

FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Oxycodone Hydrochloride Extended-Release Tablets (IPC Oxy)

**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 Immune Deficiency Syndrome
API	active pharmaceutical ingredient
AUC	area under the curve
BMI	body mass index
CDC	centers for disease control
CI	confidence interval
ER	extended-release
FDA	United States Food and Drug Administration
GRAS	generally recognized as safe
HAP	human abuse potential
HCl	hydrochloride
HFHC	high-fat, high-calorie
HIV	human immunodeficiency virus
IPC	Intellipharmaceutics International
IV	Intravenous
LS	least squares
NDA	New Drug Application
OPC	Opioid Post-marketing Consortium
PK	pharmacokinetic(s)
PSR	particle size <i>reduction</i>
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RPC	REMS Program Companies
SD	standard deviation

1 EXECUTIVE SUMMARY

Oxycodone Extended-Release Tablet (hereafter referred to as IPC Oxy) 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. Intellipharmaceutics Corp. (IPC) submitted a New Drug Application (NDA) for approval of IPC Oxy to the U.S. Food and Drug Administration (FDA) in November 2016. IPC Oxy was developed using the 505(b)(2) regulatory pathway, with OxyContin® as the reference listed drug (RLD). This NDA uses data on bioequivalence of IPC Oxy and OxyContin to support a scientific bridge to FDA's prior findings of safety and efficacy of OxyContin.

IPC Oxy has seven proposed dosage strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. These are the same as the currently marketed dosage strengths for OxyContin. IPC Oxy 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 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 as the RLD, OxyContin.

IPC Oxy is formulated with a combination of chemical barriers and aversion techniques intended to deter abuse in the treatment of pain requiring around-the-clock opioid treatment. The features intended to deter abuse include:

- Formulated to gel more quickly with greater particle size reduction
- Resistance to chemical extraction in small volumes of solvents intended to make abuse via injection difficult
- Gelling upon contact with aqueous solutions to deter intravenous (IV) abuse
- Resistance to chemical extraction in large volumes of solvents
- Resistance to dose dumping in the presence of alcohol
- Nasal irritant
- Staining blue dye that releases if crushed or chewed, which is hard to remove from the face, hands, and tongue

The current abuse-deterrent program for IPC Oxy includes a comprehensive set of Category 1 (in vitro) abuse-deterrence studies, including evaluations of particle size reduction, chemical extraction, syringeability/injectability, the ability to isolate or remove the dye from IPC Oxy, alcohol dose dumping and simulated smoking/vaporization. These studies support the proposed IV abuse-deterrent claim for the IPC Oxy label in accordance with the FDA Guidance "Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry" (FDA, 2015).

At this time, IPC is requesting abuse-deterrent labeling only for the IV route of abuse. The primary potential abuse-deterrent features of IPC Oxy for the oral and intranasal routes (i.e., nasal irritant and blue dye) have not been formally evaluated in clinical human abuse potential (HAP) studies, which are required for abuse-deterrent labeling incorporating Category 2 (pharmacokinetic [PK]) or Category 3 (pharmacodynamic [PD]) claims for the oral and intranasal routes.

Many controlled-release opioid formulations such as OxyContin have deterred abuse to a certain extent (Butler et al 2013, Havens et al 2014), however abusers can still defeat the ADF properties (Cicero and Ellis 2015). Thus there is a need for incremental innovation in ADF products.

IPC Oxy represents an incremental improvement for abuse-deterrent technologies for the IV route of abuse for ER oxycodone products. Despite the reformulation of OxyContin 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.

The Category 1 abuse-deterrent program for IPC Oxy has demonstrated the following:

- When IPC Oxy tablet is crushed or ground into smaller particles, its surface area is increased lending it the ability to form a highly viscous gel on contact with moisture.
- IPC Oxy and OxyContin both resist extraction and syringeability/injectability using simple methods to prepare an opioid tablet formulation for injection using intact or manipulated tablets.
- Recipes to overcome the gelling feature of abuse-deterrent formulations for IV abuse, found on drug abuser websites, were able to defeat OxyContin. These methods could result in relatively high yields of injectable oxycodone. In contrast, IPC Oxy resisted being prepared for injection under the conditions that defeated OxyContin, representing an incremental improvement over current abuse-deterrent technologies.
- IPC Oxy shows similar resistance to OxyContin against chemical extraction in large volumes of various solvents an abuser might use for oral abuse.
- IPC Oxy did not dose dump in the presence of alcohol.
- IPC Oxy and OxyContin have similar release profiles after physical manipulation, suggesting that there is not an increased risk of IPC Oxy for manipulated routes of abuse compared to OxyContin.
- It was not possible to eliminate the dye from IPC Oxy or isolate the oxycodone from the dye by extraction with a variety of solvents. Advanced, multi-step chemical procedures with multiple solvents would be required to overcome this feature of the formulation, which would necessitate substantially more time, effort and expertise on the part of the abuser to successfully prepare IPC Oxy for manipulated routes of abuse.
- IPC Oxy and OxyContin were not efficiently smoked or vaporized.

This briefing document provides data supporting the approvability of IPC Oxy as an efficacious ER opioid analgesic and supports the labeling of IPC Oxy with properties that can be expected to deter IV route of abuse.

Public Heath Perspective

The total number of opioid deaths in the U.S. 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 still remain at historical high levels.

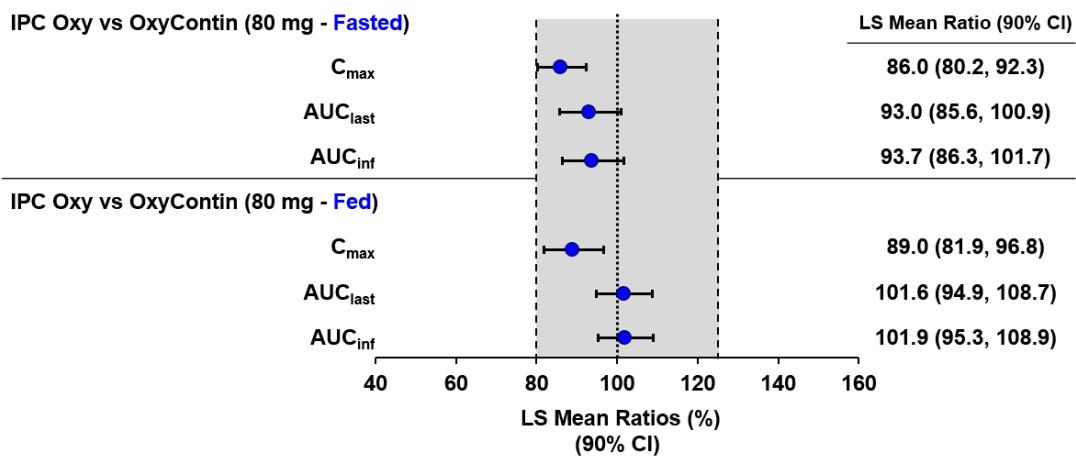
Preventing injection with prescription opioids has been one of the primary public health goals of abuse-deterrant formulations because IV abuse is associated with more severe health consequences. Data from the RADARS Poison Center Program suggest that the relative risk of death or a major adverse effect (e.g., overdose) for the IV route is 2.6 times greater than abuse by the oral route (RADARS, 2015). Furthermore, IV abuse was also associated with 6% of new HIV diagnoses and 10% of all new AIDS diagnoses in the US in 2015 (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, approximately 15% of individuals entering substance abuse treatment in 2016 who had recently abused ER oxycodone reported abusing via the IV route (RADARS Treatment Center Program, Data on File). These findings are consistent with “recipes” on drug abuser websites that provide instructions for how to prepare OxyContin for insufflation (snorting) or injection. As such, there is room for incremental improvement upon the abuse-deterrant features of OxyContin, particularly for the dangerous IV route of abuse.

Clinical PK Studies Supporting IPC Oxy for the Proposed Indication

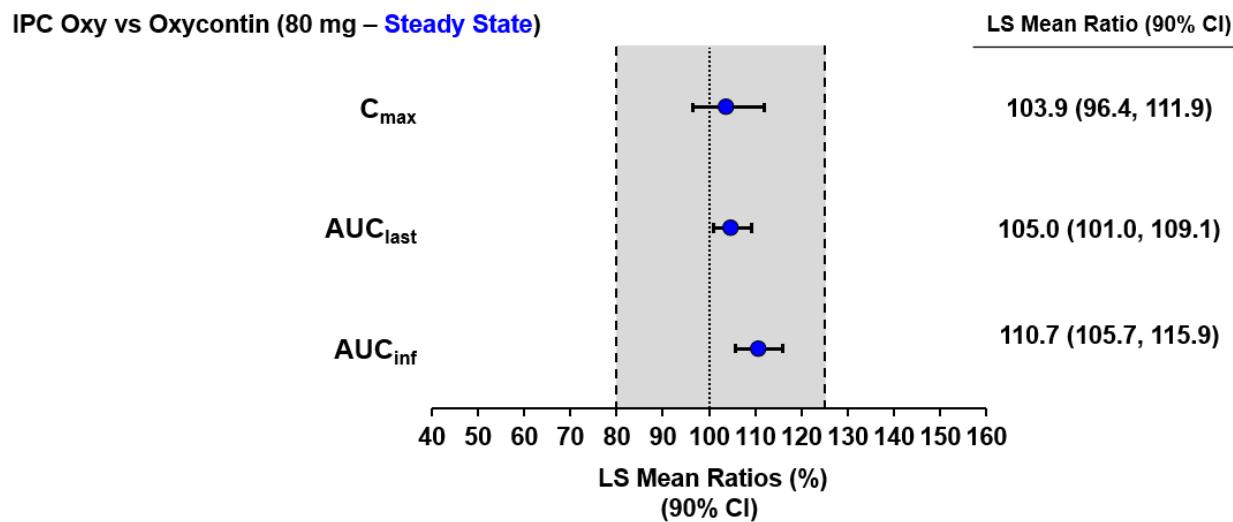
IPC Oxy was developed using the 505(b)(2) regulatory pathway. For this NDA, approval is based, in part, on bioequivalence to the RLD, OxyContin. Clinical PK single dose fasting and single dose fed studies have demonstrated that IPC Oxy is bioequivalent to OxyContin at both the lowest (10 mg) and highest (80 mg) dosage strength (see **Figure 1** for example with highest dosage strength). A clinical PK multiple dose studies under fasting conditions also demonstrated that IPC Oxy 80 mg is bioequivalent to OxyContin 80 mg (**Figure 2**).

Figure 1: Bioequivalence Results for 80 mg Dosage Strengths of IPC Oxy and OxyContin under fasted (Study 656-15) and fed conditions (Study 655-15)



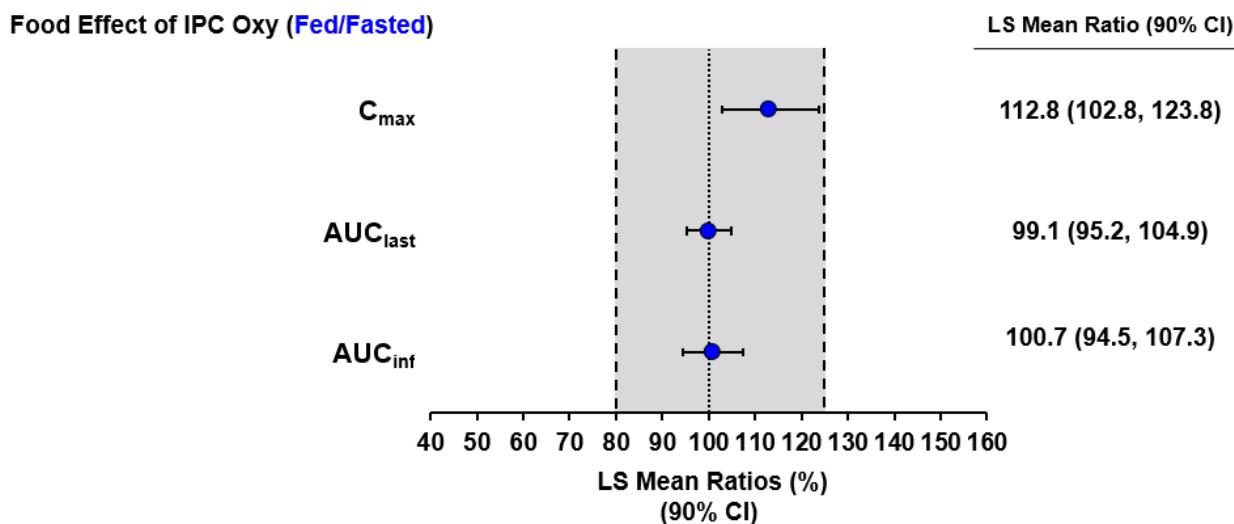
Note: gray shaded area reflects bioequivalence range of 80% to 125%.

Figure 2: Bioequivalence Results for Multiple Dose Studies for IPC Oxy 80 mg vs OxyContin 80mg (Study 80-184)



Another clinical PK study demonstrated that IPC Oxy 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 IPC Oxy is bioequivalent in the fed and fasted states, so patients can take IPC Oxy without regard to meals (**Figure 3**).

