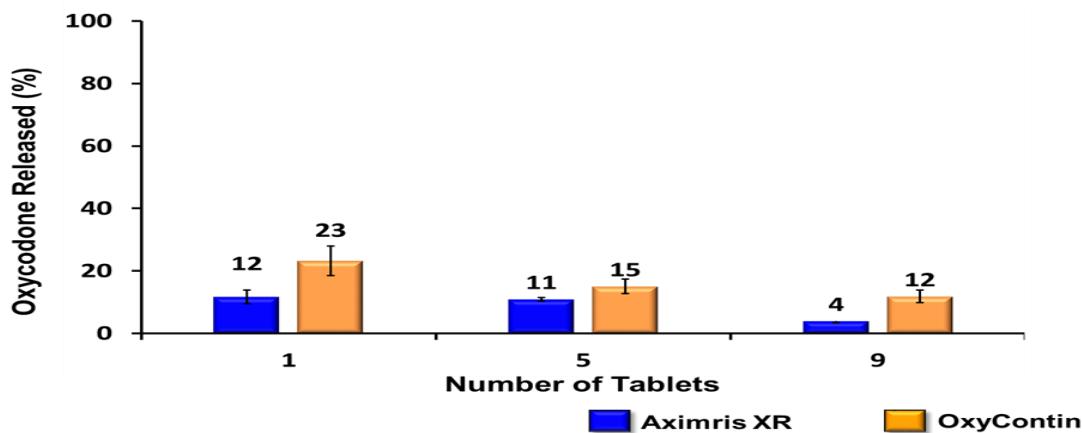
A small rolled piece of cotton (“Q-tip” size) was securely attached to very small gauge needle and attempts were made for up to 2 minutes to load the syringe with the solution from the glass container. All experiments were performed in triplicate.

#### ***Results from neutral solution with intact tablets***

The results show that from intact tablets of OxyContin, 23%, 15%, and 12% of oxycodone were recovered from 1, 5, and 9 tablets respectively, after manipulation using convection heat pre-treatment, and mixing with 30mL of neutral solution and subjecting to high agitation at elevated temperature for 30 minutes.

For intact tablets of Aximris XR, mean recoveries of oxycodone of 12%, 11% and 4% were obtained from 1, 5 and 9 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of neutral solution and subjecting to high agitation at elevated temperature for 30 minutes ([Figure 51](#)).

**Figure 51: Mean Drug Extracted From 1, 5 and 9 Intact Tablets of Aximris XR and OxyContin Using Convection Heat Pre-treatment, Elevated Temperature, in 30mL of Neutral Solution at 30 minutes**



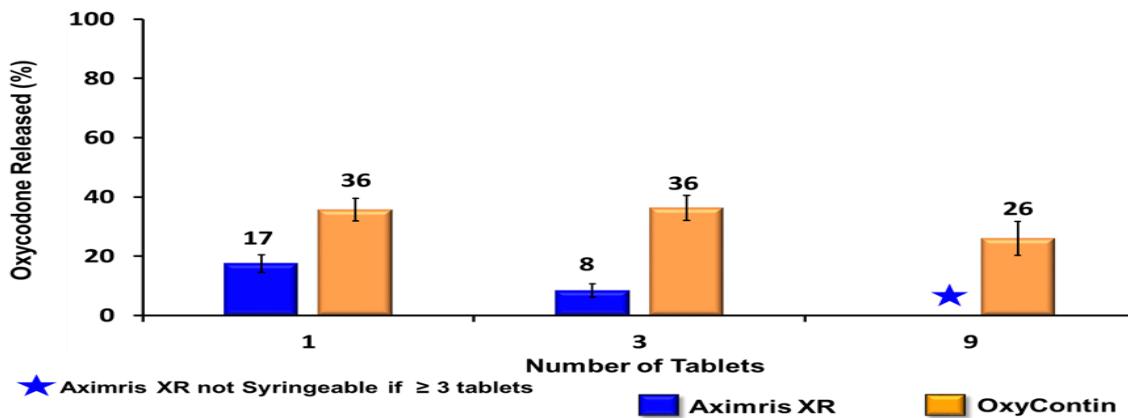
***Results from neutral solution with ground tablet***

The results show that for ground tablets of OxyContin, 36%, 36%, and 26% of oxycodone were recovered from 1, 3, and 9 tablets respectively, after manipulation using convection heat pre-treatment, and mixing with 30mL of neutral solution and subjecting to high agitation at elevated temperature for 30 minutes.

For ground tablets of Aximris XR, mean recoveries of oxycodone of 18% and 8% were obtained from 1 and 3 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of neutral solution and subjecting to high agitation at elevated temperature for 30 minutes.

It was not possible to extract drug from nine manipulated tablets of Aximris XR (**Figure 52**). These results show that for Aximris XR, as the number of tablets increased the amount of drug extractable decreased. Furthermore, less drug (amounts not suitable for IV injection) is extractable from ground Aximris XR compared to ground OxyContin.

**Figure 52: Mean Drug Extracted From 1, 3 and 9 Ground Tablets of Aximris XR and OxyContin Using Convection Heat Pre-treatment, Elevated Temperature, in 30mL of Neutral Solution at 30 minutes**

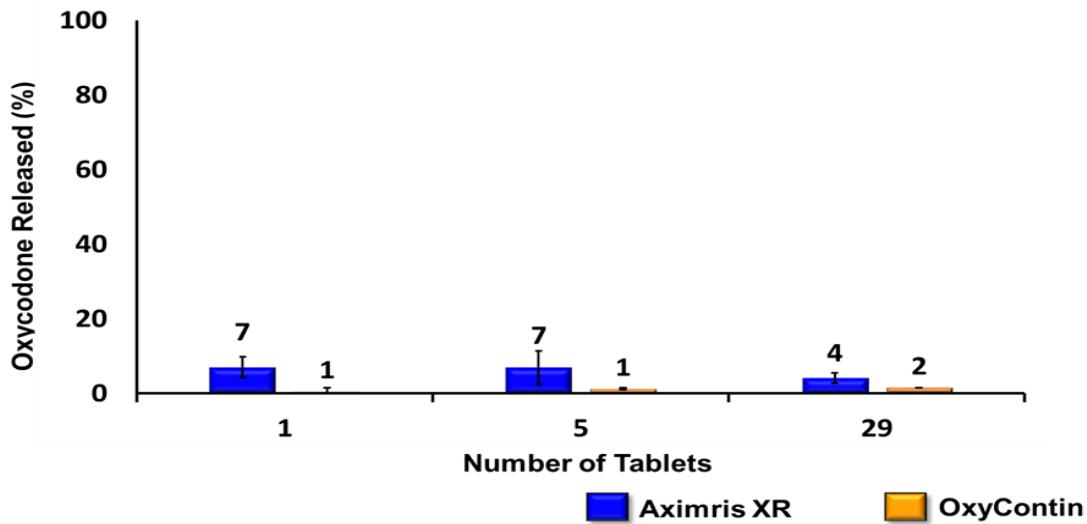


***Results from hypertonic solution with intact tablet***

The results show that for intact tablets of OxyContin, 1%, 1%, and 2% of oxycodone were recovered from 1, 5, and 29 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of hypertonic solution and subjecting to high agitation at elevated temperature for 30 minutes.

For intact tablets of Aximris XR , mean recoveries of oxycodone of 7%, 7% and 4% were obtained from 1, 5 and 9 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of hypertonic solution and subjecting to high agitation at elevated temperature for 30 minutes([Figure 53](#)). The amount of drug extracted from intact tablets of Aximris XR and OxyContin is not suitable for IV injection.

**Figure 53: Mean Drug Extracted From 1, 5 and 29 Intact Tablets of Aximris XR and OxyContin Using Convection Heat Pre-treatment, Elevated Temperature, in 30mL of Hypertonic Solution at 30 minutes**

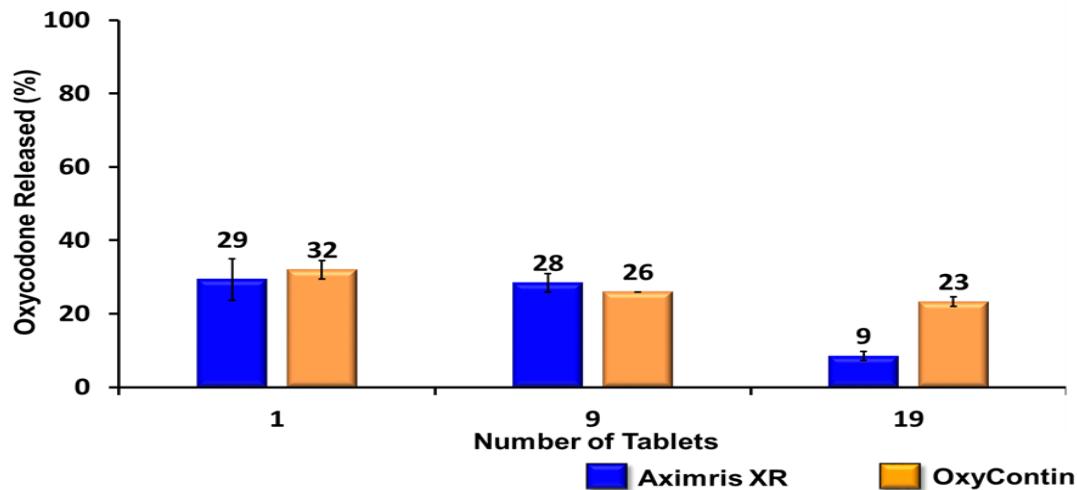
***Results from hypertonic solution with ground tablet***

The results show that for ground tablets of OxyContin, 32%, 26%, and 23% of oxycodone were recovered from 1, 9, and 19 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of hypertonic solution and subjecting to high agitation at elevated temperature for 30 minutes.

For ground tablets of Aximris XR, mean recoveries of oxycodone of 29%, 28% and 9% were obtained from 1, 9, and 19 tablets respectively after manipulation using convection heat pre-treatment, and mixing with 30mL of hypertonic solution and subjecting to high agitation at elevated temperature for 30 minutes.

The amount of drug extracted from ground tablets of Aximris XR and OxyContin are similar for 1 and 9 manipulated tablets while Aximris XR displayed more resistance to extraction as the number of tablets increased to 19 tablets ([Figure 54](#)).

**Figure 54: Mean Drug Extracted From 1, 9 and 19 Ground Tablets of Aximris XR and OxyContin Using Convection Heat Pre-treatment, Elevated Temperature, in 30mL of Hypertonic Solution at 30 minutes**



The difference in behavior between neutral and hypertonic solution is due to differences in ionic effects exhibited by the solvents.

### 5.3.4 Extractability/Syringeability/Injectability of Ground Aximris XR and Ground OxyContin Tablets Based on “Recipes” from Drug Abuse Websites (Radiant Heat Pre-treatment) Using 2mL, 5mL and 10mL of Neutral Solution at Room and Elevated Temperatures.

One of the most common methods cited on drug abuse websites (e.g., bluelight.org) to defeat the IV abuse deterrence property of OxyContin is to perform radiant heat pre-treatment prior to drug extraction. Therefore, radiant heat pre-treatment was applied to ground Aximris XR or ground OxyContin Tablets followed by extraction in 2mL, 5mL, and 10mL of neutral solution and incubation for up to 5 minutes with no agitation at room or elevated temperatures using very small gauge needle to large gauge needle. The results obtained using radiant heat pre-treated Ground Tablet, without agitation at 0.5 minutes in neutral solution and large gauge needle are representative and can be summarized as follows;

#### 2mL at room temperature

The mean oxycodone drug recovered from Aximris XR was 15.0% while that for OxyContin was 73.0%.

#### 2mL at elevated temperature

The mean oxycodone drug recovered from Aximris XR was 43.6% (small gauge needle yielded 15.4%) while that for OxyContin was 57.2% (small gauge needle yielded 65.0%).

### 5mL at room temperature

The mean oxycodone drug recovered from Aximris XR was 20% while that for OxyContin was 85.0%.

### 5mL at elevated temperature

The mean oxycodone drug recovered from Aximris XR was 51.8% (small gauge needle yielded 22.8%) while that for OxyContin was 47.8% (small gauge needle yielded 44.2%).

### 10mL at room temperature

The mean oxycodone drug recovered from Aximris XR was 33.7% (small gauge needle yielded 28.3%) while that for OxyContin was 43.1% (small gauge needle yielded 36.0%).

### 10mL at elevated temperature

The mean oxycodone drug recovered from Aximris XR was 18.5% (small gauge needle yielded 24.3%) while that for OxyContin was 25.6% (small gauge needle yielded 28.1%).

Overall, drug could be extracted from both Aximris and OxyContin. However, Aximris displayed greater resistance to extraction compared to OxyContin.

### **5.3.5 Extractability/Syringeability/Injectability of Three-Dose Equivalent of Ground Aximris XR and Ground OxyContin Using “Recipes” from Drug Abuse Websites (Radiant Heat Pre-treatment)**

Two types of experiments were conducted for Syringeability/Injectability using multiple tablets. In the first experiment, samples of three-dose equivalents of untreated ground Aximris XR Tablet and ground OxyContin Tablets were added into 10mL and 20mL of neutral solution and incubated at room or elevated temperatures for up to 10 minutes with no or high agitation. None of the conditions yielded a suitable amount of injectable oxycodone for either Aximris XR or OxyContin.

In the second experiment, samples of three-dose equivalents of ground Aximris XR and ground OxyContin Tablet, that had undergone radiant heat pre-treatment were added into 10mL and 20mL of neutral solution and incubated at room or elevated temperatures for up to 10 minutes with high agitation.

For ground Aximris XR, no suitable amount of injectable oxycodone was obtained with 10mL and 20mL of neutral solution at room temperature, while 56% and 26% of drug were obtained with ground Oxycontin in 10mL and 20mL, respectively. Additionally, at elevated temperature, Aximris XR could not be syringed to obtain a suitable amount of injectable oxycodone using 10mL of neutral solution while OxyContin yielded 63% of oxycodone. In 20mL of neutral solution, ground Aximris XR yielded 30% while ground OxyContin yielded 60%.

Once again Aximris XR displayed superiority over OxyContin in ability to resist extraction from intact or ground multiple tablets.

### 5.3.6 Gel-blob Syringeability: Aximris XR vs OxyContin

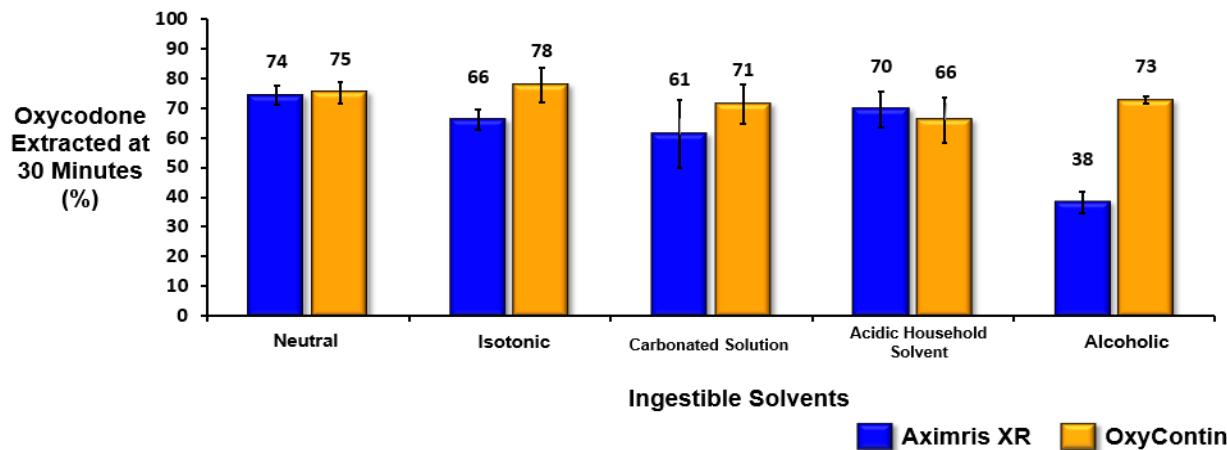
An alternate method for IV abuse involves attempting to overcome the gelling effect of abuse-deterrent products with longer incubation times (i.e., gel-blob syringeability). In this case, an abuser would place a tablet in a liquid for several hours to let the tablet gel in an attempt to get the API to leach from the tablet into the surrounding water, and then the abuser would syringe the liquid around the gel for injection. For this study, ground tablets of Aximris XR and OxyContin were added to 5mL of neutral solution and incubated for 4 and 24 hours at room or elevated temperature. It was not possible to load the syringe with solution from either product with more than 20% volume with large gauge needle at room temperature, while at elevated temperature, it was more difficult to load the syringe with solution for Aximris XR compared to OxyContin.

### 5.4 Large Volume Extraction Studies

Drug extraction in large volumes of solvent may be attempted by abusers to defeat an ER opioid product's intended release profile to speed the rate of drug absorption for oral abuse (i.e., dose dumping). Large volume extraction studies evaluated a variety of common ingestible and advanced non ingestible solvents with different chemical properties (i.e., protic, aprotic, acidic, basic, polar, and non-polar) as recommended by the 2015 FDA Guidance.

The resistance to extraction of manipulated ground tablets of Aximris XR and OxyContin equivalents in large volumes was evaluated in 20 common and advanced solvents, including under stress conditions with modifications to temperature and agitation. Overall, the resistance to large volume extraction was similar for both products. [Figure 55](#) shows the results for the most common ingestible solvents (e.g., neutral solvent, isotonic solvent, carbonated solution, acidic household solvent and alcoholic solvent).

**Figure 55: Extraction Studies of Ground Tablets of Aximris XR and OxyContin in 100mL of Ingestible Solvents at Room Temperature, No Agitation**

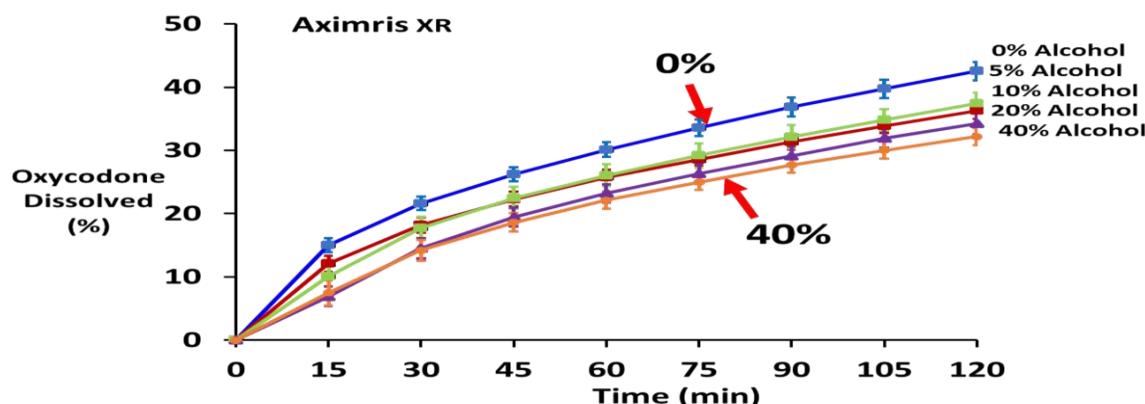


## 5.5 Alcohol Dose Dumping Study

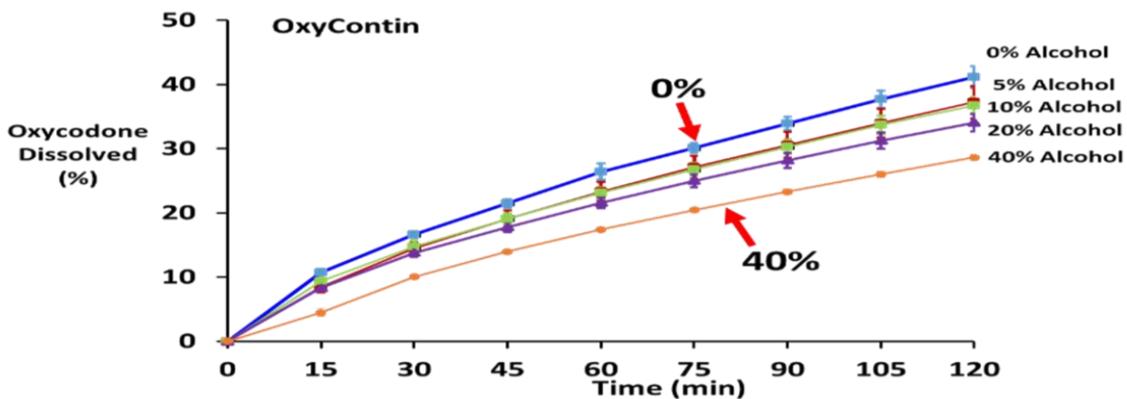
It is well known that some ER opioid formulations may rapidly release drug when co-ingested with alcohol (i.e., alcohol dose dumping), which could possibly cause toxicity, overdose, or death. Accordingly, dissolution testing in the presence of alcohol is needed to assess the potential for dose dumping when an opioid is ingested along with alcohol. To determine if co-ingestion of alcohol with Aximris XR would result in alcohol dose dumping, in vitro dissolution experiments were conducted using different concentrations of alcohol in acidic and basic dissolution media conditions.

The in vitro alcohol dissolution study provides evidence that the co-ingestion of alcohol with Aximris XR would not lead to dose dumping. **Figure 56** illustrates that oxycodone release from Aximris XR decreased as the concentration of alcohol increased just like for OxyContin. Similar results were observed in basic dissolution media condition (**Figure 57**), in which higher alcohol concentrations were associated with slower oxycodone release. Despite the lack of dose dumping with alcohol, Aximris XR, like all opioid products, should not be co-ingested with alcohol.

**Figure 56: Percent Oxycodone Dissolved from Intact Tablet of Aximris XR in Varying Concentrations of Alcohol in Acidic Dissolution Media Conditions**



**Figure 57: Percent Oxycodone Dissolved from Intact Tablets of OxyContin in Varying Concentrations of Alcohol in Basic Dissolution Conditions**



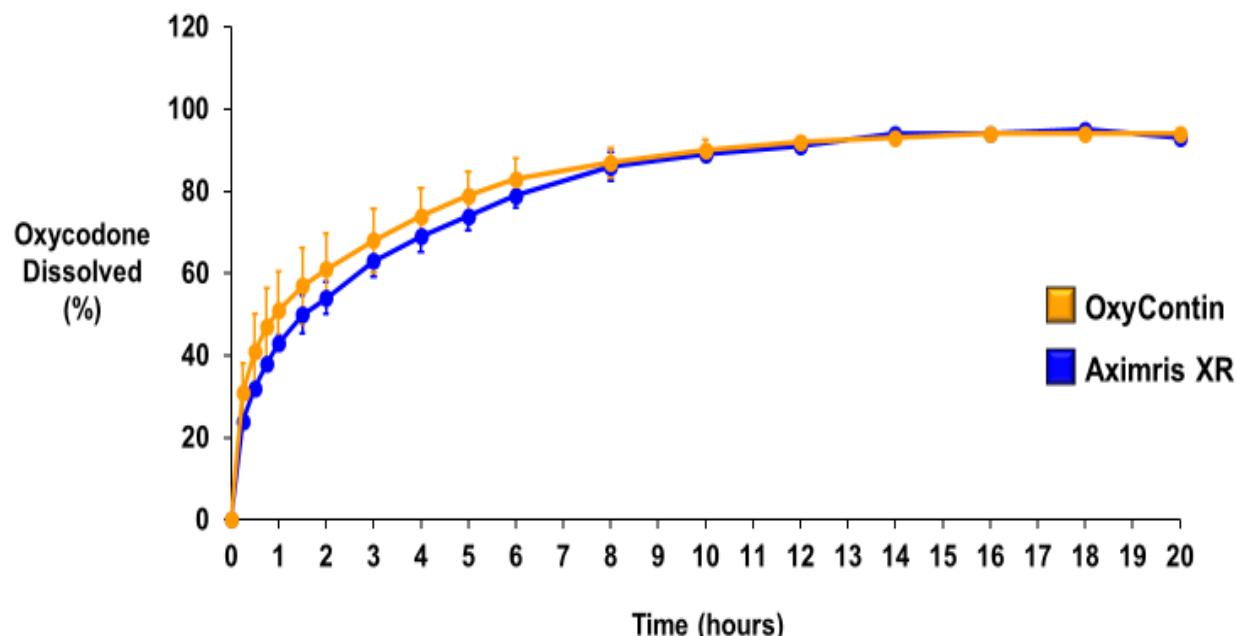
## 5.6 Manipulated Tablet Dissolution Studies

In attempts to speed the release of API in ER opioid formulations, abusers may heat, crush, cut, or grind tablets prior to ingestion. Dissolution studies were designed to evaluate the impact of different types of physical manipulation as well as a common pre-treatment cited on drug abuse websites to defeat abuse-deterring properties on the speed of drug release.

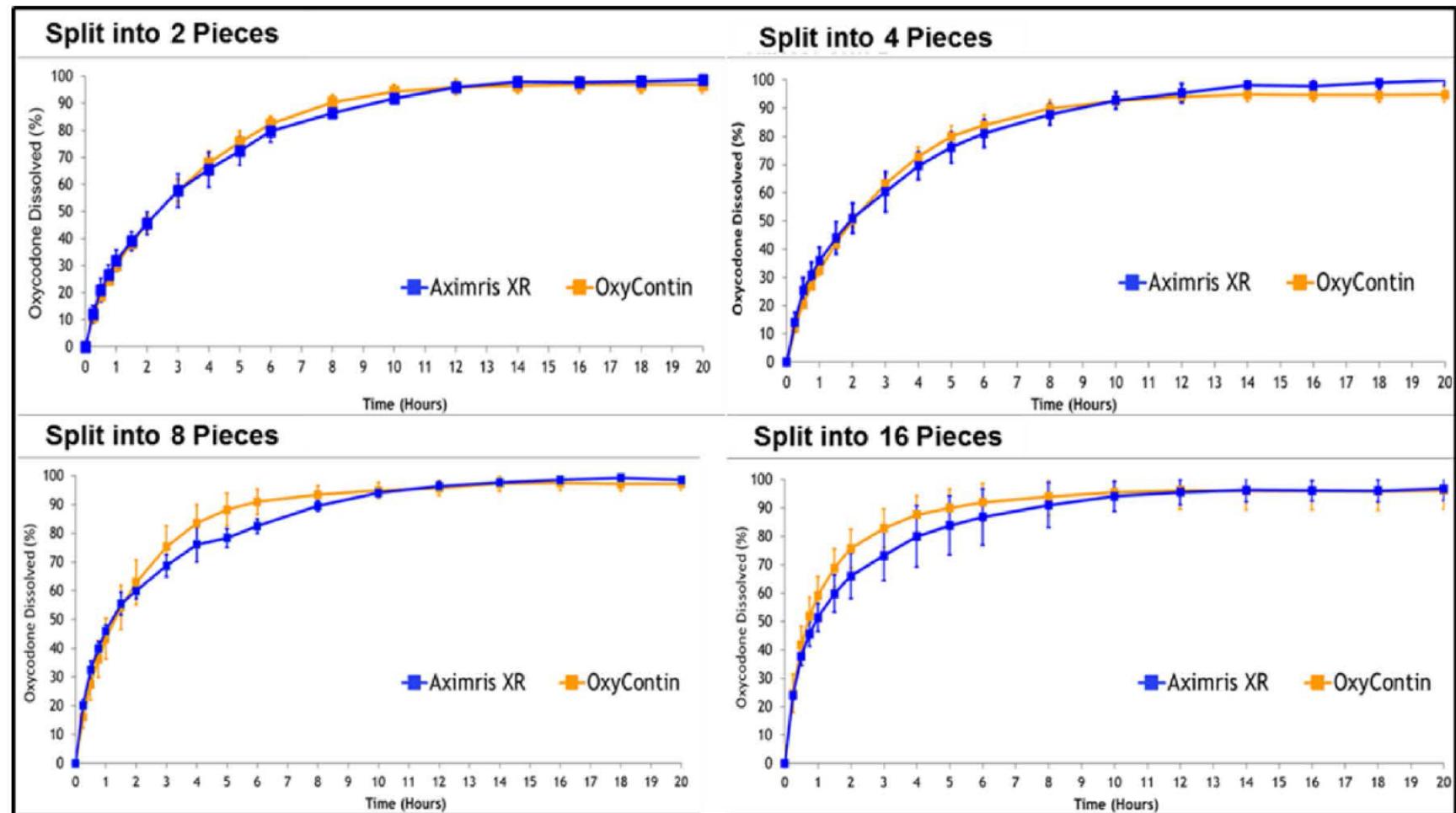
**Figure 58** illustrates the dissolution profiles of ground tablets of Aximris XR and OxyContin, which corresponds to tablets after the optimal particle size reduction procedure, in acidic dissolution media conditions. This demonstrates that the smaller particle size distribution of Aximris XR did not lead to a faster release of oxycodone than from OxyContin. Rather, the smaller particles likely enhanced the viscosity and coagulation properties and slowed oxycodone release at early time points.

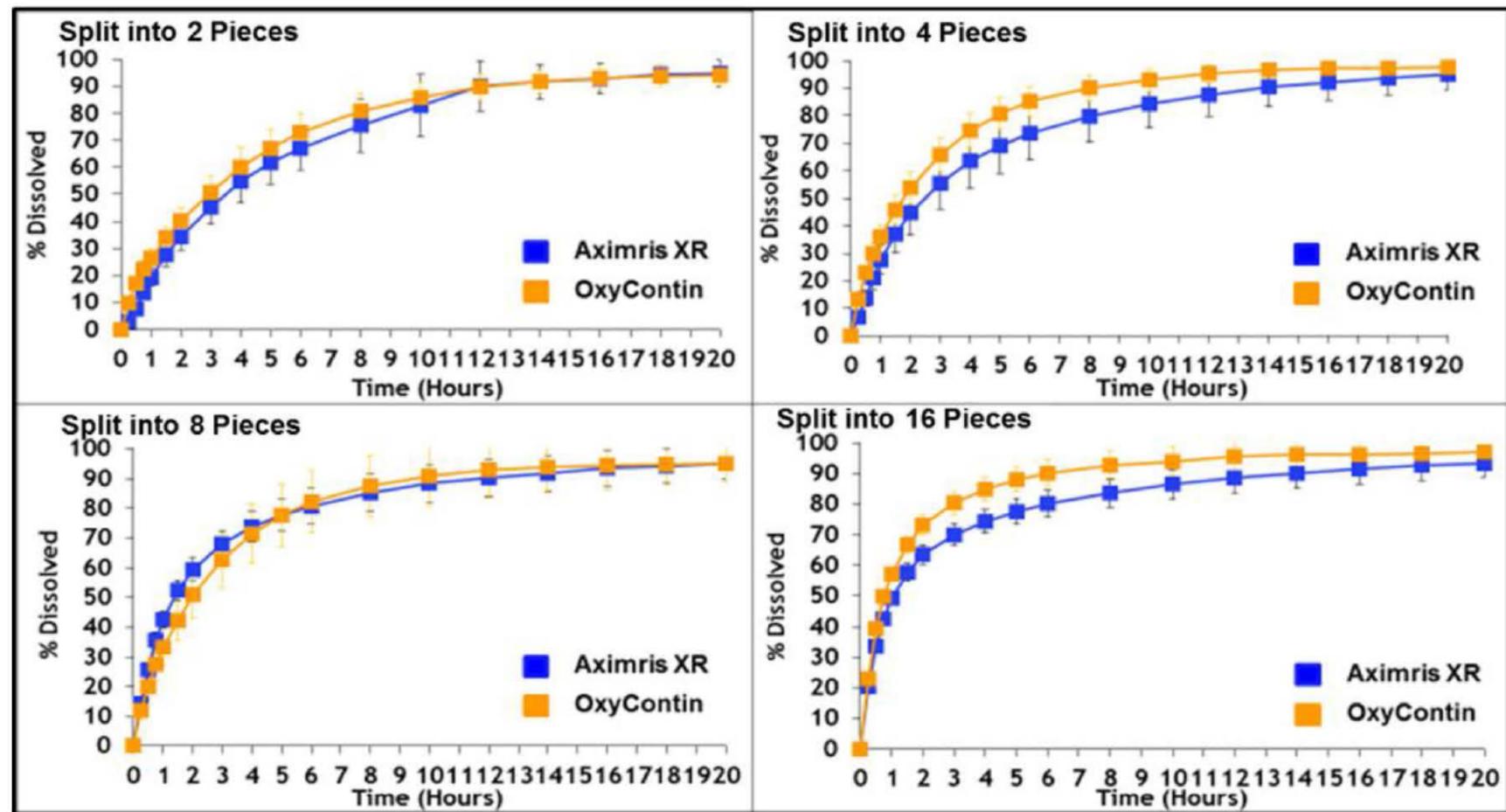
**Figure 59** and **Figure 60** show amount of drug released from Aximris XR and OxyContin tablets ground or split into 2, 4, 8 and 16 pieces using acidic or basic dissolution conditions. The release of oxycodone was similar between the products.