Figure 3: Bioequivalence Results for Food Effect Studies for IPC Oxy 80 mg Fed vs Fasted State (Study 80-186)



Abuse-Deterrent Studies

The Category 1 abuse-deterrent studies for IPC Oxy were conducted in accordance with FDA's abuse-deterrent opioid guidance (FDA 2015). These studies were also designed in consultation with FDA and experts in the evaluation and development of abuse-deterrent formulations (ADFs). The comprehensive set of Category 1 in vitro physical manipulation and chemical extraction studies evaluated the abuse-deterrent properties of IPC Oxy. These included evaluation of resistance to physical manipulation (cutting, crushing, milling, and grinding tablets), dissolution of manipulated tablets (simulated oral ingestion), small volume IV extraction (syringeability/injectability, simulated intranasal), large volume chemical extraction, alcohol dose dumping, dye elimination, complex extraction, smoking/vaporization (simulated insufflation), and more complex multi-step chemical extractions. In all studies, OxyContin was used as the comparator where applicable (no comparator was used in the dye elimination studies). In accordance with FDA Guidance, all studies were performed with the highest dosage strength (80 mg) of IPC Oxy and OxyContin.

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

Particle Size Reduction

In order to defeat the controlled-release mechanism of abuse-deterrent formulations, opioid abusers typically crush the formulation into fine particle size to defeat the controlled release mechanism in order to obtain a quick release of drug from the product. Thus, many abuse-deterrent formulations 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 "hard-to-crush" abuse-deterrent formulations

(McNaughton et al., 2014). IPC Oxy is not dependent on resistance to physical manipulation as one of its primary abuse-deterrent features.

IPC Oxy 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 with mechanical or electrical tools. Both products offered some resistance to physical manipulation. In general, OxyContin was more resistant to physical reduction than IPC Oxy; however, it is important to recognize that when IPC Oxy and OxyContin undergo physical reduction to smaller particles and are brought in contact with liquid, IPC Oxy forms a more viscous gel than OxyContin. The optimized particle size reduction method involved applying Tool 10 for 3 minutes with 20 tablets. Using this optimized procedure, both products had a particle size distribution with 99% of particles < 600 microns. This procedure was used as the method of physical manipulation for all subsequent Category 1 studies and is referred to as Tablet Form B.

Syringeability/Injectability and Small Volume Extraction

Most abuse-deterrent formulations are designed to resist common methods for IV abuse. Both IPC Oxy and OxyContin are formulated with properties intended to deter IV abuse by producing a highly viscous gel when subjected to an aqueous environment. IPC Oxy is formulated with excipients to enhance this gelling feature even if subjected to a considerable extraction volume. The in vitro IV abuse studies for IPC Oxy evaluated simple methods for preparing opioid products for injection as well as “recipes” referenced on drug abuser websites to overcome the gelling properties of abuse-deterrent formulations like OxyContin.

For standard syringeability/injectability assessments, samples of IPC Oxy and OxyContin in Tablet Form B were added into various volumes ranging from Volume 1, 2, 3, 4 and 6 of Solvents 1 or 2 and incubated for up to 30 minutes with Agitation A or C at Temperatures A or B. A similar study was performed using Tablet Form A in Solvent 2, Volume 6 incubated for 5, 10, and 30 minutes with Agitation C at Temperatures A or B. No Oxycodone was extracted at Temperature A, while less than 10% was recovered at Temperature B. None of the conditions yielded a suitable amount of injectable oxycodone (<20%) for either IPC Oxy or OxyContin, which supports that both IPC Oxy and OxyContin have abuse-deterrent properties for the IV route under these standard conditions.

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). For this study, IPC Oxy and OxyContin in Tablet Form B were added to Volume 2 of Solvent 1 and incubated for 4 and 24 hours at Temperatures A or B. It was not possible to load the syringe with solution from either product with more than 20% volume with Needle Gauge D at Temperature A, while at Temperature B it was more difficult to load the syringe with solution for IPC Oxy compared to OxyContin.

One of the most common methods cited on drug abuse websites (e.g., bluelight.org) to overcome the IV resistance of abuse-deterrent formulations is to perform Pre-treatment D prior to

extraction. For this study, Pre-treatment D was applied to IPC Oxy and OxyContin under Tablet Form B followed by extraction in Volumes 1, 2, and 3 of Solvent 1 and incubated for up to 5 minutes with Agitation A at Temperatures A or B. For example, using Needle Gauge A, at Temperature A, Volume 1, after a 30 second incubation period, a higher yield of injectable oxycodone was obtained from OxyContin (40%) compared to IPC Oxy (20%). Also, after 30 second incubation period at Temperature B, Volume 1, a higher yield of injectable oxycodone was obtained from OxyContin (65%) compared to IPC Oxy (7%).

Large Volume Extraction

The resistance to extraction of manipulated IPC Oxy and OxyContin 80 mg tablet equivalents in large volumes was evaluated in 21 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, for the most common ingestible solvents and non-ingestible solvents.

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 IPC Oxy and OxyContin was evaluated using an in vitro model with Dissolution Conditions A and B in different concentrations of alcohol. Results showed that the release of oxycodone from IPC Oxy decreased with increasing concentrations of alcohol just like for OxyContin. Despite the lack of dose dumping with alcohol, IPC Oxy, like all opioid products, should not be co-ingested with alcohol.

Dissolution of Manipulated Tablets (Simulated Oral Ingestion)

Dissolution of IPC Oxy and OxyContin in Tablet Forms B, C, D, E, and F using Dissolution Conditions A and B showed that the release of oxycodone was similar between the products.

Additional dissolution studies evaluated the effect of Pre-treatments E and F, common methods cited on drug abuser websites to overcome abuse-deterrent properties, on the release of oxycodone from IPC Oxy and OxyContin in Tablet Form A. After applying Pre-treatment E, the release of oxycodone using Dissolution Condition C was considerably lower for IPC Oxy than OxyContin at early time points.

Dye Elimination

One of the unique putative abuse-deterrent features of IPC Oxy is the blue dye that is formulated to release if a tablet is physically manipulated and comes in contact with moisture or water. If a method of separation or degradation of the dye could be found, this could make IPC Oxy more attractive to abusers. Consequently, a series of tests was designed to systematically study attempts at dye separation or degradation from the formulation.

Using a variety of solvents chosen based on knowledge of the chemical properties of the IPC Oxy formulation, none of the individual solvents were able to eliminate the dye or separate oxycodone from the dye without degrading oxycodone. A complex, multi-step, multi-solvent

procedure would be required to successfully separate out oxycodone from the dye with high purity, which would require expensive equipment, substantially more time, effort and expertise in advance chemistry on the part of the abuser.

Simulated Smoking/Vaporization Studies (Simulated Intranasal Insufflation)

Vaporization of IPC Oxy and OxyContin using optimal conditions with a block heater produced approximately 6% and 7% oxycodone in vapor. Applying direct heat with a Bunsen burner yielded 8% oxycodone recovery from IPC Oxy and 11% from OxyContin. Neither method would be considered an efficient route of abuse for either product.

Conclusions

This joint Advisory Committee will consider whether IPC Oxy should be approved for its proposed indication for use and whether, if approved, it should be granted a label reflecting abuse-deterrent properties via the IV route.

Two PK studies for IPC Oxy have demonstrated that IPC Oxy 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 IPC Oxy 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 IPC Oxy, therefore IPC Oxy may be taken without regard to meals. Furthermore, IPC Oxy can be expected to provide effective analgesia for the intended patient population, for whom alternative non-opioid therapies are inadequate.

The Category 1 in vitro abuse-deterrent studies for IPC Oxy 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 IPC Oxy and OxyContin using usual volumes and methods chosen by abusers used to prepare OxyContin for injection indicate that IPC Oxy has superior abuse-deterrent properties for the IV route. Specific internet recipes (Butler et al 2013, Havens et al 2014 and Cicero and Ellis 2015), used to overcome gelling properties of abuse-deterrent formulations cited on drug abuser websites yielded appreciable amounts of injectable oxycodone from OxyContin, but little to none from IPC Oxy.

In addition, Category 1 studies demonstrated that IPC Oxy has similar resistance to extraction in large volumes of ingestible and non-ingestible solvents compared to OxyContin and does not dose dump in alcohol. IPC Oxy has a novel potentially abuse-deterrent feature with its intense blue dye that would be released if the product was chewed or crushed. In-vitro studies demonstrate that the dye cannot be readily eliminated from the formulation without degrading oxycodone.

Simulated oral ingestion confirm that manipulation of IPC Oxy Tablet Form B, C, D, E and F 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 IPC Oxy does not increase the rate of oxycodone release relative to OxyContin.

Overall, these results demonstrate that IPC Oxy would be an effective ER opioid analgesic with incremental improvements in abuse deterrence for the IV route, which is the most dangerous route of opioid abuse.

2 PUBLIC HEALTH NEED FOR ABUSE-DETERRENT ER OPIOID ANALGESICS

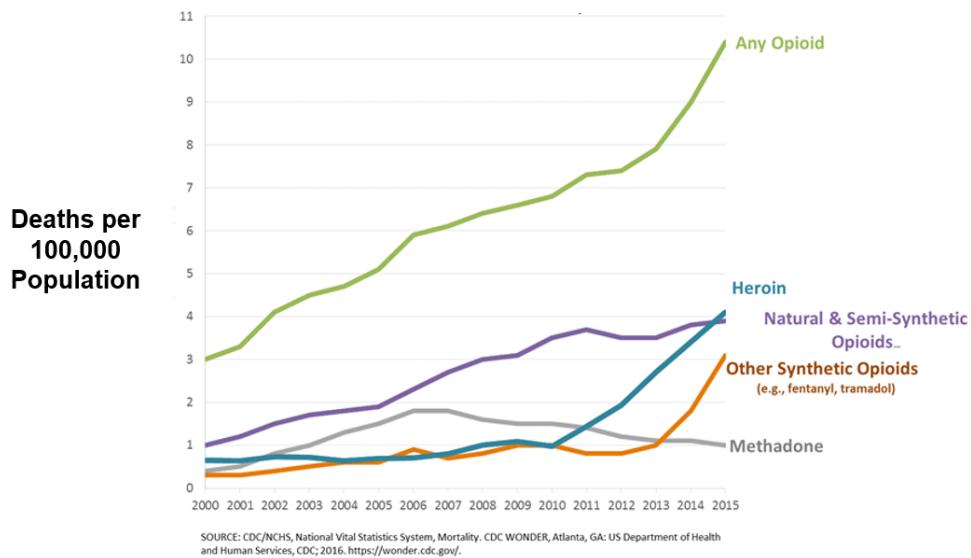
Summary

- IV abuse of opioid products is a major public health concern. According to the CDC, in 2015, IV abuse was associated with 6% of new HIV diagnoses and 10% of all new AIDS diagnoses in the US.
- 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 to prepare it for insufflation or injection and some of the recipes have been shown to be successful.
- 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 U.S. attributable to opioids continues to increase (CDC, 2016). This continuing rise in deaths is primarily attributable to increases in overdose deaths from heroin and synthetic opioids such as fentanyl (**Figure 4**). 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 4: Number of Deaths in the US Attributable to Opioids (CDC/NCHS 2016)


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 abuse-deterrent formulations because it is associated with the most severe health consequences.

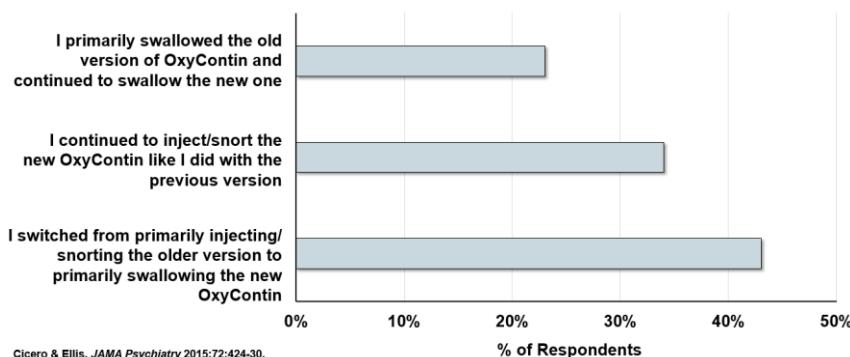
In terms of direct opioid-related effects (e.g., respiratory depression), a single instance of IV opioid abuse is associated with 2.6 times greater risk for death or a major, life-threatening adverse effect, such as an overdose, compared to a single instance of oral abuse (Researched Abuse, Diversion 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, 6% of new HIV diagnoses and 10% of AIDS diagnoses in 2015 were attributable to IV drug use (CDC 2016). Furthermore, IV drug abuse is associated with increased risks for acquisition of Hepatitis C (Bruneau et al., 2012), endocarditis (Ronan & Herzog, 2016; Gordon & Lowy, 2005), and blood clots (McLean et al., 2009).

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 (Coplan et al., 2016).