**Figure 58: Dissolution of ground Tablets of Aximris XR and OxyContin in Acidic Dissolution Media Conditions**



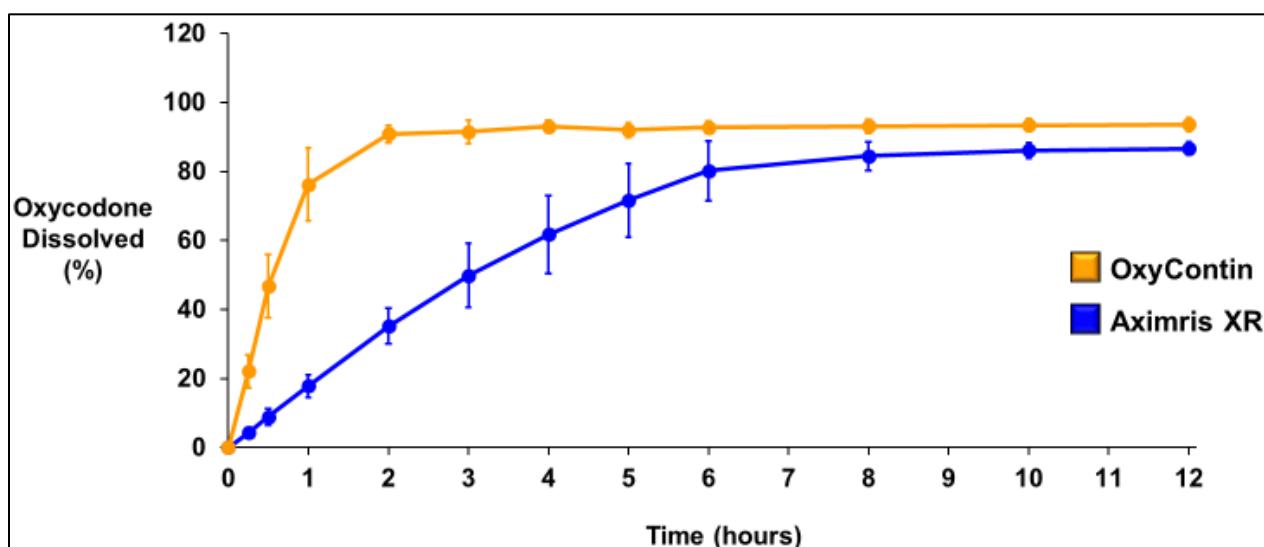
**Figure 59: Comparative Dissolution Profile: Aximris XR vs OxyContin Splitted Tablets in Acidic Dissolution Media Conditions**



**Figure 60: Comparative Dissolution Profile: Aximris XR vs OxyContin Splitted Tablets in Basic Dissolution Media Conditions**


As previously mentioned, common types of pre-treatments used to defeat ADFs (i.e., radiant heat pre-treatment, radiant heat pre-treatment without rotation and radiant heat pre-treatment with rotation) have been identified on drug abuse websites set up to defeat abuse-deterrent properties. **Figure 61** illustrates the dissolution profiles of intact tablets of Aximris XR and OxyContin following radiant heat pre-treatment with rotation in neutral dissolution media conditions. Similar results were observed for radiant heat pre-treatment without rotation. These results demonstrate that Aximris XR is not easily defeated and has greater resistance against pre-treatments known to defeat OxyContin. The release of oxycodone using neutral dissolution media conditions was considerably lower for Aximris XR than for OxyContin, especially in the first 5 hours. For example, using radiant heat pre-treatment with rotation, less than 20% of drug was released in 1 hour for Aximris XR compared to over 75% drug released for OxyContin (**Figure 61**). These results are also consistent with the results of syringeability/injectability experiments where the abuse-deterrent properties of OxyContin were compromised to a greater extent than Aximris XR following radiant heat pre-treatment, while Aximris XR remained more resistant to extraction.

**Figure 61: Dissolution of Intact Tablets of Aximris XR and OxyContin Following Radiant Heat Pre-treatment With Rotation in Neutral Dissolution Media Conditions**



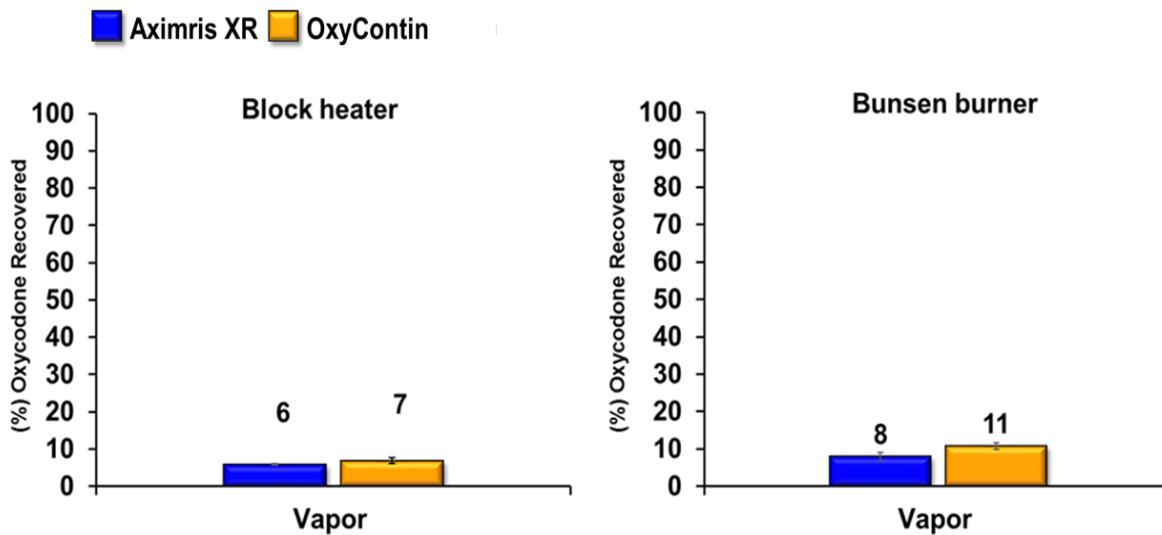
## 5.7 Simulated Smoking/Vaporization Studies

Vaporization may be attempted by abusers for the smoking route of administration. Most accounts of opioid smoking on drug abuse websites generally follow the patterns described for opium and heroin (e.g., inhaling vapors produced by heating drug on foil). The preparation procedure for smoked opioids includes crushing or cutting tablets into chunks followed by placing the ground material or chunks on foil with application of intense heat to the underside. The heat melts and chars the ground material or chunks, and some drug may be vaporized. Abusers will attempt to inhale the vapor above the foil with straws or other hollow instruments.

A standardized procedure using oxycodone (base) and oxycodone HCl (salt) was developed and used in the simulated smoking/inhalation procedure for Aximris XR and OxyContin. The temperatures and times selected for these studies were based on an exploratory study with pure API to determine the optimal heating time and temperature.

Vaporization of either Aximris XR or OxyContin using optimal conditions with a block heater produced approximately 7% oxycodone in vapor. Applying direct heat with a Bunsen burner yielded 10% oxycodone recovery from Aximris XR and 11% from OxyContin. Neither method would be considered an efficient route of abuse for Aximris XR or OxyContin ([Figure 62](#)).

**Figure 62: Simulated Smoking Using Optimal Temperature (Block Heater) and Extreme Temperature (Bunsen Burner)**



## 6 HUMAN ABUSE LIABILITY (HAL) STUDIES

To study the pharmacokinetics (Category 2) and clinical abuse potential (Category 3) of Aximris XR when manipulated for abuse via the oral and intranasal routes, Intellipharmaceutics conducted a complete assessment of abuse-deterrent properties in two HAL studies. The design of these studies is in accordance with the 2015 FDA Guidance on abuse deterrent opioids and was further agreed upon with the Agency in the February 2018 Type A Post-Action meeting. The test substances for the HAL studies were either ground using Tool 10 or crushed using Tool 3.

### 6.1 Intranasal HAL Study

The misuse, abuse, and diversion of controlled prescription opioid analgesics, such as oxycodone, are significant public health issues in the US (SAMHSA, 2014). Among the more experienced non-medical users, intranasal insufflation (“snorting”) is the most common non-oral route of administration, followed by injection (Hays et al., 2003). Therefore, this study was designed to examine the abuse potential and PK of Aximris XR when it is ground and administered intranasally compared to oxycodone immediate-release tablets (a non-abuse-deterrent oxycodone product), OxyContin (an abuse-deterrent oxycodone product), and placebo.

This study was a single-dose, randomized, double-blind, active- and placebo-controlled, 5-way crossover study in non-dependent, recreational opioid users. The five treatment arms were Aximris XR 30 mg tablets ground, Oxycodone IR 30 mg crushed, Oxycodone ER 30 mg tablets ground, placebo matched to Aximris XR tablet ground; and placebo to match oxycodone IR tablets crushed/Oxycodone ER 30 mg tablets ground. A total of 33 subjects were randomized into the treatment phase, and 30 subjects completed the planned treatments.

Plasma oxycodone concentrations were measured following administration of each drug at various time points over 24 hours. Drug liking was measured on a bipolar drug liking scale of 0 to 100, where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100, where 50 represents a neutral response, 0 represents the strongest negative response (“definitely would not take drug again”), and 100 represents the strongest positive response (“definitely would take drug again”). Ease of snorting each manipulated drug (or placebo) was measured on a bipolar scale of 0 to 100, where 50 represents a neutral response of neither being easy or difficult to snort, 0 represents maximum difficulty, and 100 represents maximum ease. In addition, adverse events for each group were recorded during the course of the study.

#### 6.1.1 Plasma Oxycodone Concentrations (Intranasal Study)

The plasma concentrations of oxycodone resulting from administration of Aximris XR, ground, Oxycodone IR, crushed, and OxyContin, ground were measured over 24 hours. **Table 5** shows the comparative pharmacokinetics of Oxycodone following intranasal administration of Aximris XR Tablets Ground versus OxyContin Ground versus Oxycodone HCl IR Tablets – Crushed. Mean peak concentrations were achieved rapidly following intranasal administration of oxycodone IR, crushed, Aximris XR and OxyContin, ground. Peak and early exposure to oxycodone were significantly higher for Aximris XR, ground, compared with oxycodone IR

crushed. Although  $C_{max}$  and partial AUCs were significantly higher for Aximris XR, the overall exposure for Aximris XR was similar to those of OxyContin ground and Oxycodone IR crushed.

OxyContin ground was no better than oxycodone IR crushed, and it had the same peak and early exposure to oxycodone compared to oxycodone IR crushed.

**Table 5: Comparative Pharmacokinetics of Oxycodone Following Intranasal Administration of Aximris XR Tablets Ground versus OxyContin Ground versus Oxycodone HCl IR Tablets - Crushed**

	Arithmetic Mean Parameters (SD)						
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)*	AUC <sub>0-1h</sub> (ng*hr/mL)	AUC <sub>0-2h</sub> (ng*hr/mL)	AUC <sub>0-last</sub> (ng*hr/mL)	AUC <sub>0-inf</sub> (ng*hr/mL)	t <sub>1/2</sub> (hr)
Aximris XR Tablets 30 mg, Ground (N=31)	92.01 (21.80)	0.5 (0.25 – 2.00)	70.52 (16.52)	147.73 (32.17)	579.57 (136.93)	589.37 (140.17)	4.00 (0.48)
OxyContin 30 mg, Ground (N=32)	55.55 (14.42)	1 (0.25 - 3.00)	39.81 (12.47)	91.38 (25.29)	520.97 (100.11)	549.02 (101.73)	5.30 (1.46)
Oxycodone IR 30 mg, Crushed (N=32)	55.42 (11.38)	2 (0.25 – 6.00)	31.91 (9.91)	74.67 (21.78)	453.55 (88.62)	465.73 (93.17)	4.25 (0.59)

\*Presented as median and range

### 6.1.2 Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> (Intranasal Study)

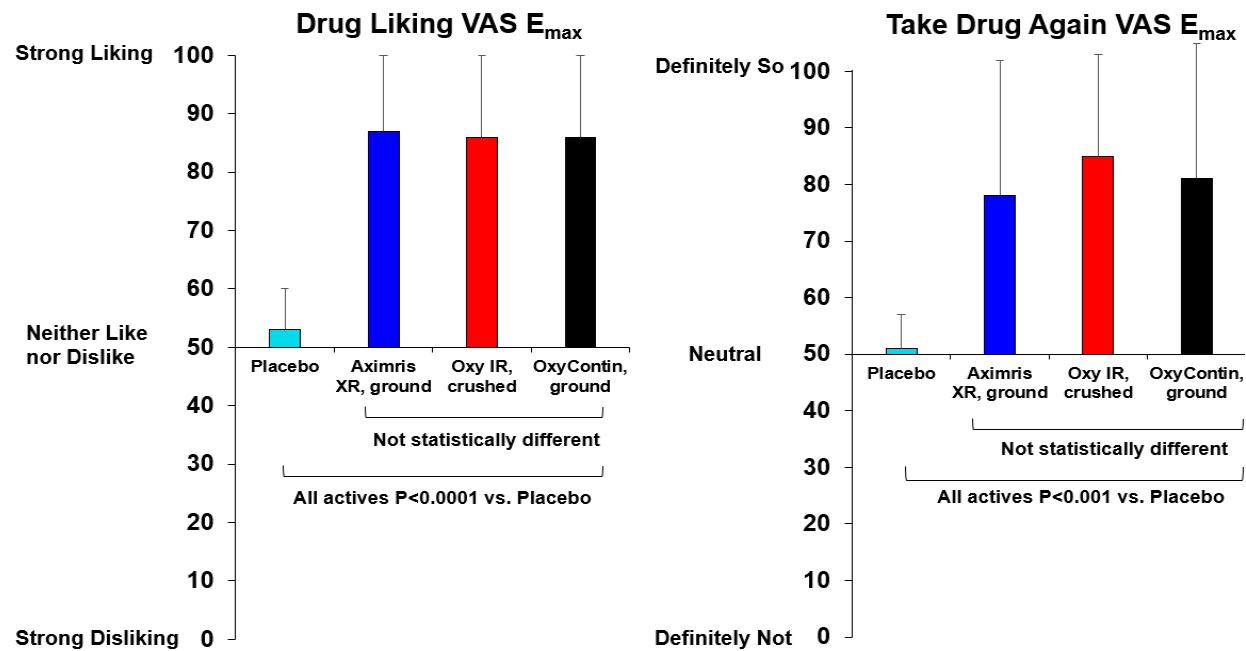
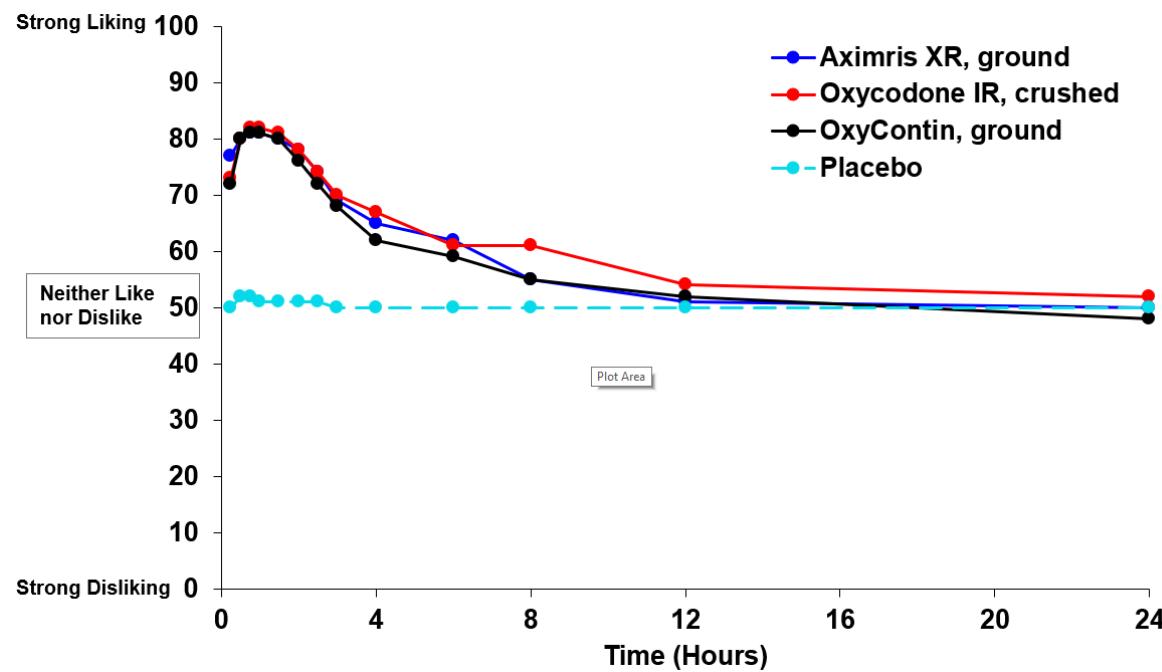
Selected descriptive statistics of Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> are provided in **Table 6** (and are provided graphically in **Figure 63**), and graphical representations of the mean drug liking and take drug again VAS scores over time are provided in **Figure 64**, **Figure 65** and **Figure 66**. Mean and median Drug Liking VAS E<sub>max</sub> values were high (>85) and similar for Aximris XR, ground, OxyContin, ground, and oxycodone IR, crushed. Both placebos had E<sub>max</sub> values near neutral (50). A similar pattern was observed for Take Drug Again VAS E<sub>max</sub>. Over time, Drug Liking VAS scores for Aximris XR, ground, OxyContin, ground, and oxycodone IR, crushed were similar.

Examination of individual Drug Liking VAS E<sub>max</sub> data showed that, overall, most subjects responded appropriately to both placebos (i.e., 26 out of 30 subjects had scores 40 to 60) and to oxycodone IR, crushed (i.e., 27 out of 30 subjects had scores >70). Similarly, most subjects responded appropriately on Take Drug Again VAS to both placebos (28 out of 30 subjects scored <60) and oxycodone IR, crushed (i.e., 23 out of 30 subjects had scores >75). Although a few subjects showed erroneous responses to a control, it is not uncommon to see a few sporadic responses in studies of this type. Aximris XR has numerically better Take Drug Again VAS E<sub>max</sub> than OxyContin while Drug Liking VAS E<sub>max</sub> score was similar between Aximris XR and OxyContin (**Table 6**, **Figure 63** and **Figure 64**).

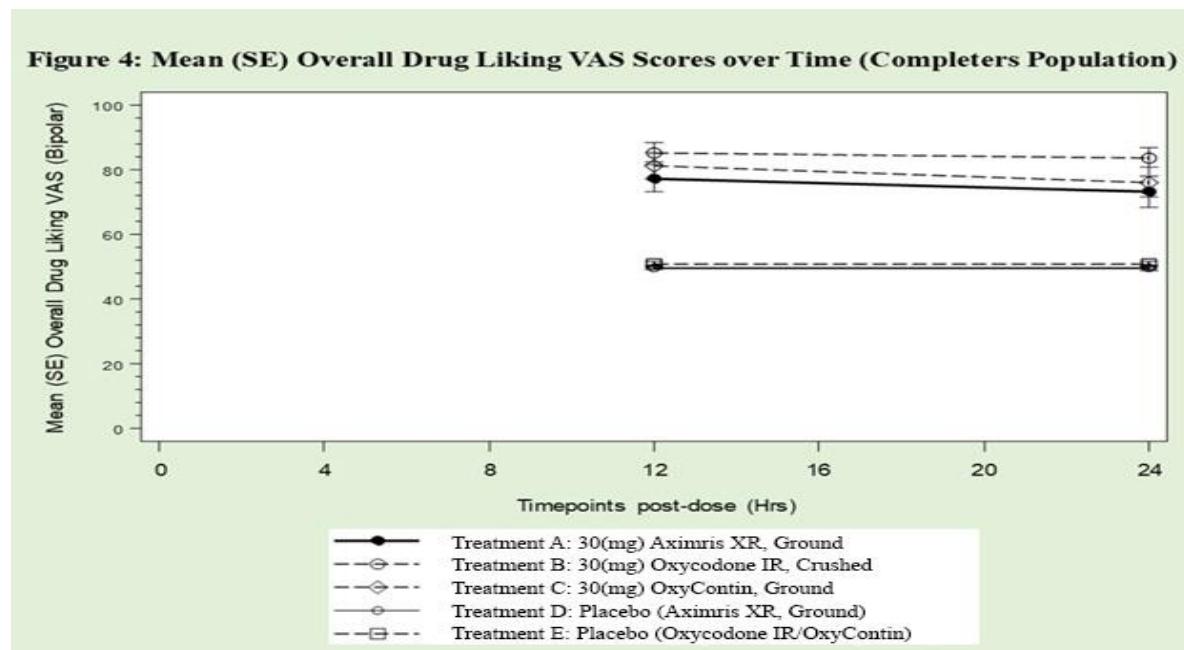
**Table 6: Selected Descriptive Statistics of Drug Liking VAS Emax and Take Drug Again VAS Emax (Completers Population) – Intranasal Study**

Statistic	AXIMRIS XR 30 mg, Ground (N=30)	OxyContin 30 mg, Ground (N=30)	Oxycodone IR 30 mg, Crushed (N=30)	Placebo (Aximris XR) (N=30)	Placebo (Oxycodone IR/Aximris XR) (N=30)
<b>Drug Liking VAS</b>					
Mean (SD)	87 (13)	86 (14)	86	51 (4)	53 (7)
Median	88.0	89.0	87.5	50.0	50.0
Range	50 – 100	50 – 100	50 - 100	50 – 69	50 – 81
<b>Take Drug Again VAS</b>					
Mean (SD)	78 (24)	81 (24)	85 (18)	49 (8)	51 (6)
Median	89.5	90.5	92	50.0	50.0
Range	0 – 100	1 – 100	41 - 100	8 – 63	50 – 83

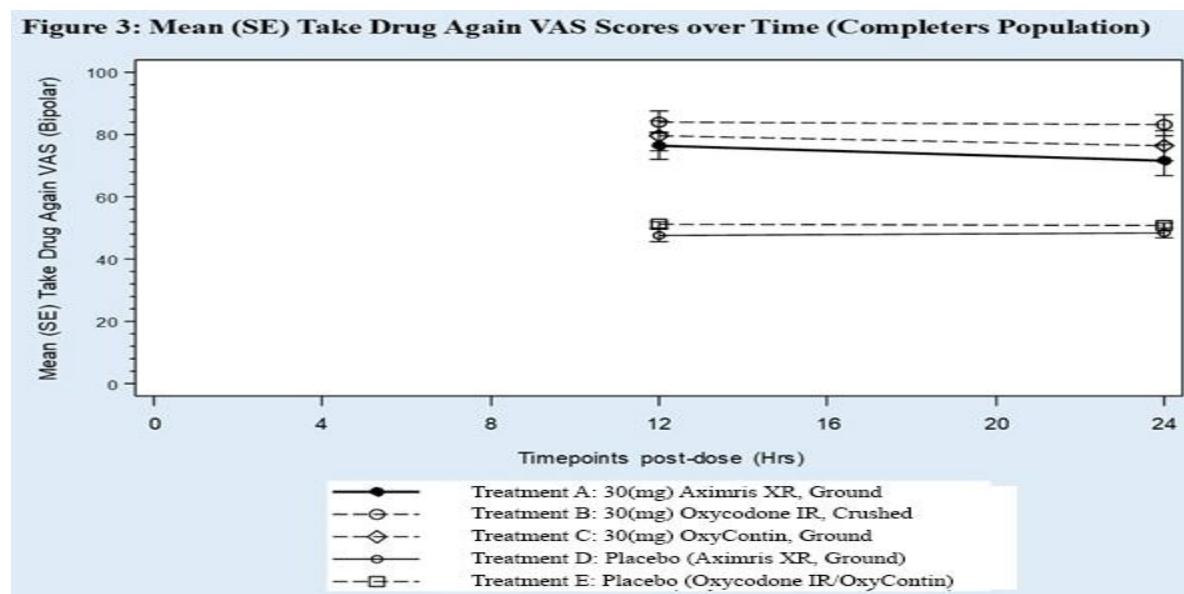
E<sub>max</sub>=maximum effect; ER=extended-release; IR=immediate-release; range=minimum – maximum; SD=standard deviation; VAS=visual analog scale

**Figure 63: Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> – Intranasal Study**

**Figure 64: Mean Drug Liking VAS Scores Over Time – Intranasal Study**


**Figure 65: Mean ( $\pm$  Standard Error (SE)) Overall Drug Liking VAS Scores Over Time (Completers Population) – Intranasal Study**



**Figure 66: Mean ( $\pm$  Standard Error (SE)) Take Drug Again VAS Scores Over Time (Completers Population) – Intranasal Study**



Based on the co-primary and secondary PD endpoints, the abuse potential of both Aximris XR and OxyContin (an approved abuse-deterrent formulation), when ground and administered via the intranasal route, are similar and did not significantly differ from that of oxycodone IR, crushed, (a non-abuse-deterrent formulation), in non-dependent, recreational opioid users. Aximris XR ground is numerically better than OxyContin ground in the Overall Drug Liking VAS scores over time and Take Drug Again VAS scores over time (completers population). See [Figures 65](#) and [66](#).

### 6.1.3 Ease of Snorting (Intranasal Study)

Mean values (assessed via a VAS scale) of the ease of snorting of Aximris XR, ground, compared to placebo, Oxycodone IR, crushed, and OxyContin, ground, is depicted in [Figure 67](#). Aximris XR, ground, was rated to be more difficult to insufflate compared with OxyContin ground and Oxycodone IR crushed. This difficulty in snorting is expected to make intranasal abuse of Aximris XR unattractive and in so doing provide abuse deterrence via the intranasal route.

Descriptive statistics of ease of snorting VAS at 5 minutes postdose and inferential analysis indicate that mean and median scores were highest for oxycodone IR, crushed (mean: 85), followed by placebo matched to oxycodone IR/OxyContin (79) and OxyContin, ground (76). Scores were lowest for Aximris XR, ground (39), and placebo matched to Aximris XR (36), indicating that Aximris XR and placebo matched to Aximris XR were more difficult to insufflate.

The overall treatment effect for ease of snorting VAS at 5 minutes postdose was statistically significant ( $p<0.0001$ ); there was a main effect of sequence ( $p=0.0003$ ). Analysis results indicated that Aximris XR, ground, was significantly more difficult to insufflate compared with oxycodone IR, crushed, OxyContin, ground, and placebo matched to oxycodone IR/OxyContin ( $p<0.0001$ ), but not statistically different from placebo matched to Aximris XR ([Table 7](#)).

OxyContin, ground, was also significantly more difficult to insufflate compared with oxycodone IR, crushed. There were no statistical differences in ease of snorting scores between oxycodone IR, crushed, and placebo matched to oxycodone IR/OxyContin, and no difference between OxyContin, ground and placebo matched to oxycodone IR/OxyContin.

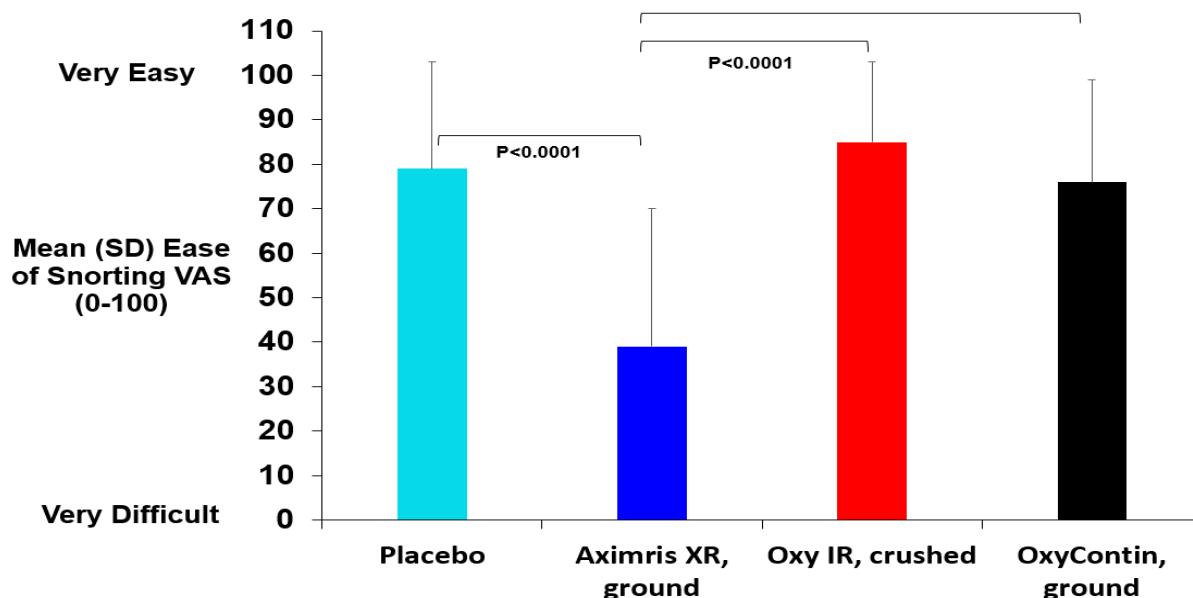
**Table 7: Inferential Analysis Results for Ease of Snorting at 5 Minutes Postdose (Completers Population)**

Pairwise Comparisons	$E_{\max}$		
	LS Mean Difference	95% CI	P-value
<i>Study Validity</i>			
Oxycodone IR, crushed – Placebo (IR/OxyContin)	7.09	-2.51, 16.69	0.9285
<i>Abuse Deterrence</i>			
Aximris XR, ground – Oxycodone IR, crushed	-47.3	-60.6, -34.0	<0.0001
<i>Other Comparisons</i>			
OxyContin, ground – Oxycodone IR, crushed	-11.2	-19.8, -2.51	0.0065
Aximris XR, ground – OxyContin, ground	-36.2	-50.5, -21.8	<0.0001
Aximris XR, ground – Placebo (IR/OxyContin)	-40.2	-55.2, -25.3	<0.0001
Aximris XR, ground – Placebo (Aximris XR)	2.50	-13.3, 18.30	0.6241
OxyContin, ground – Placebo (IR/OxyContin)	-4.08	-15.2, 7.02	0.2313

Source: Table 14.2.3.132 - study report # OXC3/2/0816

CI=confidence interval;  $E_{\max}$ =maximum effect, XR=extended-release; IR=immediate-release; LS=least square

A mixed effect analysis of variance (ANOVA) model was used. The model included treatment, period and treatment sequence as fixed effect, and subject nested within treatment sequence as a random effect. Since the carryover effect was found to be significant at alpha=0.25, this effect was added into the analysis model.