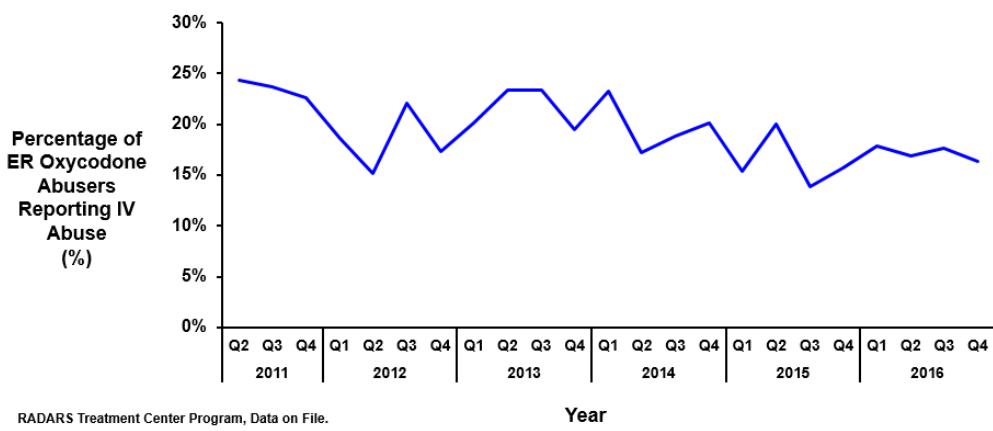
The effect of OxyContin's reformulation on changes in its abuse patterns has been evaluated in the Survey of Key Informants' Patients (SKIP) program, which is part of the RADARS system. A subset of these patients were interviewed to evaluate their changes in abuse pattern (Cicero & Ellis, 2015). Individuals 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 5**).

Figure 5: Change in OxyContin Abuse Patterns Following Reformulation with Abuse-Deterrent Properties



While OxyContin is resistant to many 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, just over 15% reported abuse via the IV route across the four quarters of data in 2016 (**Figure 6**).

Figure 6: Percentage of Individuals Entering Substance Abuse Treatment in RADARS Treatment Center Program Reporting Abuse of ER Oxycodone Abusing via IV Route



2.3 Incremental 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 acknowledges that “FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties.” IPC Oxy was developed to address the public health need for incremental improvement in abuse-deterrent technology, particularly for the IV route, which is the most dangerous route of abuse.

3 IPC OXY DEVELOPMENT AND FORMULATION

Summary

- IPC Oxy 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
- IPC Oxy was developed in accordance with the 505(b)(2) regulatory pathway where approval relies on some information from an approved product, the reference listed drug (RLD). The RLD for IPC Oxy 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 IPC Oxy is bioequivalent to the listed drug, 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.
- IPC Oxy is formulated with physical and chemical barriers to deter various forms of tampering commonly used by abusers.
- IPC has performed a comprehensive set of Category 1 in vitro physical manipulation and chemical extraction studies to evaluate the abuse-deterrent properties of IPC Oxy. These studies were designed in consultation with FDA as well as experts in the evaluation and development of abuse-deterrent formulations.
- At this time, IPC is requesting abuse-deterrent labeling for the IV route based on Category 1 findings compared to OxyContin.

3.1 Formulation

IPC Oxy 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 RLD, OxyContin.

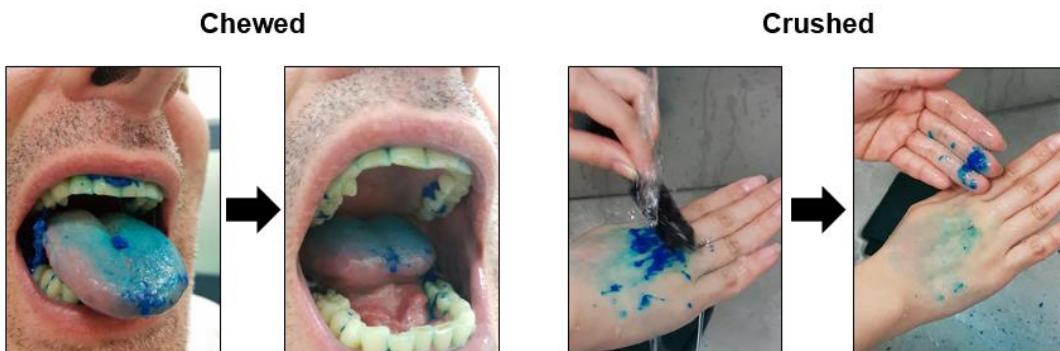
IPC Oxy has seven proposed dosage strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. These are the same currently marketed dosage strengths as OxyContin. The excipients and structure of the tablet formulation are the same for all IPC strengths with the exception of the coloring agents on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

3.2 IPC Oxy Abuse-Deterrent Technology

IPC Oxy tablets are 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 hydrogel when subjected to an aqueous environment to deter syringing, injecting, and snorting.

In addition to inactive ingredients such as polyethylene oxide (PEO), which gels upon contact with liquid, IPC Oxy has two additional putative abuse-deterrent features. IPC Oxy tablets include sodium lauryl sulfate (SLS), which is a nasal irritant that has been used in other products formulated to discourage snorting (e.g., Oxaydo®). The product also contains a staining blue dye that is formulated to be released if the product is crushed or chewed. Based on an initial exploratory investigation, the dye is difficult to remove from the face, hands, or clothes, and requires intense scrubbing with a brush for 30 to 40 minutes to remove (**Figure 7**). Further clinical testing of the nasal irritant and the blue dye, including human abuse potential (HAP) studies, would need to be performed in order to include these features as abuse-deterrent properties in the IPC Oxy label.

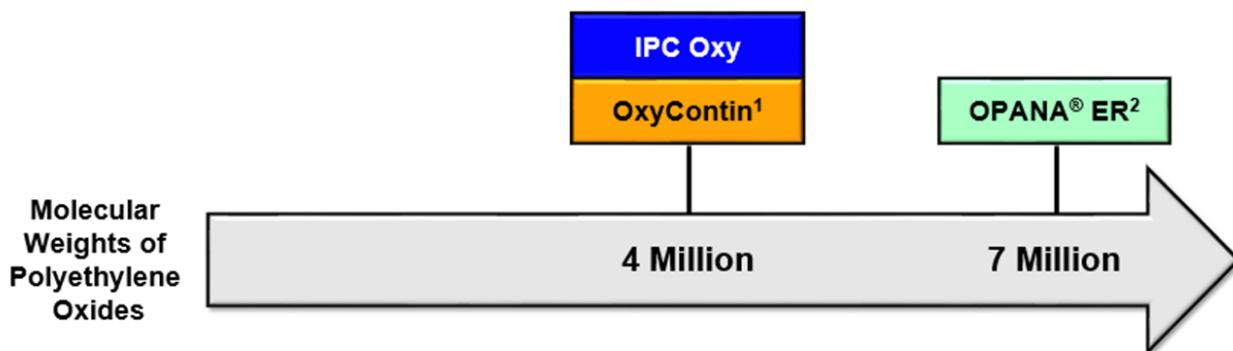
Figure 7: Blue Dye in IPC Oxy Formulated to Release When Chewed or Crushed



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® 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 whose PEO has a molecular weight of approximately 4 million (**Figure 8**).

IPC Oxy uses PEO with the same molecular weight as that of OxyContin, so it is not anticipated that IV abuse of IPC Oxy 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 IPC Oxy.

Figure 8: Molecular Weight of IPC Oxy, 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.

3.4 Overview of IPC Oxy Development Program

IPC developed IPC Oxy using the 505(b)(2) regulatory pathway with OxyContin as the RLD. Following demonstrated bioequivalence to OxyContin, a waiver for Phase III studies was granted by FDA. The approval of IPC Oxy is supported by several clinical PK studies that evaluated the relative bioavailability of IPC Oxy and OxyContin as well as the dose proportionality of the various dosage strengths of IPC Oxy. The proposed IV abuse-deterrent labeling is supported by a series of Category 1 in vitro studies. FDA and experts in abuse-deterrent products provided input and feedback into the design of the development program and the study protocols. IPC submitted a NDA to the FDA requesting approval of IPC Oxy in November 2016.

3.5 Clinical Pharmacokinetic Studies and Effect of Food

Randomized, open-label, crossover studies in healthy volunteers were conducted to evaluate the relative bioavailability of IPC Oxy to OxyContin at both 10 mg and 80 mg dosage strengths, the dose proportionality of IPC Oxy at all proposed dosage strengths, and the effect of food on bioavailability of IPC Oxy (**Table 1**). All studies were conducted under naltrexone blockade.

Table 1: 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 IPC Oxy (fasted) 10 mg OxyContin (fasted)
1879	Fed bioequivalence study at 10 mg dose	29	10 mg IPC Oxy (fed) 10 mg OxyContin (fed)
656-15	Fasted bioequivalence study at 80 mg dose	30	80 mg IPC Oxy (fasted) 80 mg OxyContin (fasted)
655-15	Fed bioequivalence study at 80 mg dose	29	80 mg IPC Oxy (fed) 80 mg OxyContin (fed)
80-184	Steady state study at 80 mg dose (6 consecutive doses every 12 hours)	24	80 mg IPC Oxy 80 mg OxyContin
80-185	Dose proportionality study	22	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg IPC Oxy (fasted)
80-186	Food effect study at 80 mg dose	25	80 mg IPC Oxy (fasted and fed)

3.6 Category 1 Studies

In consultation with the FDA and experts in the field of abuse deterrence, IPC 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, large volume extraction, alcohol dose dumping, complex extraction and isolation of oxycodone base, and simulated smoking/vaporization.

In addition to these standard experiments, IPC also conducted several additional studies in attempts to evaluate the ability to eliminate the dye or isolate the oxycodone from the dye in IPC Oxy, since a method that could produce a colorless solution or white ground material would potentially make IPC Oxy more attractive for abuse.

3.7 Rationale for Approval and IV Abuse-Deterrent Labeling

In light of the incremental improvement in IV abuse deterrence (described in detail in Section 5.3), IPC is requesting approval of IPC Oxy and IV abuse-deterrent labeling prior to the completion of the additional clinical studies that will be required to support oral and nasal abuse-deterrent claims. While IPC is committed to completing these studies, they remain in the design phase and it is not anticipated that a supplemental NDA will be ready to submit in support of these claims for approximately 2 years.

IPC contends that it is reasonable to approve IPC Oxy given its bioequivalence to OxyContin and its demonstration of enhanced IV abuse deterrence. In the interim, IPC proposes to work with the FDA to design a series of Category 4 post-approval epidemiologic studies to evaluate the effect of IPC Oxy and the blue dye on abuse in the real world concurrently as the Category 2 and Category 3 studies for the oral and nasal routes are completed and submitted to the Agency.

4 CLINICAL PHARMACOLOGY

Summary

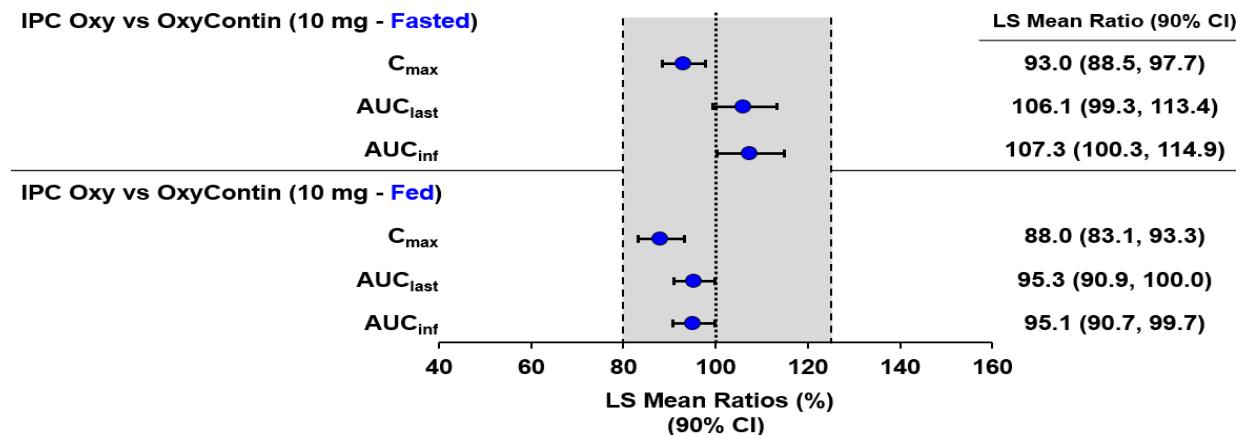
- In single-dose clinical PK studies, IPC Oxy demonstrated bioequivalence to OxyContin at the lowest and highest dosage strengths in the fed and fasted states, supporting the scientific bridge to prior findings of efficacy and safety of OxyContin.
- A multiple-dose clinical PK study demonstrated bioequivalence of IPC Oxy to OxyContin at steady state.
- IPC Oxy 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 IPC Oxy, so IPC Oxy may be taken without regard to meals.

4.1 Single-Dose Bioequivalence of IPC Oxy to OxyContin

Study 1878 and Study 1879 evaluated the relative bioavailability of the lowest (10 mg) dosage strengths of IPC Oxy 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 9 provides a summary of the key study results, which demonstrated that IPC Oxy 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%.