**Figure 67: Mean Ease of Snorting VAS Scores – Intranasal Study**


## 6.1.4 Safety Results (Intranasal Study)

### TEAEs

As described in **Section 6.1.1**, mean peak concentrations were achieved rapidly following intranasal administration of oxycodone IR, crushed, Aximris XR and OxyContin, ground. While the peak and early exposure to oxycodone were significantly higher for Aximris XR, ground, compared with oxycodone IR crushed, the highest incidence of TEAEs was observed with Aximris XR, ground, compared with the other treatments. The majority of subjects experienced TEAEs of mild severity, and no subject experienced a serious adverse event (SAE). One subject was discontinued from the study due to a TEAE following administration of Aximris XR, ground.

Notably, Aximris XR, ground, was associated with a higher incidence of TEAEs of nausea and dizziness compared with oxycodone IR, crushed.

### Subject-Rated Assessment of Intranasal Irritation (SRAII)

The subject-rated assessment of intranasal irritation (SRAII) was used to assess subjective effects of insufflating the study drug. The SRAII was derived based on the Sino-Nasal Outcome Test-20 (SNOT-20) and the FDA Guidance on the evaluation of abuse-deterrent opioids (Baumann et al., 2007; FDA, 2015).

Intranasal irritation was rated by subjects on a 6-point scale (0=not observed/no problem, 1=very mild problem, 2=mild/ slight problem, 3=moderate problem, 4=severe problem, 5=very severe problem/“as bad as it can be”). Assessments were based on 5 categories:

- Burning
- Need to blow nose
- Runny nose/nasal discharge
- Facial pain/pressure
- Nasal congestion

For SRAII measures of Burning, Need to Blow Nose, Runny Nose/Nasal Discharge and Facial Pain/Pressure, the majority of subjects reported 0 across all timepoints for each treatment.

A larger proportion of subjects reported scores of 1 (very mild problem) through 3 (moderate problem) at early timepoints (e.g., up to 2 hours postdose) following administration of Aximris XR, ground, and placebo matched to Aximris XR compared with the other treatments on Burning, with a higher proportion of subjects continuing to report scores of 1 or 2 (mild/ slight problem) up to 8 hours postdose.

A similar pattern of effects was observed for Facial Pain/Pressure and Nasal Congestion, with an even higher proportion of subjects scoring 3 through 5 (very severe problem) following placebo matched to Aximris XR.

For Need to Blow Nose, a higher proportion of subjects reported scores of 1 through 4 following administration of Aximris XR, ground, compared with oxycodone IR, crushed, during the early time course (e.g., up to 3 hours postdose), and positive scores persisted up to 8 hours postdose. A similar pattern of scores was observed following placebo matched to Aximris XR as well as following OxyContin, ground, though for OxyContin, scores were generally lower. Response on Need to Blow Nose varied quite a bit following placebo matched to oxycodone IR/OxyContin, though most subjects reported 0 or 1 throughout the assessment period.

For Runny Nose/Nasal Discharge, there was no notable difference in the proportion of subjects responding positively across active treatments; however, a larger proportion of subjects scored 2 or 3 following placebo matched to Aximris XR.

Selected descriptive statistics of SRAII E<sub>max</sub> are provided in **Table 8**. Median E<sub>max</sub> values for all SRAII measures were 0 for oxycodone IR, crushed, indicating that overall, no problems were experienced following insufflation of oxycodone IR, crushed. Similar results were observed for the placebo matched to oxycodone IR/OxyContin, with the exception of very mild effects (median score=1) on Need to Blow Nose.

Median E<sub>max</sub> values on Need to Blow Nose, Facial Pain/Pressure and Nasal Congestion indicated that subjects experienced very mild or mild effects following administration of Aximris XR, and very mild effects were reported on Need to Blow Nose and Nasal Congestion for OxyContin, ground. Median values for placebo matched to Aximris XR indicated very mild to moderate effects on Need to Blow Nose, Runny Nose/Nasal Discharge, and Nasal Congestion. Median TE<sub>max</sub> for all treatments and measures was 0.3 hours postdose, with the exception of 0.5 hours postdose for Need to Blow Nose, following placebo matched to Aximris XR.

Inferential analysis results for Emax of select SRAII subscales are presented in **Table 9**. The overall treatment effects for the Emax of each SRAII subscale were statistically significant ( $p<0.01$ ).

There were no between treatment differences for the pairwise comparisons of Emax for Burning, Need to Blow Nose, or Runny Nose/Nasal Discharge and Facial Pain/Pressure, Aximris XR, ground, had a statistically higher Emax compared with oxycodone IR, crushed, OxyContin, ground, and placebo matched to oxycodone IR/OxyContin; there were no other statistical differences on this endpoint.

For Nasal Congestion, Aximris XR, ground, and OxyContin, ground, had a statistically higher Emax compared with oxycodone IR, crushed, and placebo matched to oxycodone IR/OxyContin ( $p<0.05$ ). OxyContin, ground, also had a statistically higher Emax compared with oxycodone IR, crushed ( $p=0.0008$ ).

**Table 8: Selected Descriptive Statistics of SRAII E<sub>max</sub> (Completers Population)**

Statistic	Aximris XR 30 mg, Ground (N=30)	Oxycodone IR 30 mg, Crushed (N=30)	OxyContin 30 mg, Ground (N=30)	Placebo (Aximris XR) (N=30)	Placebo (Oxycodone IR/OxyContin) (N=30)
<b>Burning</b>					
Mean (SD)	1 (1)	0 (1)	1 (1)	1 (1)	0 (1)
Median	0.0	0.0	0.0	0.0	0.0
Range	0 - 3	0 - 2	0 - 2	0 - 3	0 - 2
<b>Need to Blow Nose</b>					
Mean (SD)	1 (1)	0 (1)	1 (1)	2 (1)	1 (1)
Median	1.0	0.0	1.0	2.0	1.0
Range	0 - 4	0 - 3	0 - 4	0 - 4	0 - 5
<b>Runny Nose/Nasal Discharge</b>					
Mean (SD)	1 (1)	0 (1)	0 (1)	1 (1)	1 (1)
Median	0.0	0.0	0.0	1.0	0.0
Range	0 - 4	0 - 3	0 - 3	0 - 4	0 - 4
<b>Facial Pain/Pressure</b>					
Mean (SD)	1 (1)	0 (1)	1 (1)	1 (2)	0 (1)
Median	1.0	0.0	0.0	0.0	0.0
Range	0 - 3	0 - 3	0 - 2	0 - 5	0 - 2
<b>Nasal Congestion</b>					
Mean (SD)	2 (1)	1 (1)	1 (1)	2 (1)	1 (1)
Median	2.0	0.0	1.0	2.0	0.0
Range	0 - 4	0 - 3	0 - 3	0 - 5	0 - 5

**Table 9: Inferential Analysis Results for SRAII Facial Pain/Pressure E<sub>max</sub> and Nasal Congestion E<sub>max</sub> (Completers Population)**

Pairwise Comparisons	E <sub>max</sub>		
	Mean Difference*	95% CI	P-value
<b>Facial Pain/Pressure</b>			
<i>Study Validity</i>			
Oxycodone IR, crushed – Placebo (IR/OxyContin)	0.07	-0.27, 0.40	1.0000
<i>Abuse Deterrence</i>			
Aximris XR, ground – Oxycodone IR, crushed	0.63	0.16, 1.10	<b>&lt;0.0001</b>
<i>Other Comparisons</i>			
OxyContin, ground – Oxycodone IR, crushed	0.17	-0.19, 0.53	0.8209
Aximris XR, ground – OxyContin, ground	0.47	0.00, 0.93	<b>0.0245</b>
Aximris XR, ground – Placebo (IR/OxyContin)	0.70	0.25, 1.15	0.0014
Aximris XR, ground – Placebo (Aximris XR)	-0.10	-0.79, 0.59	0.6138
OxyContin, ground – Placebo (IR/OxyContin)	0.23	-0.09, 0.56	0.0800
	LS Mean Difference*	95% CI	P-value
<b>Nasal Congestion</b>			
<i>Study Validity</i>			
Oxycodone IR, crushed – Placebo (IR/OxyContin)	-0.20	-0.67, 0.27	1.0000
<i>Abuse Deterrence</i>			
Aximris XR, ground – Oxycodone IR, crushed	1.10	0.67, 1.54	<b>&lt;0.0001</b>
<i>Other Comparisons</i>			
OxyContin, ground – Oxycodone IR, crushed	0.70	0.28, 1.13	<b>0.0008</b>
Aximris XR, ground – OxyContin, ground	0.40	-0.09, 0.90	0.0551
Aximris XR, ground – Placebo (IR/OxyContin)	0.90	0.37, 1.44	<b>0.0007</b>
Aximris XR, ground – Placebo (Aximris XR)	-0.50	-1.11, 0.11	0.9478
OxyContin, ground – Placebo (IR/OxyContin)	0.50	-0.02, 1.02	0.0300

CI=confidence interval; E<sub>max</sub>=maximum effect, XR=extended-release; IR=immediate-release; LS=least square

\* A paired t-test was used to assess the mean difference between the 2 treatments; mean is presented.

\*\*A mixed effect analysis of covariance (ANCOVA) model was used. The model included treatment, period and treatment sequence as fixed effect, and subject nested within treatment sequence as a random effect. Since the carryover effect was found to be non-significant at alpha=0.25, this effect was dropped from the analysis model. Bolded p-values are statistically significant.

## 6.2 Oral HAL Study

While intranasal insufflation (“snorting”) is the most common non-oral route of administration, followed by injection, among more experienced nonmedical users, the initial method of administration for non-medical (recreational) purposes is overwhelmingly via the oral route (Hays et al., 2003). Therefore, this study was designed to examine the oral abuse potential and PK of Aximris XR when it is manipulated compared to oxycodone immediate-release tablets (a non-abuse-deterrent oxycodone product), oxycodone ER (OxyContin, an abuse-deterrent oxycodone ER product), and placebo.

This study was a randomized, double-blind, placebo- and active-controlled crossover study in non-dependent, recreational opioid users. Subjects received single intact oral and ground oral doses of Aximris XR (40 mg), crushed oxycodone IR (40 mg), ground oxycodone ER (40 mg), and ground placebo in a triple-dummy manner during the treatment phase of the study. The manipulation method selected for Aximris XR and oxycodone ER was based on Category 1 testing. Briefly, Tool 10 was used to manipulate Aximris XR, matching placebo tablets, and oxycodone ER, as this provides the largest and most consistent particle size reduction prior to dissolution. Tool 3 was used to crush oxycodone IR tablets into a fine powder prior to dissolution.

### 6.2.1 Plasma Oxycodone Concentrations (Oral Study)

The plasma concentrations of oxycodone resulting from administration of Aximris XR, milled in solution, OxyContin, milled in solution, Oxycodone IR in solution and Aximris XR, intact, were measured over 24 hours (**Table 10**). Peak and early exposure to oxycodone were significantly lower following administration of Aximris XR, intact, compared with the other groups. Rate ( $C_{max}$ ) and extent ( $AUC_{0\text{-last}}/AUC_{0\text{-inf}}$ ) of exposure, as well as  $AUC_{0\text{-}4h}$ , were similar for both Aximris XR and OxyContin milled in solution, and crushed oxycodone IR. Additionally, early exposure ( $AUC_{0\text{-}1h}$  and  $AUC_{0\text{-}2h}$ ) was significantly lower for Aximris XR, milled in solution, as compared with crushed oxycodone IR. Rate and extent of exposure to oxycodone was similar for Aximris XR compared with OxyContin, both milled in solution.

**Table 10: Comparative Pharmacokinetics of Oxycodone Following Oral Administration of Aximris XR Milled in Solution and Intact Aximris XR Tablets versus Crushed Oxycodone Immediate-Release Tablets and Milled in Solution OxyContin Tablets**

	Arithmetic Mean Parameters (SD)							
	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)*	AUC <sub>0-1h</sub> (ng*h/mL)	AUC <sub>0-2h</sub> (ng*h/mL)	AUC <sub>0-4h</sub> (ng*h/mL)	AUC <sub>0-last</sub> (ng*h/mL)	AUC <sub>0-inf</sub> (ng*h/mL)	t <sub>1/2</sub> (hour)
Aximris XR 40 mg, Milled in Solution (N=40)	67.20 (20.32)	1.30 (0.53 – 5.03)	31.57 (12.83)	90.55 (30.60)	184.80 (51.81)	503.11 (144.16)	509.50 (146.96)	4.76 (0.84)
OxyContin 40 mg, Milled in Solution (N=40)	69.64 (20.63)	1.03 (0.53 – 5.03)	34.28 (14.93)	92.59 (29.82)	183.08 (45.51)	491.31 (137.03)	497.36 (139.62)	4.70 (0.75)
Oxycodone IR 40 mg, Crushed in Solution (N=40)	74.05 (23.55)	1.03 (0.28 – 5.07)	41.63 (16.59)	102.02 (34.34)	197.53 (56.80)	533.71 (147.47)	539.98 (150.81)	4.69 (0.82)
Aximris XR 40 mg, Intact	36.15 (9.33)	5.02 (1.05 – 12.05)	5.01 (4.15)	24.55 (12.36)	80.15 (29.28)	553.77 (143.83)	568.20 (149.19)	6.30 (1.90)