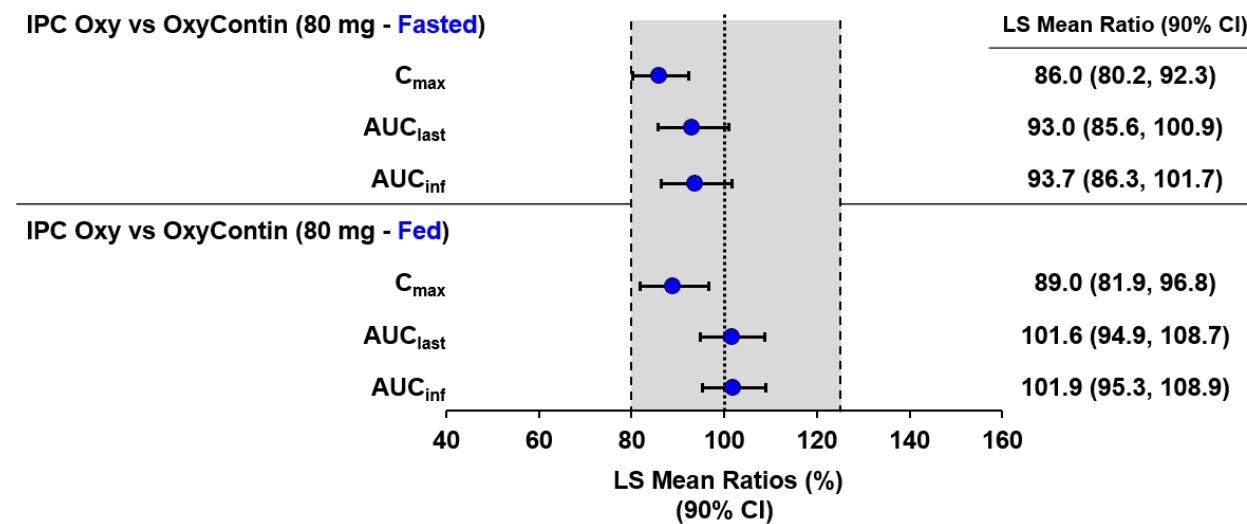
Figure 9: Single-Dose Bioequivalence Results of 10 mg Dosage Strengths of IPC Oxy and OxyContin under Fasted (Study 1878) (N=31) and Fed Conditions (Study 1879) (N=29)



Study 656-15 and Study 655-15 evaluated the relative bioavailability of the highest (80 mg) dosage strengths of IPC Oxy 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 10 provides a summary of the key study results, which demonstrated that IPC Oxy 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 10: Single-Dose Bioequivalence Results of 80 mg Dosage Strengths of IPC Oxy and OxyContin under Fasted (Study 656-15) (N=30) and Fed Conditions (Study 655-15) (N=29)

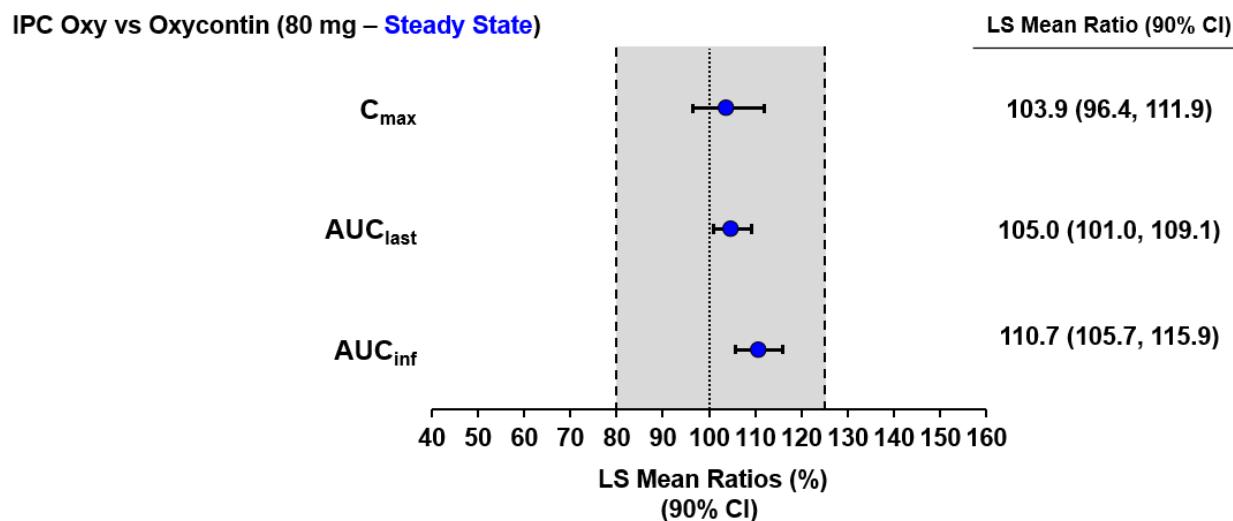


4.2 Multiple-Dose Bioequivalence of IPC Oxy to OxyContin

Study 80-184 evaluated the relative bioavailability of IPC Oxy 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 11 illustrates the primary results of the study, which demonstrated that IPC Oxy 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 11: Multiple-Dose Bioequivalence Results of 80 mg Dosage Strengths of IPC Oxy and OxyContin (Study 80-184)



4.3 Dose Proportionality

Study 80-185 evaluated the dose proportionality of all 7 proposed dosage strengths of IPC Oxy 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 IPC Oxy 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 12 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 12: Dose Proportionality Results for IPC Oxy (Study 80-185) (N=22)

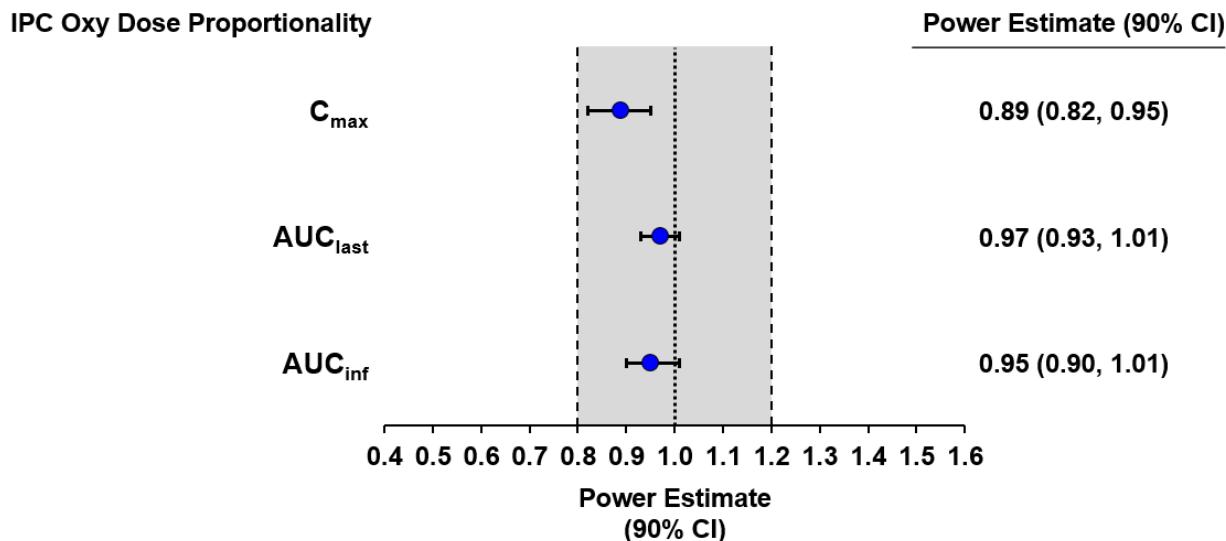


Figure 13, **Figure 14**, and **Figure 15** provide the least-squares means for the ln-transformed pharmacokinetic parameters for each dose. In these analyses, in addition to Subject and Period effects, Dose was also considered as a classification variable. Plots of these least-squares means illustrate the dose proportional responses obtained in this study.

Figure 13: Least Squares Mean Graph for C_{max} (Dose Proportionality Study 80-185) (N=22)

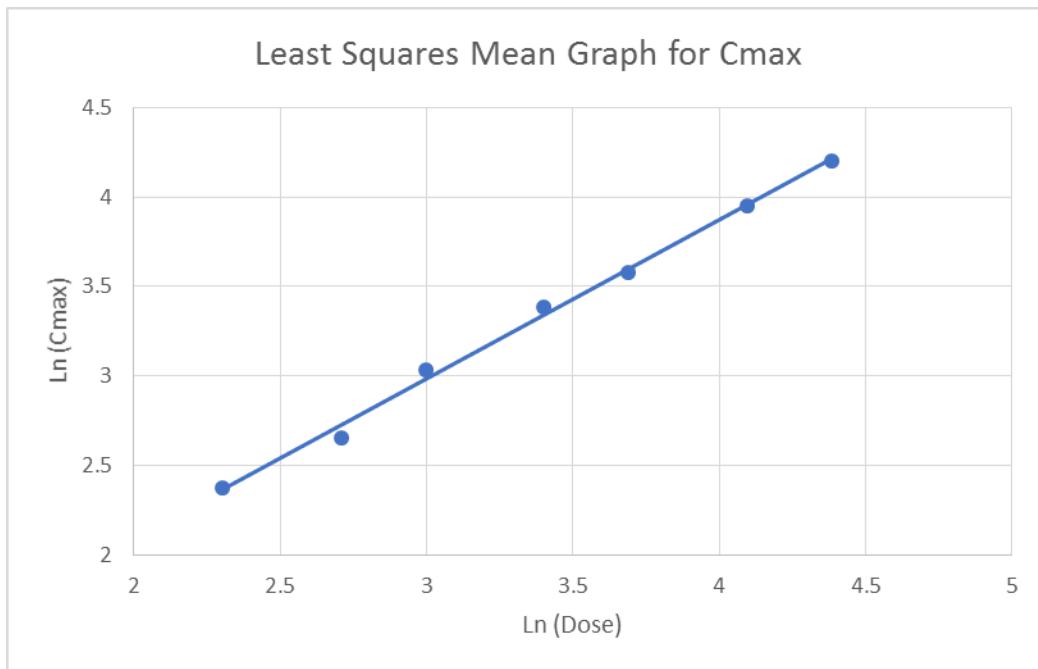


Figure 14: Least Squares Mean Graph for AUC_{0-t} (Dose Proportionality Study 80-185) (N=22)

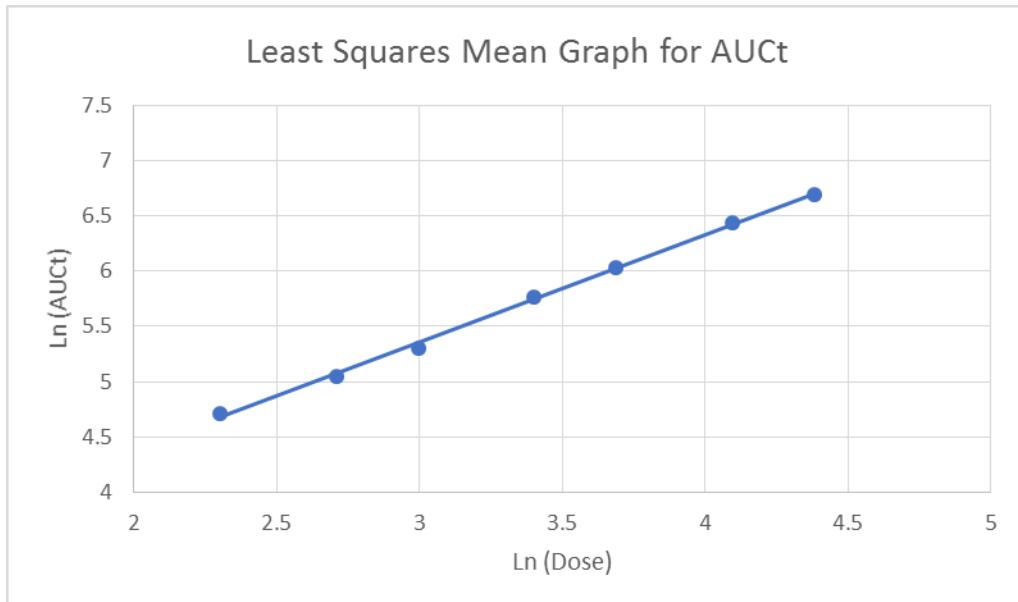
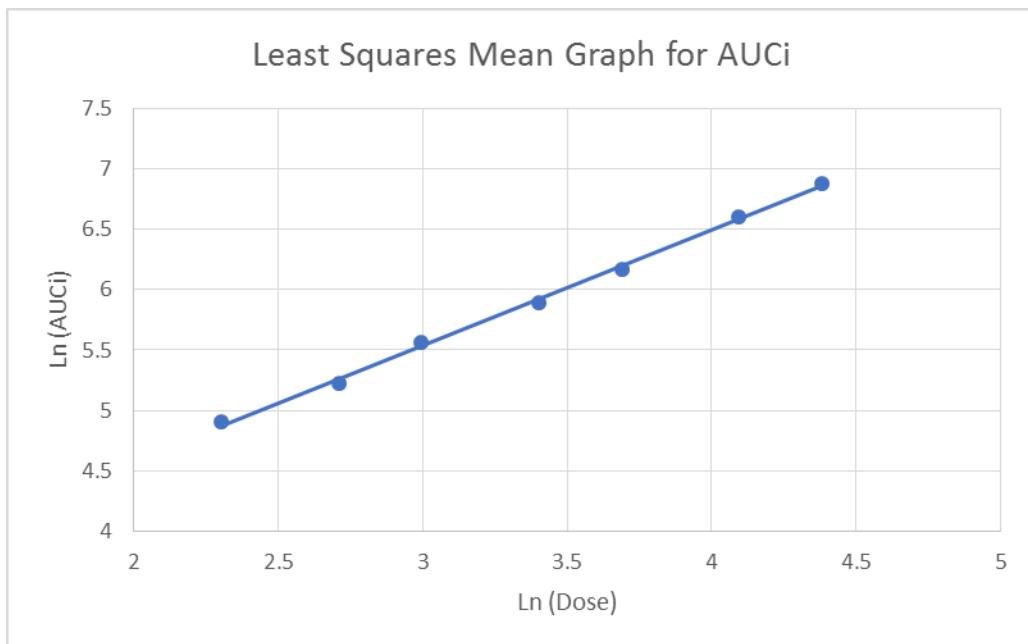


Figure 15: Least Squares Mean Graph for AUC_{0-∞} (Dose Proportionality Study 80-185) (N=22)

4.4 Effect of Food on Bioavailability

Study 80-186 evaluated the effect of food on bioavailability of IPC Oxy at the 80mg 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.

Figure 16 illustrates the mean oxycodone plasma concentration curves in the fed and fasted states.

Figure 17 summarizes the primary study results demonstrating that IPC Oxy 80 mg is bioequivalent in the fed and fasted states. Based on these data, the product may be taken without regard to meals.

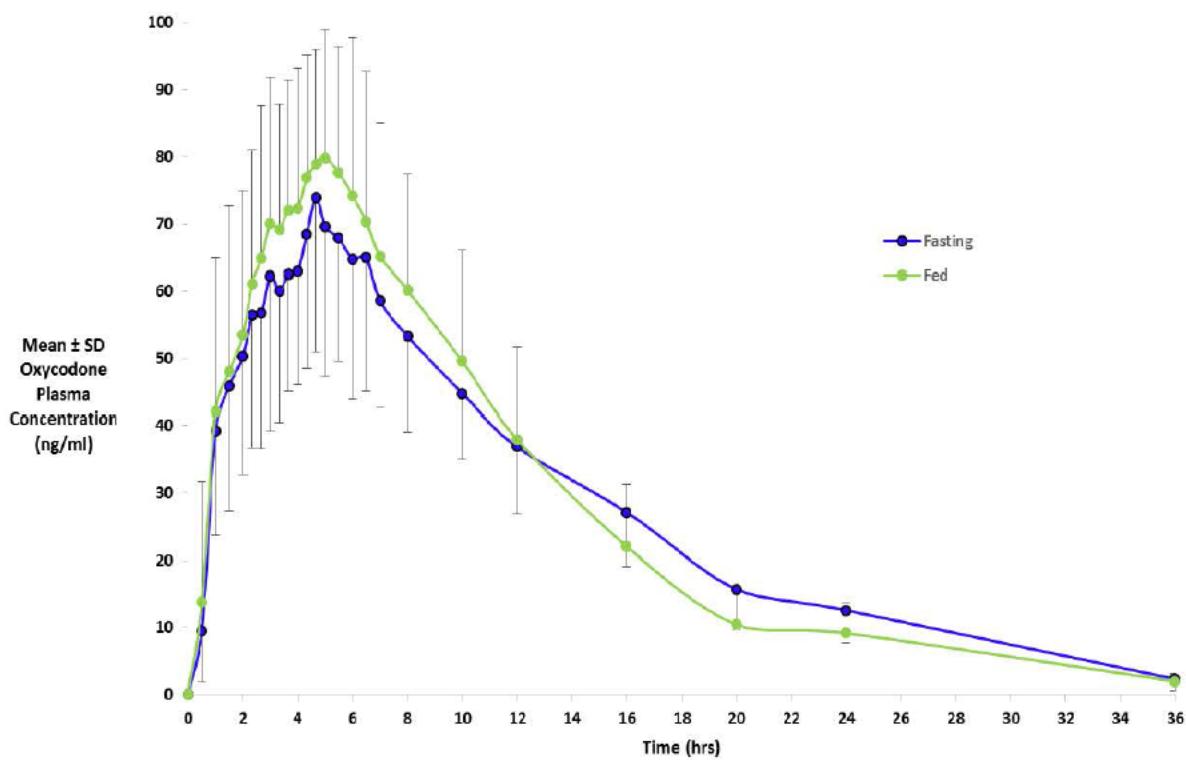
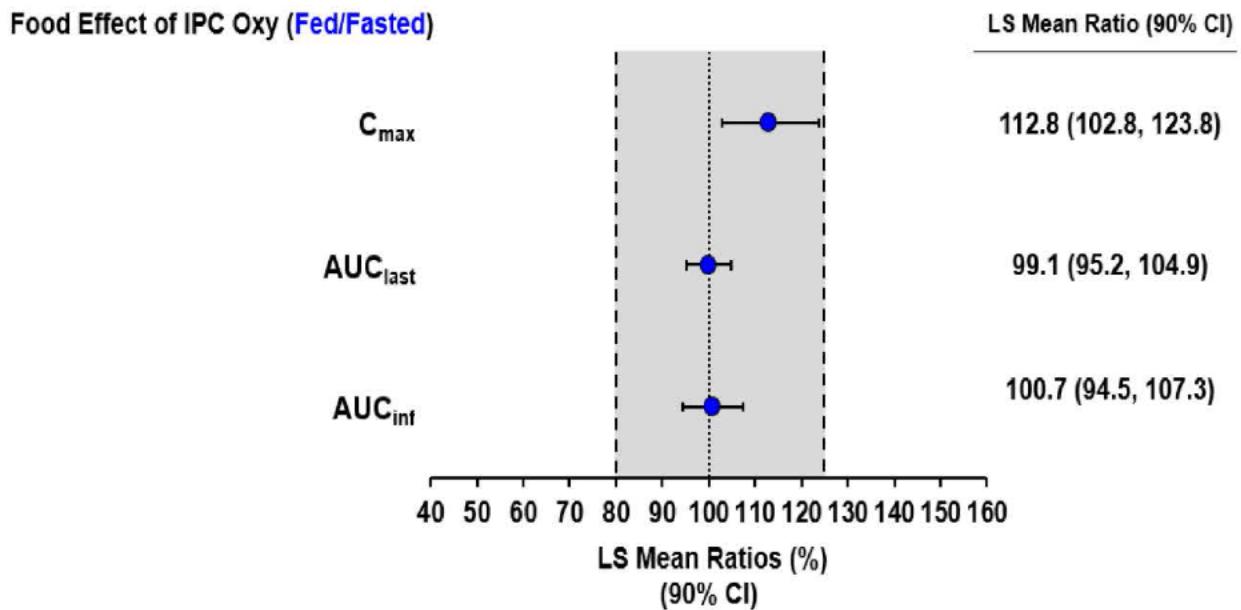
Figure 16: Oxycodone Plasma Concentration Curves for IPC Oxy 80 mg in the Fed and Fasted States (Study 80-186) (N=25)

Figure 17: Bioequivalence Results of IPC Oxy 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 abuse-deterrent formulations.
- OxyContin offered greater resistance to particle size reduction than IPC Oxy, which was expected given the goals of the formulations (i.e., IPC Oxy is formulated to gel more quickly with greater particle size reduction). Both products could be reduced to relatively fine particles.
- IPC Oxy demonstrated greater viscosity when subjected to a liquid environment compared to OxyContin.
- IPC Oxy and OxyContin both offered considerable resistance to the standard methods abusers use to inject solid oral opioid dosage forms.
- Using common “recipes” on drug abuse websites to defeat abuse-deterrent formulations, several conditions were able to yield >60% injectable oxycodone from OxyContin (5/16 conditions), but none for IPC Oxy (0/16 conditions).
- IPC Oxy and OxyContin demonstrated comparable resistance to extraction in large volumes of various solvents that an abuser might use for oral abuse.
- IPC Oxy, just like OxyContin did not dose dump in the presence of alcohol.
- In dissolution studies, the release of oxycodone from IPC Oxy and OxyContin under Tablet Form B, C, D, E and F were similar, which suggests that there is not an increased risk of IPC Oxy for manipulated routes of abuse (e.g., manipulated oral, intranasal) compared to OxyContin. Using Pre-treatment F and G, a common method to overcome abuse-deterrent properties, oxycodone from IPC released considerably more slowly in dissolution than from OxyContin.
- It was not possible to remove the dye or isolate the oxycodone from the dye with IPC Oxy by extraction with a variety of solvents. A considerable amount of time and complex, multi-step, multi-solvent chemical procedures requiring expensive laboratory equipment and advanced chemistry knowledge would be required to isolate oxycodone from the blue dye in IPC Oxy.
- IPC Oxy and OxyContin were not efficiently smoked or vaporized (all conditions released <15% oxycodone in vapor).
- Overall, IPC Oxy demonstrated an incremental 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, IPC conducted a comprehensive series of Category 1, laboratory-based in vitro studies to evaluate the physical and chemical abuse-deterrent properties of IPC Oxy. The studies were conducted in accordance with the 2015 FDA Guidance “*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*”.

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 IPC Oxy and OxyContin as well as the 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. The FDA Guidance recognizes that abuse-deterrent formulations 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.

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.

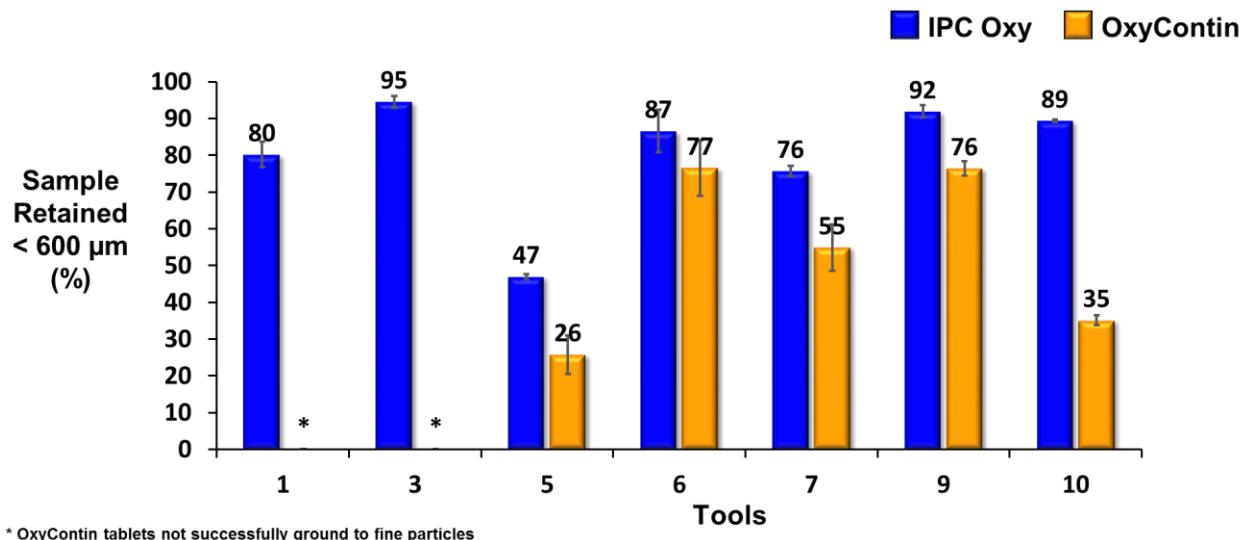
- Oral route, such as by chewing
- Intranasal route, in which the manipulated material is snorted

- 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 of the notion that 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, IPC Oxy tablets have specifically been formulated to deter abuse with enhanced gelling properties when its particle size is reduced or its surface area is increased.