## 6.2.2 Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> (Oral Study)

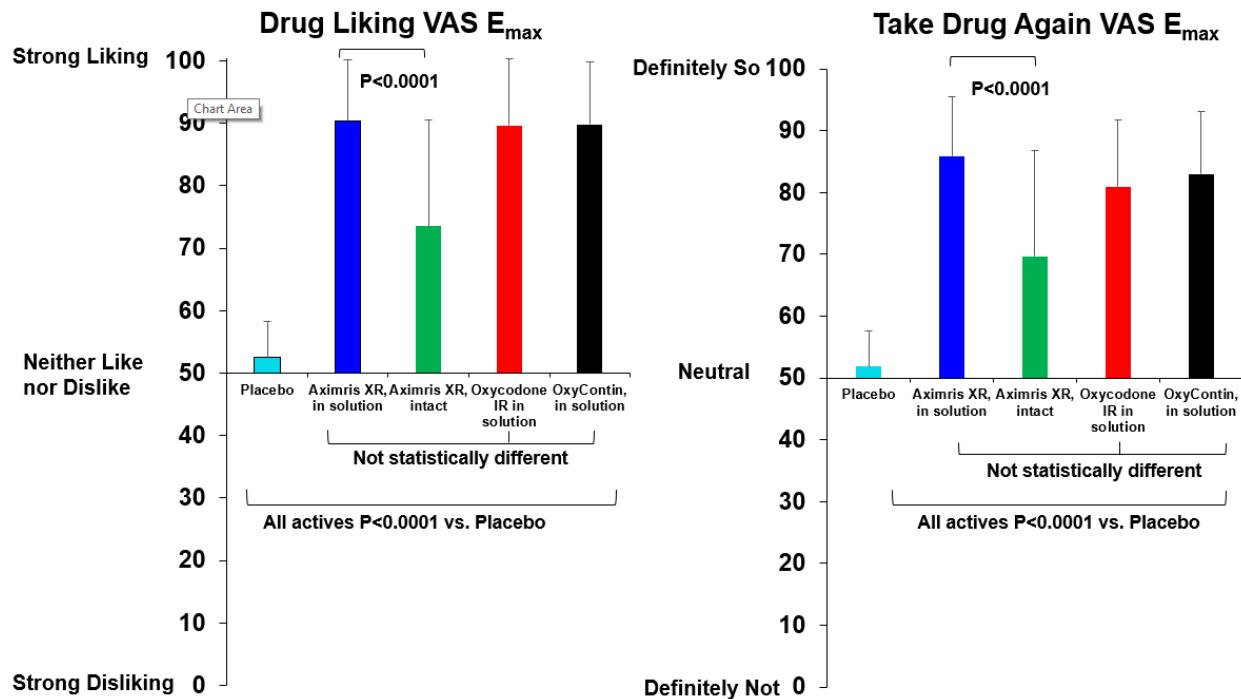
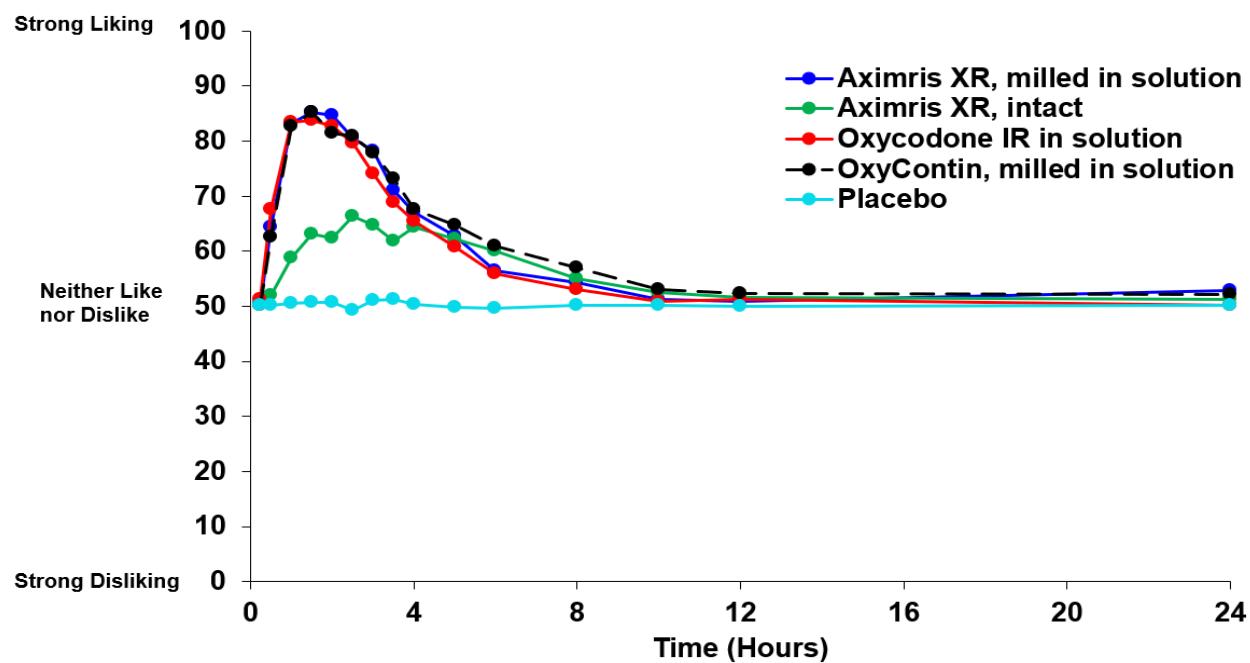
Selected descriptive statistics of Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> are provided in **Table 11** (graphical representation in **Figure 68**), and a graphical representation of the mean drug liking VAS scores over time is provided in **Figure 69**. Mean and median Drug Liking VAS E<sub>max</sub> values were high (>89) and similar for oxycodone IR, Aximris XR, ground in solution, and oxycodone ER, ground in solution. Drug Liking VAS E<sub>max</sub> was lower for intact Aximris XR (~75), and approximately neutral for placebo (~50). A similar pattern was observed for Take Drug Again VAS E<sub>max</sub>. Over time, drug liking for Aximris XR, intact, was lower than all of the active treatment groups, while Aximris XR, milled in solution and OxyContin, milled in solution, had a similar drug liking profile to oxycodone IR, in solution (**Figure 69**).

Examination of individual Drug Liking VAS E<sub>max</sub> data showed that overall, most subjects responded appropriately to placebo (i.e., 36 out of 40 subjects had E<sub>max</sub> scores between 40 and 60) and to oxycodone IR (i.e., 37 out of 40 subjects had scores >70). Similarly, most subjects responded appropriately on Take Drug Again VAS to both placebo (38 out of 40 subjects scored <60) and oxycodone IR (i.e., 32 out of 40 subjects had scores >70). Although a few subjects showed erroneous responses to a control, it is not uncommon to see a few sporadic responses in studies of this type.

**Table 11: Selected Descriptive Statistics of Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> (Completer Population) – Oral Study**

Statistic	AXIMRIS XR 40 mg, Milled in Solution (N=40)	OxyContin 40 mg, Milled in Solution (N=40)	Oxycodone IR 40 mg, Crushed in Solution (N=40)	AXIMRIS XR 40 mg, Intact (N=40)	Placebo (N=40)
<b>Drug Liking VAS</b>					
Mean (SD)	90.4 (9.79)	89.8 (10.11)	89.7 (10.71)	73.5 (17.05)	52.5 (5.80)
Median	91.0	93.0	93.0	75.0	50.0
Range	60 – 100	68 - 100	65 – 100	50 – 100	50 – 72
<b>Take Drug Again VAS</b>					
Mean (SD)	85.8 (18.71)	83.0 (18.55)	81.0 (22.71)	69.7 (23.47)	51.9 (8.42)
Median	92.0	88.5	88.0	67.5	50.0
Range	24 – 100	22 - 100	22 – 100	0 – 100	41 – 100

E<sub>max</sub>=maximum effect; IR=immediate-release; range=minimum – maximum; SD=standard deviation; VAS=visual analog scale

**Figure 68: Drug Liking VAS Emax and Take Drug Again VAS Emax – Oral Study**

**Figure 69: Mean Drug Liking VAS Scores Over Time – Oral Study**


Inferential analysis results for Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> showed that the main effects of treatment were statistically significant ( $p<0.001$ ) in the ANOVA model; there was no effect of period or treatment sequence ( $p>0.10$ ).

The Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> for OxyContin, ground in solution, were not statistically different from oxycodone IR ( $p=0.4761$  and  $0.2652$ , respectively), nor did these differentiate from Aximris XR, ground in solution ( $p=0.3539$  and  $0.1458$ , respectively). Aximris XR, ground in solution, had significantly higher Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> compared with intact Aximris XR. All active test treatments had significantly higher Drug Liking VAS E<sub>max</sub> and Take Drug Again VAS E<sub>max</sub> compared with placebo (all,  $p<0.0001$ ).

Based on the co-primary and secondary PD endpoints, the abuse potential of Aximris XR and OxyContin, when milled and administered via oral solution, did not significantly differ from that of oxycodone IR, a non-abuse-deterrent formulation, in non-dependent, recreational opioid users.

### **6.2.3 Safety Results**

There were no deaths or SAEs during this study. Overall, the highest incidence of TEAEs was observed with oxycodone IR (97.5%), followed by Aximris XR, ground in solution, and oxycodone ER, ground in solution (95.0% each), intact Aximris XR (72.5%), and placebo (25.0%).

The majority of subjects experienced TEAEs of mild severity. A few moderate TEAEs were reported following administration of active treatments; the incidence was similar between Aximris XR, ground in solution, intact Aximris XR, and OxyContin, ground in solution. No subject experienced an SAE or was discontinued from the study due to a TEAE during the treatment phase, and most TEAEs were considered related to study drug.

## 7 TOXICOLOGICAL RISK ASSESSMENTS

As Aximris XR contains oxycodone, a Schedule II controlled substance, it has a high potential for abuse and is subject to misuse, addiction, and criminal diversion. Due to the potential for abuse of Aximris XR, FDA requested in the CRL and Type A Post Action meeting that Intellipharmaceutics perform several toxicological risk assessments on the chemical components of Aximris XR following manipulation for abuse. These risk assessments were performed to assess the safety of Aximris XR excipients (or degradation products thereof) if it is abused by the oral, intranasal, vaping, or intravenous routes.

### 7.1 Oral, Intranasal, and Vaping Excipient Exposure Risk Assessments

#### 7.1.1 Methods

For the oral route assessment, excipients in Aximris XR at the Maximum Tolerable Daily Dose (MTDD) of oxycodone hydrochloride (1000 mg) were compared to maximum levels listed in the FDA Inactive Ingredient Database (IID) for oral administration or information from published studies. For excipients that exceeded FDA IID levels, a safety review was carried out.

For the intranasal route assessment, particle size distribution of Aximris XR was determined following tablet manipulation using sieves of the following sizes: 600 µm, 300 µm, 106 µm, 53 µm, and PAN (anything smaller than 53 µm). The amount of sample and the amount of recovered oxycodone hydrochloride was assessed for each size. The amount of Aximris XR excipients at risk of being deposited in the middle or lower respiratory tract per tablet was determined based on the mean percentage of sample retained that was < 53 µm. These amounts were compared to maximum levels listed in the FDA Inactive Ingredient Database (IID) for intranasal/inhalation administration or information from published studies. For excipients that exceeded FDA IID levels or were not listed in the IID via the intranasal/inhalation route, a safety review was carried out.

For the vaping route assessment, the vapor from the simulated smoking device (heat block or Bunsen burner) was assayed for active pharmaceutical ingredient content. An analysis of excipient exposure from the vaping route of abuse was determined in the context of the available information on FDA IID levels of the excipients for inhalation administration, as well as from published studies.

#### 7.1.2 Results

When the oral route of abuse was considered, most excipients in the Intellipharmaceutics' product at the Maximum Tolerable Daily Dose (MTDD, 1000 mg) were below maximum levels listed in the FDA Inactive Ingredient Database (IID). Two excipients (Polyethylene oxide MW 4,000,000 and Opadry II white) were above IID levels at the MTDD; however, the oral safety of these excipients is qualified by safety data in the published literature. Therefore, the exposure of these excipients by the oral route when the Sponsor's product is abused at the MTDD is anticipated to be low risk of toxicity.

Overall, when considering the intranasal and vaping routes of abuse, insufficient information was available to conclusively determine the risk of excipient exposure by these routes of abuse.

The excipients used in Aximris XR were not designed for inhaled use; therefore, the information to support its safe use when abused by the intranasal route is limited. Additionally, any identified information that suggested that the excipients would be irritating or toxic was only in the context of very high level of exposure or chronic exposure.

Based on this evaluation, many excipients do not have any information to evaluate the risks of intranasal or inhalation administration (crospovidone, microcrystalline cellulose, Eudragit RL PO, and Eudragit E PO). Other excipients are known to be a low safety risk when inhaled, due to the physicochemical properties of the compound (polyethylene oxide MW 4,000,000 and simethicone). However, other excipients are known respiratory irritants in humans (magnesium stearate, Opadry II White, sodium lauryl sulfate, stearic acid, and talc). The irritating effects range from mild, transient irritation to more severe manifestations like bronchospasm or asphyxia when exposed to large amounts or under chronic conditions. Of these irritants, a limited amount of published literature describing the inhaled toxicity of these excipients was identified for 3 excipients: sodium lauryl sulfate, stearic acid, and talc.

## 7.2 Intravenous Excipient Exposure Risk Assessment

An abuse deterrent characteristic of Aximris XR is the ability of the manipulated product to display high viscosity and hypercoagulability upon exposure to liquid. This characteristic deters abuse by the intravenous route. Intellipharmaceutics has performed Category 1 studies to assess the syringeability of the product under various methods of manipulation and preparation.

In the 2018 Type A Post-action meeting, FDA requested that Intellipharmaceutics address the potential IV toxicity of chemical compounds that may be present in a syringe following the most effective methods of product manipulation (e.g., microwaving or heating).

Data from analysis of syringeable material from manipulated product was used to assess risk from abuse of the product by the intravenous route.

Additionally, a hemocompatibility study was conducted on Aximris XR to evaluate the effect of the drug on blood components if injected intravenously, and an in vivo rabbit toxicology study was conducted to determine the toxicity of syringeable material from Aximris XR.

### 7.2.1 Assessment of the Intravenous Toxicity of Individual Excipients

#### 7.2.1.1 Methods

Open characterization of volatile organic components and semi-volatile organic components of syringeable material from Aximris XR (80 mg) and the comparator, OxyContin (80 mg) was performed. The syringeable material, for both Aximris XR 80 mg and OxyContin 80 mg, were obtained from ground tablets (80 mg) manipulated by Pre-treatment E, vigorously mixed with Volume 3 of Solvent A, incubated for 30 minutes without agitation at Temperature A. Needle Gauge A, was used to withdraw the solution into the syringe.

An analysis was conducted by gas chromatography/mass spectrometry to identify any organic substances in the syringeable material from manipulated Aximris XR or OxyContin that could be injected by drug abusers. The exposures per manipulated tablet were estimated, and possible health risks were assessed.

### 7.2.1.2 Results

Syringeable material was obtained using 10 mL of solvent separately from Aximris XR (80 mg) and OxyContin (80 mg). An average volume of 3.9 mL with oxycodone recovery of 29% of the label claim was obtained for Aximris XR (80 mg) while an average volume of 7.4 mL with oxycodone recovery of 62% of label claim was obtained for OxyContin (80 mg).

The analytical assessment of the injectable material from Aximris XR detected a number of organic substances that could be injected by drug abusers.

Based on 29% extractability for Aximris XR, the amount extracted (23 mg) would be above the 20 mg oxycodone threshold for liking (Stoops et al., 2010; Backonja et al., 2016), so an abuser would be unlikely to extract from multiple tablets. Therefore, amounts of Aximris XR components extracted from a single 80 mg tablet were used for the risk assessment.

This health risk assessment was carried out by comparing the estimated exposure from one manipulated tablet (either once or daily) with derived figures for tolerable exposure. In most cases, lifetime permitted daily exposures (PDEs) were derived using formal ICH guidance, or existing ICH PDEs were adopted directly. Expert Group reports served as valuable sources of tolerable exposure figures and critical toxicity studies (that underpinned the derivation of such figures). Where necessary and appropriate, toxicity data on structurally-similar analogues were also considered (in a read-across approach), and the Toxtree structure-activity relationship (SAR) software (version 3.1.0, with plug-ins) was also used to identify structural alerts for key toxicity endpoints.

Based on laboratory studies, Expert Group conclusions and/or Toxtree SAR, most of the identified compounds were concluded to lack mutagenic potential and were thus assessed as threshold toxins. In each case, the margin of safety (MOS) determined by comparing the PDE with the exposure was  $>1$  (and often  $>>1$ ), supporting the conclusion that the exposure would not pose any significant risk to health (even in someone exposed daily for lifetime). This conclusion applied to 1-dodecanol, 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene, 1,3-dioxolane (and its alkyl and its ethoxylated derivatives), 2-hydroxybenzaldehyde, 2-methylcyclopentanone, 2,2'-bis-1,3-dioxolane (and its ethoxylated derivatives), 2H-pyran-2,6(3H)-dione, acetic acid, acetone, acetophenone, benzaldehyde, benzoic acid, butanoic/heptanoic/pentanoic acids, crinan-11-ol (a crown ether and two derivatives), diethylene glycol, formic acid, furfural, n-hexadecanoic acid, n-hexane, 5-hydroxymethylfurfural, isopropyl alcohol, pentane and 3-methylpentane, propanal, and triacetin and monoacetin.

Ethanol, though a known human carcinogen, was not considered mutagenic by Expert Groups and was assessed using the existing ICH PDE (with supporting information from a different Expert Group). Acrolein has given some evidence of genotoxic potential but was not carcinogenic in the laboratory, and so was assessed on the basis of threshold toxicity. Again, the MOSs for these two compounds were  $>1$ , leading to a conclusion of tolerability.

Several remaining compounds were assessed as mutagenic carcinogens on the basis of laboratory evidence and Expert Group opinion. This group included 1,4-dioxane, 2(5H)-furanone, acetaldehyde, and furan. For 1,4-dioxane, it was concluded (based on an existing ICH PDE and Expert Group figures derived for a tolerable cancer risk) that exposure every day for lifetime

would not pose any significant cancer risk. For 2(5H)-furanone, no substance-specific cancer potency data were available, so the cancer risk was judged by applying the threshold of toxicological concern (TTC). At the estimated exposure level, it was calculated that a person could inject the compound every day for 13 years before reaching a 1 in 100,000 cancer risk.

Overall it was concluded that the assessed compounds in the syringeable material from a manipulated Oxycodone HCl Extended-Release 80 mg tablet would be highly unlikely to pose any significant health risks to a person who injects this material, either once or repeatedly.

## **7.2.2 Assessment of the Hemocompatibility of Aximris XR**

### **7.2.2.1 Methods**

The hemocompatibility of syringed solutions extracted (Test Item 1 and Test Item 2) from Aximris XR Tablets Form B manipulated by Pre-treatment E, which contain oxycodone and various excipients were determined using human plasma, serum, and whole blood. Test Item 1 was provided in an Isotonic Solution and Test Item 2 was provided in Tap Water. Additional samples of these test items were created (10-fold dilutions of Test Item 1 and Test Item 2 in sterile saline). All samples were combined 1:1 with plasma and serum for compatibility (flocculation) testing, and 1:1 with whole blood for hemolysis testing.

Compatibility testing of the test items at all dose levels (i.e., test item dilutions) involved the determination of the potential to form flocculent material arising in plasma or serum from test item treatment. Following incubation with human serum and plasma for 1–2 minutes at room temperature, each sample was inspected both by eye and using light microscopy ( $\geq 40x$ ) to determine if precipitation or coagulation had occurred. Saline was used as the negative control.

The hemolytic potential of the test item formulations at the dose levels above was evaluated. Following incubation with human whole blood for a period of 15 minutes at 37°C, plasma was isolated, and the hemoglobin content of the samples was quantified using a standard curve (OD absorbance at 540 nm). Saponin (1%) was included as a positive control and saline as the negative control. Test Items 1 and 2 were found to be slightly colored and, where applicable, the OD (optical density) from a blank sample for each Test Item was subtracted from the assay result. Percent hemolysis values < 10% were considered non-hemolytic.

### **7.2.2.2 Results**

Results from these hemocompatibility studies showed that no precipitation or coagulation was observed macroscopically (by eye) or microscopically, and there was no issue with compatibility for the plasma and serum matrices. Additionally, corrected % hemolysis values for Test Items 1 and 2 were below 10% (0 and 6.6%, respectively), indicating that the samples were non-hemolytic. Therefore, it can be concluded that Aximris XR is compatible with human blood as it is non-hemolytic and does not cause flocculation.

## **7.2.3 Assessment of the In Vivo Toxicity of Syringeable Material in Rabbits**

To further investigate the potential toxicity of the syringeable material from ground Aximris XR, Intellipharmaceutics has conducted an *in vivo* rabbit toxicology study.

### 7.2.3.1 Methods

In vivo assessment of toxicity of syringed solutions extracted (Test Item G2 and Test Item G3) from pretreated Aximris XR Tablets, which contain oxycodone and various excipients, were conducted to evaluate the potential for local effects, hematological effects, thrombotic microangiopathy, overt toxicity, and tissue damage.

In this study, 4 rabbits per group were injected intravenously with a 1 mL/kg bolus of syringeable material from ground Aximris XR in 10 mL tap water (G2), ground Aximris XR in 10 mL of 0.9% normal saline (G3), or normal saline alone (G1) as vehicle control. Rabbits were injected once per day for a total of 3 days by slow bolus injection into the marginal ear vein. The site of injection (i.e. left or right ear) was alternated each dosing day, and the injection site on the ear was marked post injection. Toxicities resulting from the administration of test materials were determined thus;

#### 7.2.3.1.1 Hematology

The key hematology parameters measured in the study are listed in [Table 12](#); other hematology parameters were also measured.

**Table 12: In Vivo Multiple-Dose Toxicity Study of Syringeable Material in Rabbits: Key Hematology Parameters**

Parameter (Abbreviation)	
Haemoglobin (Hb)	Mean Corpuscular Hemoglobin (MCH)
Red Blood Corpuscles (RBC)	Mean Corpuscular Hemoglobin Concentration (MCHC)
White Blood Corpuscles (WBC)	Mean platelet volume (MPV)
Platelets (PLT)	Reticulocyte count (Retic)
Hematocrit (HCT)	Differential leucocyte count (DLC) – absolute and per cent
Mean Corpuscular Volume (MCV)	

#### 7.2.3.1.2 Coagulation Analyses

Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) analysis were carried out with plasma.

#### 7.2.3.1.3 Clinical Chemistry

Clinical chemistry parameters analyzed are listed in [Table 13](#).

**Table 13: In Vivo Multiple-Dose Toxicity Study of Syringeable Material in Rabbits: Clinical Chemistry Parameters**

Parameter (Abbreviation)	
Glucose (Glu)	Aspartate amino transferase (AST)
Total bilirubin (T.Bil)	Alkaline phosphatase (ALP)
Creatinine (Creat)	Total Cholesterol
Inorganic phosphorous (Pi)	Urea (calculated)
Total plasma protein (T.Pro)	Calcium (Ca)
Albumin (Alb)	Triglycerides (Trig)
Globulin (Glob) calculated value	Chloride (Cl)*
Alanine amino transferase (ALT)	Sodium (Na)*
Blood Urea Nitrogen (BUN)	Potassium (K)*

#### 7.2.3.1.4 Urinalyses

Urine was collected by cystocentesis at the time of necropsy. For each urine sample, following qualitative and microscopic parameters were evaluated.

##### Qualitative Tests

Urinalysis parameters volume, color and appearance were performed by visual observations and recorded manually. Specific gravity, pH, Total Protein, Glucose, Blood, Bilirubin, Ketones and Urobilinogen was evaluated by using urocolor™ 10 strips and Urometer 720 analyzer.

##### Microscopic Examination

For microscopic examination, urine samples (an aliquot) were centrifuged at approximately 2500 rpm for 10 minutes, and resulting sediments were taken and spread out on a glass slide for microscopic evaluation. Sediments were evaluated microscopically for (but not limited to) the following parameters:

- Pus cells, epithelial cells, erythrocytes, crystals, microbes, casts, etc.

#### 7.2.3.1.5 Necropsy and Gross Pathology

Complete necropsies were carried out on all animals, and gross pathology findings were recorded for each animal. Fasting body weights were recorded before euthanasia for determination of organ-body weight ratios.

#### 7.2.3.1.6 Organ collection, weighing and fixation

On completion of the gross pathology examination, the tissues and organs listed in **Table 14** were collected and weighed from each animal. Eyes along with Harderian gland and optic nerve were fixed in Davidson's fixative for 24 hours and preserved in 10% neutral buffered formalin. All other tissues (including gross lesions) were preserved in 10% neutral buffered formalin. Lungs were inflated with 10% neutral buffered formalin before preservation in 10% neutral buffered formalin.

**Table 14: In Vivo Multiple-dose Toxicity Study of Syringeable Material in Rabbits: Organ Collection, Weighing, Fixation, and Examination**

List of Organs/Tissues			
Organ/tissue	Organ Weights	Collection & Preservation	Microscopic Examination
Adrenal glands (both)	✓	✓	-
Aorta	-	✓	✓
Brain (cerebrum, cerebellum, medulla/pons)	✓	✓	-
Cecum	-	✓	-
Colon	-	✓	-
Duodenum	-	✓	-
Esophagus	-	✓	-
Eyes (with optic nerve) <sup>1</sup>	-	✓	✓
Femur with joint <sup>2</sup>	-	✓	-
Gross lesions	-	✓	✓
Harderian glands	-	✓	-
Heart	✓	✓	✓
Ileum with Payer's Patch	-	✓	-
Jejunum	-	✓	-
Kidneys (both)	✓	✓	✓
Liver	✓	✓	✓
Lungs	✓	✓	✓
Lymph nodes (mesenteric and mandibular)	-	✓	-
Mammary gland	-	✓	-
Nerves, sciatic	-	✓	-
Ovaries (both)	✓	✓	-
Oviducts	-	✓	-
Pancreas	-	✓	-
Pituitary	-	✓	-
Rectum	-	✓	-
Salivary glands (both)	-	✓	-
Skeletal muscle (biceps femoris)	-	✓	-
Skin	-	✓	-
Spinal cord (cervical, thoracic and lumbar)	-	✓	-
Spleen	✓	✓	✓
Sternum with marrow <sup>2</sup>	-	✓	-
Stomach	-	✓	-
Thymus	✓	✓	-

**Table 14: In Vivo Multiple-dose Toxicity Study of Syringeable Material in Rabbits: Organ Collection, Weighing, Fixation, and Examination**

List of Organs/Tissues				
Organ/tissue	Organ Weights	Collection & Preservation	Microscopic Examination	
Thyroid with parathyroid (both)	-	✓	-	
Trachea	-	✓	-	
Urinary bladder	-	✓	-	
Uterus <sup>3</sup>	✓	✓	-	
Cervix <sup>3</sup>	✓	✓	-	
Vagina	-	✓	-	
Injection Site	-	✓	✓	

**Note:** Tissues indicated with ‘✓’ symbol was collected, weighed and/or subjected for histopathology evaluation. Paired organs were weighed together.

1. Eyes along with optic nerve and Harderian glands were fixed in Davidson's fluid
2. Bony tissues were decalcified in Gooding and Stewart's fluid prior to processing
3. Uterus was weighed along with cervix.

#### 7.2.3.2 Results

The key findings from the in vivo study are summarized in **Table 15**. Overall, the study found no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retinal damage, or acute kidney injury.

There was no mortality and/or morbidity in the present study, and all rabbits survived until the end of experimental period. There were no clinical signs noticed in any rabbits from the vehicle (negative) control group (G1 – sterile 0.9% NaCl solution). Rabbits from groups G2 (syringed solutions of pretreated Aximiris XR 80 mg containing oxycodone 6.10 mg/mL and various excipients using tap water) and G3 (syringed solutions of pretreated Aximiris XR 80 mg containing oxycodone 6.43 mg/mL and various excipients using 0.9% normal saline) showed signs of catalepsy, hypoesthesia, miosis and decreased/shallow respiration immediately or during dose administration attributed to the presence of Oxycodone HCl in G2 and G3. These clinical signs were observed on all 3 days of treatment and transient in nature which reversed within approximately 2 hours post injection/treatment.

Very minimal (Grade 1) erythema was observed at injection sites on the left ear at 2 and 4 hours on day 1 in both the treatment groups (G2 and G3). Similarly, on day 2 and 3, very minimal (Grade 1) to minimal (Grade 2) erythema was noticed at injections sites on the left, right or both the ears in treatment groups (G2 and G3). Very minimal (Grade 1) erythema was also noticed at injections sites on the left, right or both the ears of rabbits from the vehicle(negative) control group (G1: sterile 0.9% NaCl solution) on day 2 and 3. In general, administration of both test solutions, i.e., G2 and G3 were well tolerated and no signs of pain noticed during or after slow intravenous (bolus) injections. Overall, the injection site reactions in both the treatment groups

G2 and G3 were comparable within the groups. Therefore, the injection site reactions/changes (erythema) have been considered as procedure (intravenous dosing) related changes/findings.

There were no significant or treatment related changes noticed in the mean body weights and/or body weight gain of rabbits on any treatment day.

There were no other treatment related changes noticed in any hematology parameters except for significant ( $p<0.05$ ) decreases in the absolute reticulocyte count in both the treatment groups G2 and G3 and per cent (%) reticulocyte count in G3. In absence of any associated changes in the related hematology parameters such as red blood cell levels and any gross or histologic changes, it is difficult to ascertain the exact reason for the decrease in the levels of absolute and percent (%) reticulocyte counts in the treatment groups.

There were no treatment related changes noticed in the coagulation parameters (PT and APTT) in the present study. However, a slight but significant ( $p<0.05$ ) increase in Activated Partial Thromboplastin Time (APTT) was noticed in G3 syringed solution of 0.9 % Normal Saline Extract - containing Oxycodone HCl 6.43 mg/mL and various excipients as compared to vehicle (negative) control G1 sterile 0.9% NaCl solution group.

Clinical chemistry analyses did not reveal any treatment related changes in groups G2 or G3. Similarly, urinalysis did not reveal any treatment related or significant changes in both the treatment groups G2 and G3 as compared with the negative control group G1.

There were no significant or treatment related changes noticed in the absolute and relative organ weights of rabbits from G2 and G3 as compared to vehicle (negative) control G1.

On external examination, none of the terminally euthanized animals belonging to G1 and treatment groups G2 and G3 showed any findings except slight/minimal erythema at injection sites on left, right or both the ears.

Internal examination of the carcasses from G1 and treatment groups G2 and G3 did not reveal any abnormalities of pathological significance.

Although slightly variable in their severity but more or less similar incidence of various histopathology findings were observed in different organs/tissues (lung, liver, kidneys and heart) from rabbits belonging to the vehicle (negative) control G1 and treatment groups G2 and G3. All such findings have been considered as spontaneous/incidental findings unrelated with the treatment.

Gross and histopathology evaluation of the injection sites (left and right ear) from G1 and treatment groups G2 and G3 also showed some vascular and inflammatory changes. In general, the severity and incidence of these changes in left ear (given two injections on day 1 and day 3) was slightly more than that of the right ear (given only one injection on day 2). The lesions observed at injection sites in the treatment groups G2 and G3 were similar and not different than that of the respective control sites in the negative control group (G1). Therefore, the gross and histologic findings observed at injections sites were considered to be procedure related changes.

**Table 15: In Vivo Multiple-Dose Toxicity Study of Syringeable Material in Rabbits: Summary of Histopathological Findings**

Evaluation	Vehicle (negative) Control (G1): sterile 0.9% NaCl solution	Test (G2): Syringed solution of Tap Water Extract of ADF Aximiris XR Tablets 80 mg	Test G3: Syringed solution of 0.9% Normal Saline Extract of ADF Aximiris XR Tablets 80 mg
Injection site	Slight/minimal erythema - procedure related	Slight/minimal erythema -procedure related	Slight/minimal erythema - procedure related
Coagulation	No treatment related changes noticed in the coagulation parameters (PT and APTT)	No treatment related changes noticed in the coagulation parameters (PT and APTT)	No treatment related changes noticed in the coagulation parameters (PT), slight but significant ( $p<0.05$ ) increase in Activated Partial Thromboplastin Time (APTT)
Urine analysis	Did not reveal any treatment related changes	Did not reveal any treatment related changes	Did not reveal any treatment related changes
Hematology	Normal	Normal	Normal
Clinical Chemistry	Did not reveal any treatment related changes	Did not reveal any treatment related changes	Did not reveal any treatment related changes
Macroscopic	No findings	No findings	No findings
Organ weight	No significant or treatment related changes noticed in the absolute and relative organ weights	No significant or treatment related changes noticed in the absolute and relative organ weights	No significant or treatment related changes noticed in the absolute and relative organ weights
Carcass (Internal examination)	No abnormalities of pathological significance	No abnormalities of pathological significance	No abnormalities of pathological significance
Microscopic (Histopathology)*	Eye, normal <u>Lung</u> , congestion (1/4), MNC/PMN infiltration (3/4), alveolar histiocytosis (4/4) and granulomas (3/4)	Eye, normal <u>Lung</u> , congestion (0/4), MNC/PMN infiltration (4/4), alveolar histiocytosis (4/4) and granulomas (1/4)	Eye, infiltration (1/4) MNC, interstitial, Unilateral <u>Lung</u> , congestion (2/4), MNC/PMN infiltration (1/4), alveolar histiocytosis (1/4) and granulomas (0/4)

**Table 15: In Vivo Multiple-Dose Toxicity Study of Syringeable Material in Rabbits: Summary of Histopathological Findings**

Evaluation	Vehicle (negative) Control (G1): sterile 0.9% NaCl solution	Test (G2): Syringed solution of Tap Water Extract of ADF Aximiris XR Tablets 80 mg	Test G3: Syringed solution of 0.9% Normal Saline Extract of ADF Aximiris XR Tablets 80 mg
	<u>Spleen</u> , Normal  <u>Liver</u> , hepatocellular vacuolation (0/4) and foci of necrosis (1/4) with MNC/PMN infiltration (1/4)  <u>Kidneys</u> , interstitial MNC (2/4) and PMN infiltration in the cortex/medulla (2/4) and degenerating tubules (1/4)  <u>Heart</u> , MNC/PMN infiltration (0/4) and degeneration in myocardium (1/4)  [These are spontaneous incidental findings unrelated with the treatment]  <u>Injection sites</u> , perivascular hemorrhage, MNC/PMN infiltration, endothelial sloughing, thrombosis or subepidermal or epidermal exudate	<u>Spleen</u> , Normal  <u>Liver</u> , hepatocellular vacuolation (2/4) and foci of necrosis (2/4) with MNC/PMN infiltration (2/4)  <u>Kidneys</u> , interstitial MNC (1/4) and PMN infiltration in the cortex/medulla (0/4) and degenerating tubules (0/4)  <u>Heart</u> , MNC/PMN infiltration (1/4) and degeneration in myocardium (1/4)  [These are spontaneous incidental findings unrelated with the treatment]  <u>Injection sites</u> , perivascular hemorrhage, MNC/PMN infiltration, endothelial sloughing, thrombosis or subepidermal or epidermal exudate	<u>Spleen</u> , Normal  <u>Liver</u> , hepatocellular vacuolation(1/4) and foci of necrosis (1/4) with MNC/PMN infiltration (1/4)  <u>Kidneys</u> , interstitial MNC (2/4) and PMN infiltration in the cortex/medulla(1/4) and degenerating tubules (1/4)  <u>Heart</u> , MNC/PMN infiltration (1/4) and degeneration in myocardium (0/4)  [These are spontaneous incidental findings unrelated with the treatment]  <u>Injection sites</u> , perivascular hemorrhage, MNC/PMN infiltration, endothelial sloughing, thrombosis or subepidermal or epidermal exudate

APTT = activated partial thromboplastin time; MNC = mononuclear cells; PMN = polymorphonuclear leukocyte; PT = prothrombin time.