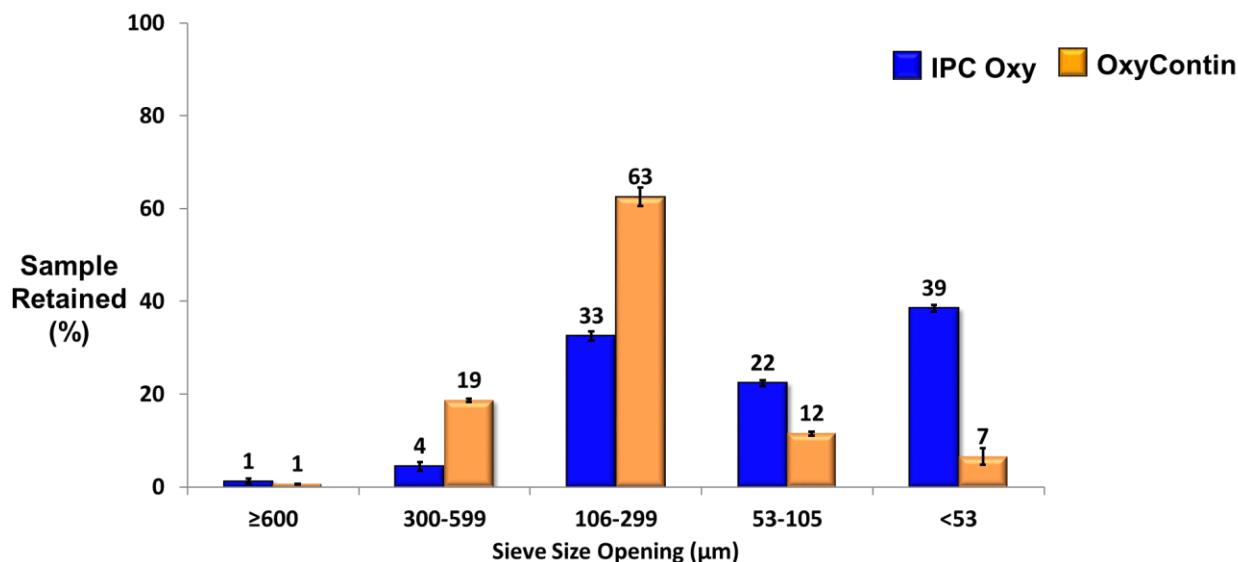
IPC Oxy and OxyContin were evaluated for their resistance to physical manipulation using 10 household tools representative of the different mechanisms used by abusers to crush, cut, grate, or grind solid oral dosage forms with mechanical or electrical tools. Given that tablet hardness is not the primary abuse-deterrent feature of IPC Oxy, it yielded a higher percentage of small particles across the various tools in comparison to OxyContin (**Figure 18**).

Figure 18: Percentage of Particles < 600 Microns Following Particle Size Reduction



Tool 10 was further evaluated because it is known that adding additional tablets to this tool can produce smaller particle size output than a single tablet. Tool 10 was applied for 1, 3, and 5 minutes in an optimization procedure with multiple tablets. After iterative testing, the particle size reduction procedure was optimal when manipulating 20 tablets for 3 minutes. The particle size distribution of IPC Oxy and OxyContin is shown in **Figure 19**. While IPC Oxy 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, IPC Oxy demonstrates rapid gelling when subjected to hydration with small volumes of aqueous solvents. Although IPC Oxy yielded finer particles than OxyContin, the smaller particles actually increased gelling and did not increase drug release or extraction, which is illustrated in the dissolution studies later in this document in Section 5.6.

Figure 19: Particle Size Distribution of IPC Oxy and OxyContin Following Optimal Particle Size Reduction Procedure (Tablet Form B)



5.3 Syringeability/Injectability and Small Volume Extraction 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 abuse-deterrent formulations are designed to resist common methods for IV abuse. Both IPC Oxy and OxyContin are formulated with properties intended to deter IV abuse by producing a highly viscous gel when subjected to an aqueous environment. IPC Oxy is formulated with excipients to enhance this gelling feature even if subjected to a considerable extraction volume or pre-treatment. The in vitro IV abuse studies for IPC Oxy evaluated simple methods for preparing opioid products for injection as well as “recipes” referenced on drug abuse websites to overcome the gelling properties of abuse-deterrent formulations like OxyContin.

In general, following the small volume extraction procedure, laboratory technicians attempted to syringe the material through a small cotton filter starting with the largest needle, Needle Gauge D. If the attempt was successful with Needle Gauge D, the technicians tested smaller needles.

Standard Syringeability/Injectability Studies

For standard syringeability/injectability assessments, samples of IPC Oxy and OxyContin in Tablet Form B were added into various volumes ranging from Volume 1, 2, 3, 4 and 6 of Solvents 1 or 2 and incubated for up to 30 minutes with Agitation A or C at Temperatures A or B. **Figure 20** and **Figure 21** illustrate the gelling properties of both formulations under a standard condition. A similar study was performed using Tablet Form A in Solvent 2, Volume 6 incubated for 5, 10, and 30 minutes with Agitation C at Temperature A or B (No Oxycodone was extracted at Temperature A, while less than 10% was recovered at Temperature B). None of the conditions yielded an appreciable volume of injectable oxycodone (i.e., only able to load <20%) for either IPC Oxy or OxyContin, which supports that both IPC Oxy and OxyContin have abuse-deterrent properties for the IV route under these standard conditions.

Figure 20: Syringeability/Injectability Assessments - IPC Oxy and OxyContin Tablet Form B, Solvent 1, Agitation A, Temperature A (2.5 Minutes)

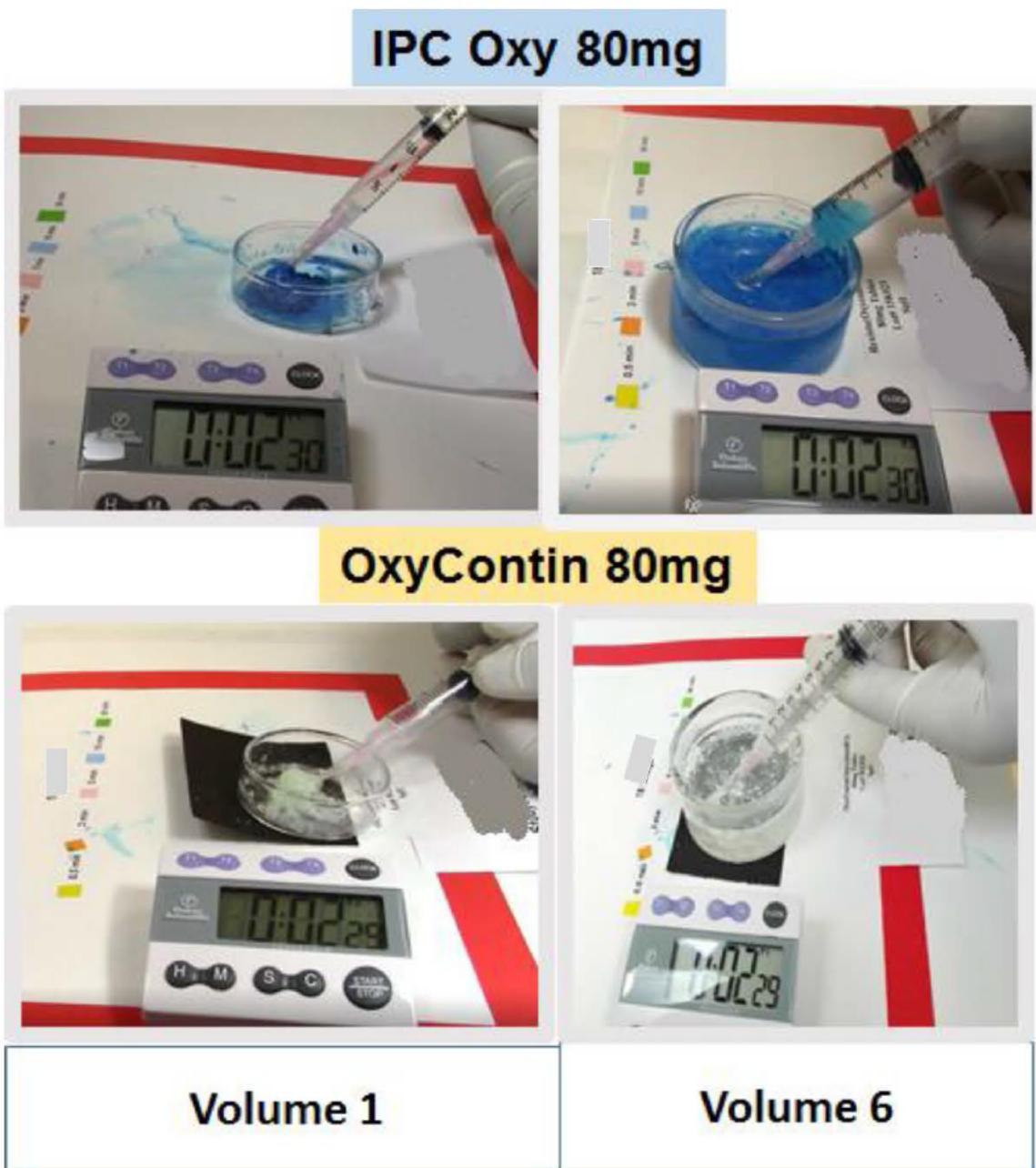
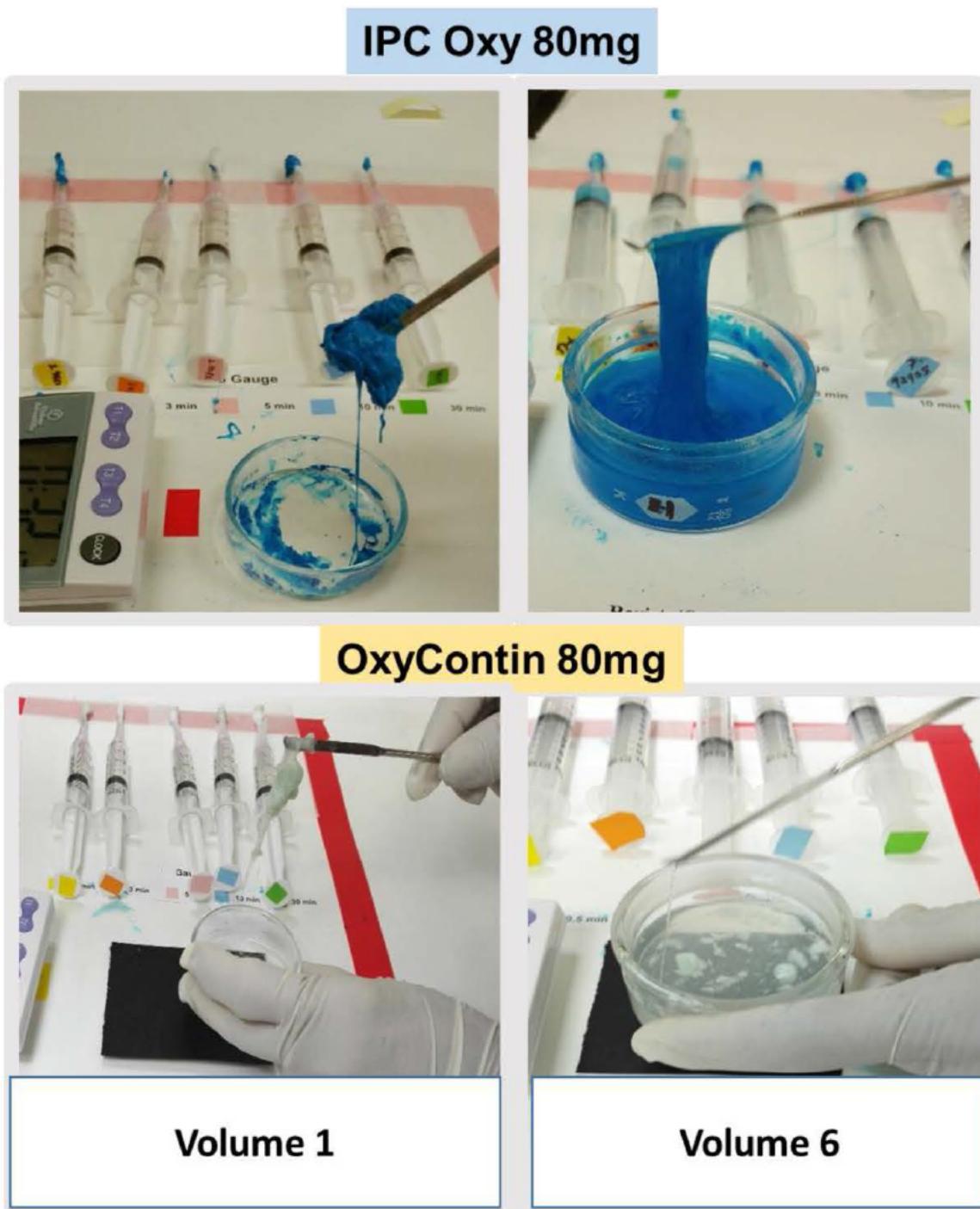


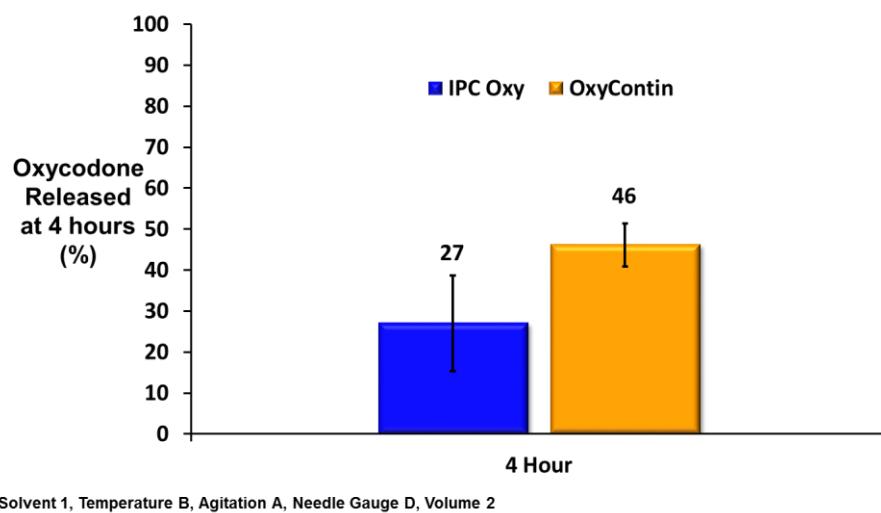
Figure 21: Syringeability/Injectability Assessments - IPC Oxy and OxyContin Tablet Form B, Solvent 1, Agitation A, Temperature A (30 Minutes)



Gel-Blob Syringeability

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, IPC Oxy and OxyContin in Tablet Form B were added to Volume 2 of Solvent 1 and incubated for 4 and 24 hours at Temperature A and B. It was not possible to load the syringe with solution from either product with more than 20% volume with Needle Gauge D at Temperature A, while at Temperature B it was more difficult to load the syringe with solution for IPC Oxy compare to OxyContin, **Figure 22**.

Figure 22: Gel-Blob Syringeability Studies - IPC Oxy vs OxyContin Tablet Form B, Solvent 1, Temperature B, Agitation A, Needle Gauge D, Volume 2

Syringeability/Injectability Studies Using Recipe from Drug Abuse Websites

One of the most common methods cited on drug abuse websites (e.g., bluelight.org) to overcome the IV resistance of abuse-deterrent formulations is to perform Pre-treatment D prior to extraction. For this study, Pre-treatment D was applied to IPC Oxy and OxyContin under Tablet Form B followed by extraction in Volumes 1, 2, and 3 of Solvent 1 and incubated for up to 5 minutes with Agitation A at Temperatures A or B. For example, using Needle Gauge A, at Temperature A, Volume 1, after a 30 second incubation period, a higher yield of injectable oxycodone was obtained from OxyContin (40%) compared to IPC Oxy (20%). Also, after 30 second incubation period at Temperature B, Volume 1, a higher yield of injectable oxycodone was obtained from OxyContin (65%) compared to IPC Oxy (15%). **Figure 23** and **Figure 24** show pictures from these studies and **Figure 25** shows yield of oxycodone.

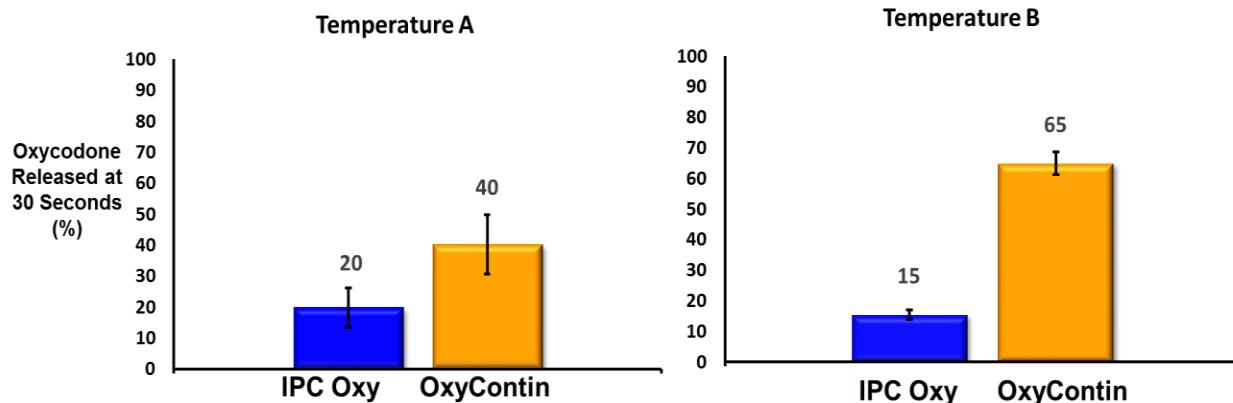
Figure 23: Photos of IPC Oxy Tablet Form B (left) and OxyContin Form B (right) following Pre-treatment D and Extraction in Solvent 1 after 30 Seconds of Incubation with Agitation A at Temperature A using Needle Gauge A



Figure 24: Photos of IPC Oxy Tablet Form B (left) and OxyContin Tablet Form B (right) following Pre-treatment D and Extraction in Solvent 1 after 30 Seconds of Incubation with Agitation A at Temperature B using Needle Gauge A



Figure 25: IPC Oxy vs. OxyContin Tablet Form B, Yield of Oxycodone in Volume 1 of Solvent 1 following Pre-treatment D after 30 Seconds of Incubation with Agitation A at Temperature A and Temperature B using Needle Gauge A



Similar results were found when multiple-tablet extractions were attempted with Pre-treatment D. Ultimately, across the 16 different combinations of Pre-treatment D conditions evaluated (i.e., temperature, agitation, solvent volumes, single vs. multiple-tablet extractions), 5 of the 16 conditions with OxyContin yielded >60% recovery of oxycodone, while for IPC Oxy, none of the 16 conditions yielded >60% recovery of oxycodone.

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 and advanced 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 IPC Oxy and OxyContin 80 mg Tablet Form B equivalents in large volumes was evaluated in 21 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, for the most common ingestible solvents (e.g., Solvent 1, 2, 4, 5, and 14, **Figure 26**, and non-ingestible solvents (e.g., Solvent 3, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, **Figure 27**).

Figure 26: Extraction Studies of IPC Oxy and OxyContin Tablet Form B in Ingestible Solvents in Temperature A, Agitation A, Volume 7

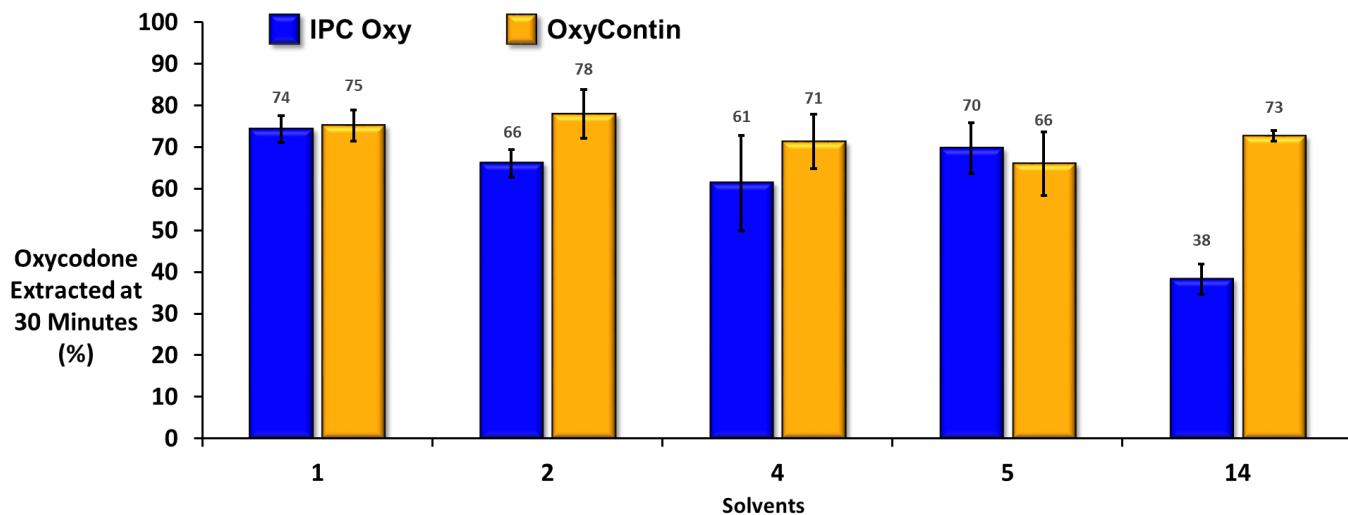
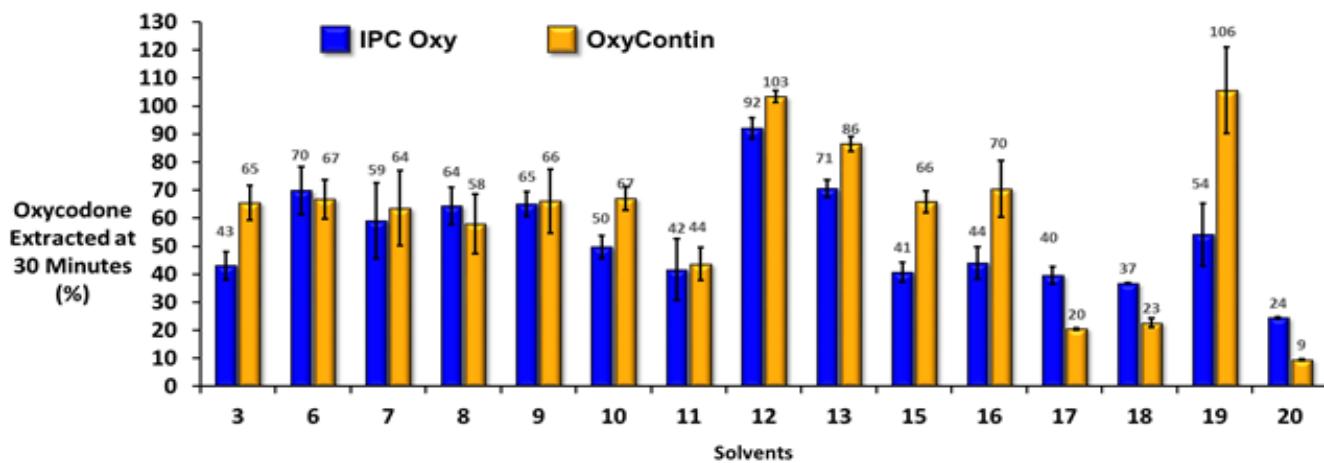


Figure 27: Extraction Studies of IPC Oxy and OxyContin Tablet Form B in Non-Ingestible Solvents in Temperature A, Agitation A, Volume 7

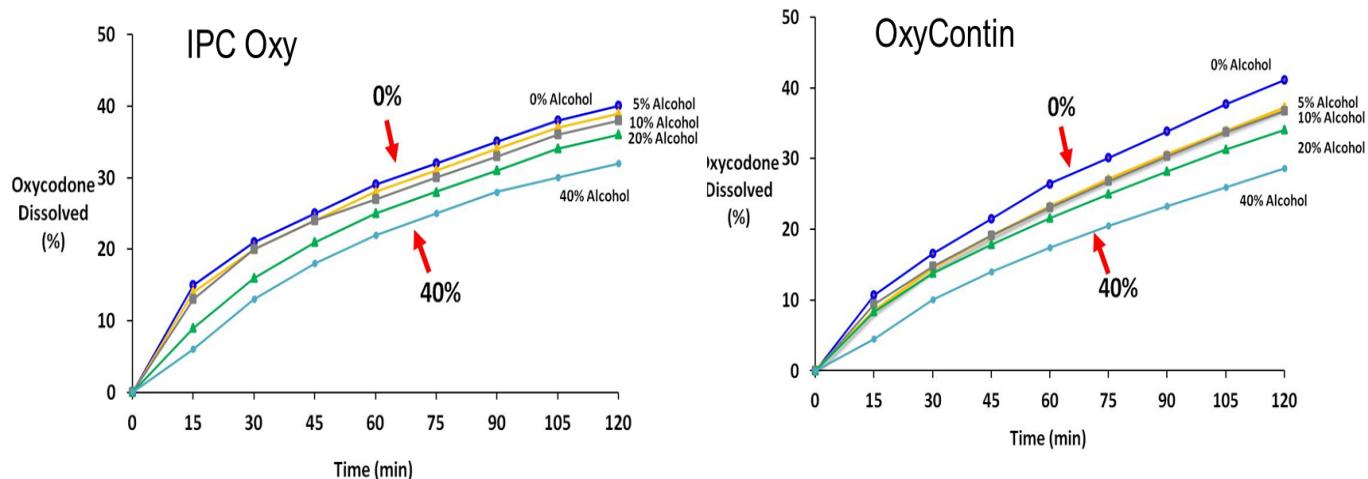


5.5 Alcohol Dose Dumping Study

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 IPC Oxy would result in alcohol dose dumping, in vitro dissolution experiments were conducted using different concentrations of alcohol under Dissolution Conditions A and B.

The in vitro alcohol dissolution study provides evidence that the co-ingestion of alcohol with IPC Oxy would not lead to dose dumping. Rather, **Figure 28** illustrates that oxycodone release from IPC Oxy decreased as the concentration of alcohol increased just like for OxyContin. Similar results were observed in Dissolution Condition B, in which higher alcohol concentrations were associated with slower oxycodone release.