### 7.2.3.3 Conclusion

In conclusion, overall, based on the gross and histopathology evaluation, administration of the test items, G2 (syringed solutions of pretreated Aximris XR 80 mg containing oxycodone 6.10 mg/mL and various excipients using tap water) and G3 (syringed solutions of pretreated Aximris XR 80 mg containing oxycodone 6.43 mg/mL and various excipients using 0.9% normal saline), in New Zealand White rabbit for 3 consecutive days were well tolerated and did not produce any local or systemic effects in any organs/systems. Mild, procedure-related injection site reactions were observed in all groups. Urine analysis did not reveal any treatment related changes. No treatment related changes were noticed in the coagulation parameters (PT and APTT) for all groups except for slight but significant ( $p<0.05$ ) increase in Activated Partial Thromboplastin Time (APTT) seen in G3 group. All findings were normal with regards to hematology. Internal examination of the carcasses from the three groups studied showed no abnormalities of pathological significance. In terms of microscopic findings, MNC/PMN infiltration were observed for liver, kidney, heart, and injection sites with more or less similar severity found across the groups. These minimal to slight changes are not considered to be adverse in the context of the study findings by the independent pathologist. Overall, this study has found no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retinal damage, or acute kidney injury.

## 7.3 Aluminum Exposure Risk Assessment for Oral, Inhalation, and Intravenous Routes of Abuse

As requested by the Agency in the Type A Post-action Meeting, Intellipharmaceutics conducted a risk assessment of exposure from aluminum when Aximris XR is abused by various routes. Aximris XR tablets have been developed as 7 strengths, each with a different color coating. These color coatings contain Opadry films. Of the 7 Opadry films used to distinguish the different strengths of product, 5 contain Aluminum lake dyes: Opadry II Purple (85F100052), Opadry II Gray (85F175013), Opadry II Orange (Y-22-13158), Opadry II Blue (85F105031), and Opadry II Green (85F110100). The other excipient that contains aluminum is talc (at levels of 0.3%).

### 7.3.1 Methods

The aluminum content from the Opadry films (per tablet) and potential amounts of aluminum exposure from oral, inhalation, and intravenous routes of abuse were determined. These amounts of aluminum were compared to the upper limit of safe systemic exposure for aluminum in sensitive subpopulations administered parenteral nutrition, as defined in 21 CFR 201.323 (4 to 5  $\mu\text{g}/\text{kg}/\text{day}$ ).

### 7.3.2 Results

The total amount of aluminum for each strength of Aximris XR (from the color coat and talc product specifications) ranged from 0.012-0.320 mg/tablet. This risk assessment was based on the amount of aluminum in the excipients of Aximris XR. Also, Intellipharmaceutics measured the aluminum content of samples of each strength of Aximris XR tablets using an ICP-MS

validated method. The amount of aluminum per tablet in the laboratory analysis at Intellipharmaceutics ranged from 0.026–0.277 mg/tablet.

Relative to the oral route of abuse, a 7.9-fold increase and 28.5-fold increase in potential aluminum systemic exposure are predicted when the Aximris XR is abused by the intranasal and intravenous routes, respectively. While the relative aluminum systemic exposures by the intranasal and intravenous routes of abuse are higher than the oral route of abuse, these levels are still below the upper limit on safe systemic exposures for aluminum (4 to 5 µg/kg/day). Therefore, the potential risk of the Intellipharmaceutics' product to cause toxicity due to systemic aluminum exposure when abused by the oral, inhalation, or intravenous routes is low.

Based on the evaluation of amounts of aluminum in the new formulation in Aximris XR, the potential amounts of aluminum exposure by oral, inhalation, and intravenous routes of abuse are predicted to be below the upper limit of safe exposures for aluminum. Therefore, the potential risk of the Sponsor's product to cause toxicity due to aluminum exposure when abused by the oral, inhalation, or intravenous route is low.

### **7.3.2.1 Oral Abuse**

For the oral route of abuse, Intellipharmaceutics assessed the oral aluminum exposure from Aximris XR tablets at the oral oxycodone MTDD of 1000 mg/day as advised by FDA. For this assessment, it was assumed that the highest strength of the Sponsor's product would be used to reach the MTDD. Based on a 1000 mg/day MTDD and the highest strength of Aximris XR tablets (80 mg), this equates to 13 tablets needed to reach the MTDD.

The 80 mg strength of Aximris XR tablets contains 0.186 mg aluminum/tablet. Based on 13 tablets, 2.418 mg of aluminum would be ingested at the MTDD. Based on a human mass of 60 kg, the amount of aluminum ingested per day would be 40.3 µg/kg/day.

Orally ingested aluminum has low bioavailability (< 0.1%, (Krewski et al., 2007)); therefore, the systemic exposure of aluminum from Aximris XR tablets is much less than 40.3 µg/kg/day. When taking into account a bioavailability of ingested aluminum of 0.1%, the systemic exposure of aluminum when abused by the oral route is 0.0403 µg/kg/day, which is well below the upper limit of safe systemic exposures (4 to 5 µg/kg/day), as defined in 21 CFR 201.323.

### **7.3.2.2 Intranasal Abuse**

For the intranasal route of abuse, Intellipharmaceutics assessed the intranasal aluminum exposure from Aximris XR tablets when administered at a 30 mg dose. This dose is commonly used in intranasal drug liking studies (Lofwall et al., 2012; Harris et al., 2014; Setnik et al., 2017) and is the recommended dose for abuse deterrence evaluation for bioequivalence determination of abuse-deterring generic oxycodone (CDER, 2018). For this evaluation, Intellipharmaceutics assessed the aluminum exposure from a single 30 mg tablet as well as 3–10 mg tablets.

The 10 mg and 30 mg strengths of Aximris XR tablets contain 0.320 mg/tablet (which equates to 0.960 mg aluminum for 3–10 tablets) and 0.022 mg/tablet of aluminum, respectively. While the intranasal bioavailability is not well characterized, the estimated aluminum bioavailability from inhalation (in ambient air) is estimated as 2% from the lungs (Krewski et al., 2007). It is not likely that absorption of aluminum by the intranasal route would be greater than 2%, since part of the dose administered by the intranasal route would be swallowed (and constitute a much

lower bioavailability), and absorption across the nasal mucosa is expected to be lower than in the lung. Based on an aluminum bioavailability of 2%, the resulting systemic aluminum exposure by the intranasal route equates to 0.019 mg for 3–10 mg tablets and 0.00044 mg for 1–30 mg tablet.

Based on a human mass of 60 kg, the amount of aluminum absorbed after intranasal administration would be 0.317 µg/kg/day for 3–10 mg tablets and 0.0073 µg/kg/day for 1–30 mg tablet. Based on these estimations, the potential aluminum systemic exposure by the intranasal route would be well below the upper limit of safe exposure of 4 to 5 µg/kg/day.

### 7.3.2.3 *Intravenous Abuse*

An abuse deterrent characteristic of Aximris XR is the ability of the manipulated product to gel upon exposure to liquid. This characteristic deters abuse by the intravenous route.

Intellipharmaceutics has performed Category 1 studies to assess the syringeability of their product under various methods of manipulation and preparation. Based on these studies, the highest amount of oxycodone hydrochloride recovered from the syringeable material was 37%.

Intellipharmaceutics assessed the potential aluminum exposure by the intravenous route of abuse; based on the maximum amount of syringeable material from an 80 mg tablet, as the abuser is unlikely to extract from multiple tablets. Based on an 80 mg tablet and 37% extraction, this equates to 29.6 mg oxycodone. In studies of intravenous abuse, 20 mg oxycodone has been shown to induce drug liking (Stoops et al., 2010; Backonja et al., 2016).

The 80 mg strength of Aximris XR contain 0.186 mg of aluminum. Considering 37% syringeability (and assuming the aluminum and oxycodone are equally extracted), the potential aluminum intake when injected intravenously is 0.0688 mg. Based on a human mass of 60 kg, the amount of aluminum administered intravenously would be 1.147 µg/kg/day. Based on this estimate, the potential aluminum exposure by the intravenous route would be well below the upper limit of safe exposure of 4 to 5 µg/kg/day.

## 8 CLINICAL PERSPECTIVE ON AXIMRIS XR

### 8.1 Bioequivalence of Aximris XR to OxyContin

All the clinical pharmacology studies supporting the Aximris XR NDA were performed with the pre-change Aximris XR formulation (containing blue dye). However, the results from these studies are valid for the current post-change formulation (blue dye removed), because (as the Agency agreed in Intellipharmaceutics' Type A Post-action meeting) removal of the blue dye is a Level 1 change per the SUPAC-MR guidance (CDER, 1997).

The clinical PK program has demonstrated that Aximris XR is bioequivalent to OxyContin at the highest and lowest dosage strengths, in fed and fasted states, and at steady state. Additionally, as shown in **Table 4**, it was observed from the clinical PK study that the  $T_{max}$  values under fed conditions for Aximris XR and OxyContin are similar (5 hours vs. 5.5 hours, respectively). For Aximris XR, the  $T_{max}$  was slightly delayed under fed conditions compared to fasted conditions (5 hours vs. 4.834 hours, respectively). Together, these data provide evidence that Aximris XR can be expected to have a safety and efficacy profile similar to OxyContin when taken as intended. Furthermore, the lack of a clinically significant food effect will allow patients to take Aximris XR without regard to meals. Therefore, Aximris XR has met the standard for the 505(b)(2) regulatory approval to support its proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

### 8.2 Improvement in IV Abuse Deterrence

The IV route of abuse is the most dangerous form of opioid abuse, not only for its higher risk of respiratory depression and overdose, but also for the risks inherent to injection. Unfortunately, despite reformulation, IV abuse continues to be reported by approximately 15% of individuals entering substance abuse treatment who abuse OxyContin. Purportedly, much of this abuse is facilitated by the “recipes” to defeat ADFs, which can be found easily on drug abuse websites. Aximris XR has demonstrated superior resistance compared to OxyContin against these procedures to defeat ADFs. This represents an important improvement in abuse-deterrent technology in line with FDA’s anticipated “iterative improvements in products with abuse-deterrent properties” and Agency’s continued support for the innovation of opioids having abuse-deterrent properties. It is important to note that it is practically impossible to defeat Aximris XR’s extended-release abuse properties using common/standard methods abusers use. From the foregoing, Aximris XR has also met the standard outlined in the 2015 FDA Guidance for abuse-deterrent labeling for the IV route of abuse.

### 8.3 Other Potential Abuse-deterrent Properties of Aximris XR

Based on results from the Sponsor’s Category 2 and 3 studies on oral and intranasal abuse, Aximris XR may also present potential abuse deterrence for the oral and intranasal routes. This is due to the incidence of treatment-emergent adverse events (TEAEs) such as “nasal congestion” and “throat irritation” that are observed when the product (or its vehicle control) is administered

intranasally, as well as TEAEs such as “pruritus” and “headache” when the product is ground and administered in oral solution. Aximris XR is also rated difficult to snort.

#### 8.4 Post-Marketing Plans

Intellipharmaceutics is very committed to safe and responsible use of Aximris XR.

Intellipharmaceutics is currently an observer company (non-voting member) of the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) in the REMS Program Companies (RPC). When Aximris XR is approved, Intellipharmaceutics will become an active (voting) member. As such, Intellipharmaceutics can fulfill the post-marketing study requirements of the Opioid Post-marketing Consortium (OPC) regarding the safe use of ER/LA opioid analgesics.

Intellipharmaceutics plans to establish a safe use program for Aximris XR through which the company plans to provide educational support to key stakeholders such as patients, physicians and pharmacists. In addition to the package insert and standard Medication Guide, educational materials will be developed for patients, prescribers, pharmacists and nurses consistent with the class-wide REMS.

Intellipharmaceutics is committed to responsible sales and marketing of Aximris XR. Our sales force will be extensively trained and periodically retrained to be compliant with all pertinent regulations. This training will include knowledge of appropriate prescribing as well as tools for the sales force to identify prescribers who may be using the drug outside of acceptable practice, and therefore, require more extensive prescriber education or other interventions.

As required by the FDA, Intellipharmaceutics will have a surveillance program, such as drug safety and abuse as well as post-marketing pharmacovigilance programs to monitor for AE's, product information, recalls, and complaints.

Our manufacturing and supply chain will be monitored for compliance of all Drug Enforcement Administration (DEA) requirements.

An extensive monitoring system will be employed to determine how and to what extent Aximris XR may be contributing to the misuse, abuse, addiction, diversion, and overdoses associated with ER prescription opioids as follows:

- Prescriber level and prescription pattern monitoring – inappropriate prescribing, patients who pay cash and use multiple prescribers and pharmacies, pharmacies that are dispensing exceptional amounts of Aximris XR, and distributors filling exceptional orders.
- Surveillance program – prescription drug abuse monitoring or assessment program utilizing poison control center, drug diversion, opioid treatment, informant, and web data sources.
- In addition, Internet chat rooms will be monitored to see what comments are being made about the use and abuse of Aximris XR and attempts to compromise our abuse-deterrent technology.
- Local print and electronic media will also be regularly monitored to determine if there are any reports of misuse, abuse, addiction, overdose, or diversion.

In addition, when Aximris XR is approved, Intellipharmaceutics will work with the FDA to design a series of Category 4 post-approval epidemiologic studies to evaluate the effect of Aximris XR on abuse in the real world.

Intellipharmaceutics is aware of the problems associated with prescription drug abuse and will use the programs described above to help reduce this problem and to collect data that will facilitate necessary changes to the programs. Intellipharmaceutics aims to contribute to the public health goal of mitigating opioid abuse, not only by creating a product with superior abuse-deterrent properties, but also by implementing the proposed extensive educational programs for all stakeholders and collecting data that will help us understand the issues and applying strategies to reduce the problems of drug abuse.

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