Figure 28: Percent Oxycodone Dissolved of IPC Oxy and OxyContin Tablet Form A in Varying Concentrations of Alcohol in Dissolution Condition A



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 29 illustrates the dissolution profiles of IPC Oxy and OxyContin under Tablet Form B, which corresponds to tablets after the optimal particle size reduction procedure, in Dissolution Condition A. This demonstrates that the smaller particle size distribution of IPC Oxy did not lead to a faster release of oxycodone than from OxyContin. Rather, the smaller particles likely enhanced the gelling properties and slowed oxycodone release at early time points.

Figure 30 and **Figure 31** show amount of drug released from IPC Oxy and OxyContin in Tablet Forms B, C, D, E, and F using Dissolution Conditions A and B. The release of oxycodone was similar between the products.

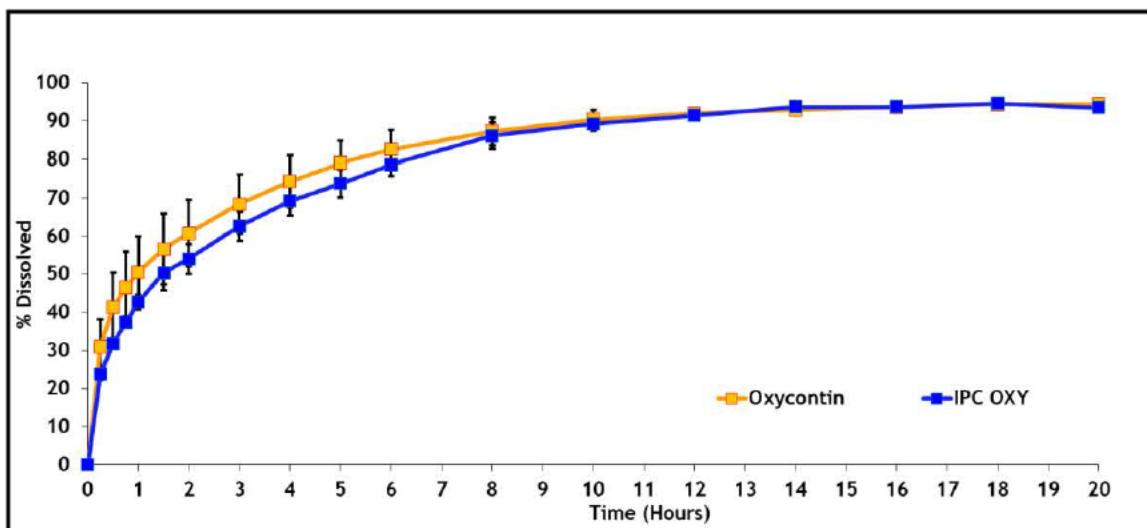
Figure 29: Dissolution of IPC Oxy and OxyContin under Tablet Form B in Dissolution Condition A

Figure 30: Comparative Dissolution Profile: IPC Oxy vs. OxyContin Tablet Form C, D, E and F in Dissolution Condition A

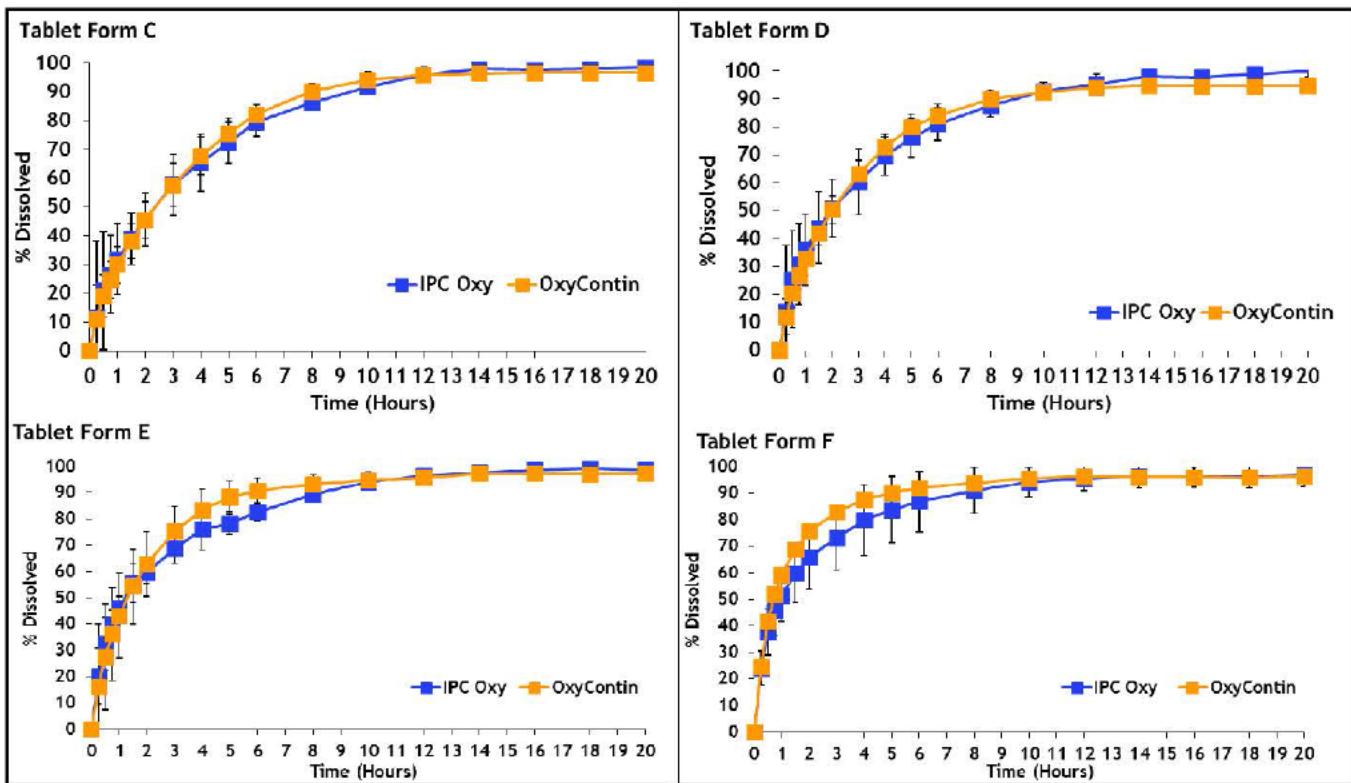
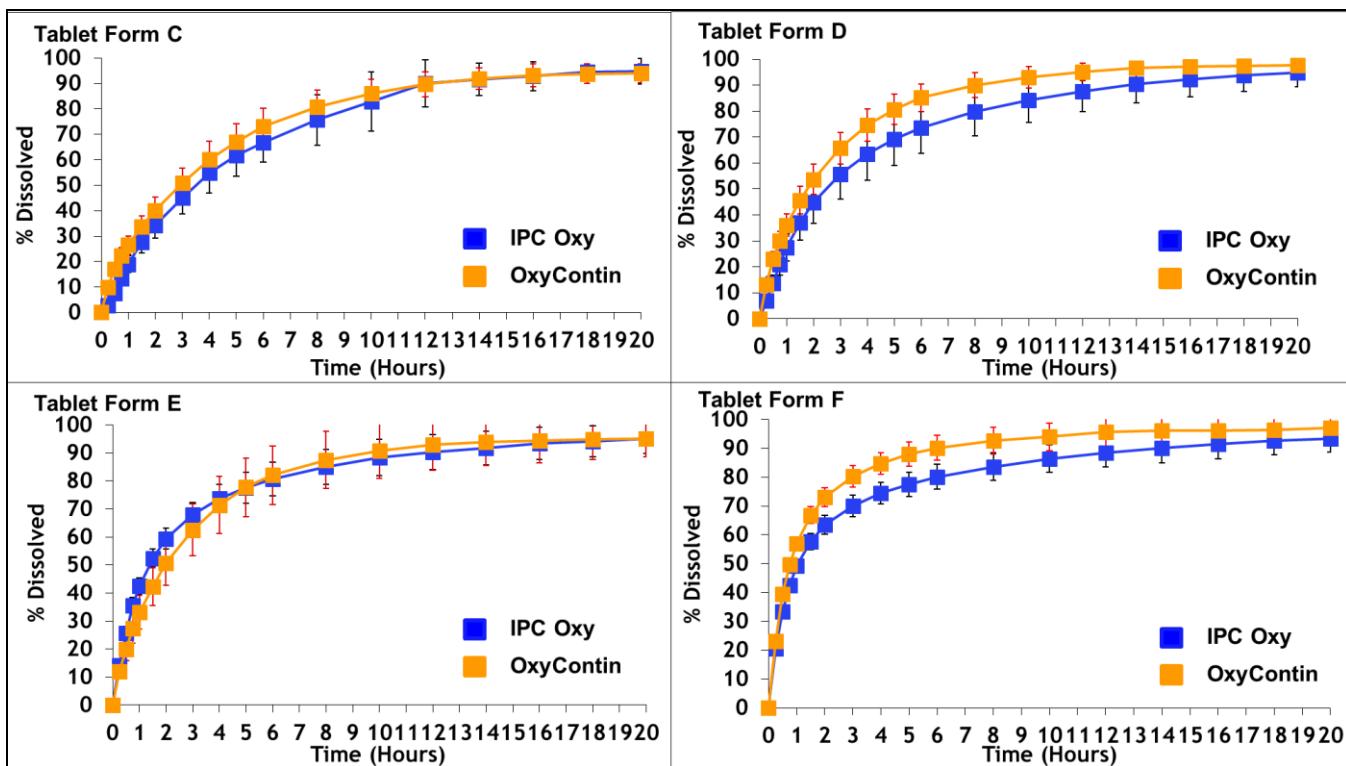
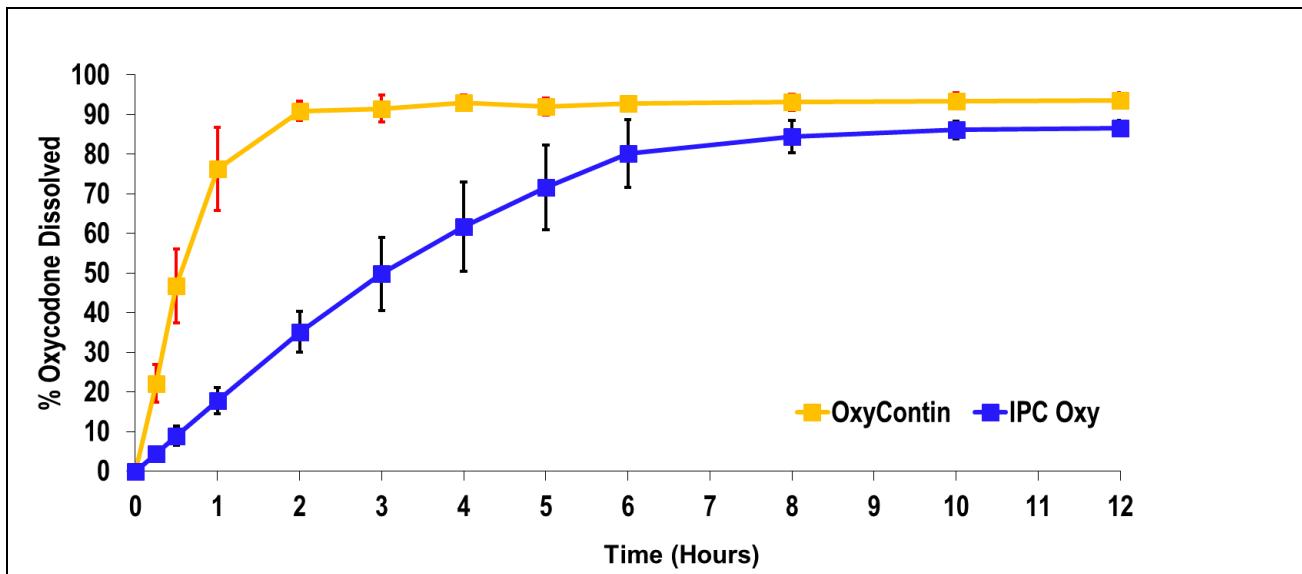


Figure 31: Comparative Dissolution Profile: IPC Oxy vs. OxyContin Tablet Form C, D, E and F in Dissolution Condition B


As previously mentioned, a common set of pre-treatments to abuse-deterrent formulations (i.e., Pre-treatment D, F, and G) have been identified on drug abuse websites to defeat abuse-deterrent properties. **Figure 32** illustrates the dissolution profiles of IPC Oxy and OxyContin under Tablet Form A following Pre-treatment F in Dissolution Condition C. (Similar results were observed for Pre-treatment G.) These results demonstrate that IPC Oxy has greater resistance against pre-treatments known to defeat currently-marketed abuse-deterrent formulations. These results are also consistent with the results of syringeability/injectability experiments where the abuse-deterrent properties of OxyContin were compromised following Pre-treatment D, while IPC Oxy remained resistant to syringing.

Figure 32: Dissolution of IPC Oxy and OxyContin under Tablet Form A Following Pre-Treatment G in Dissolution Condition C

5.7 Dye Elimination Studies

One of the unique putative abuse-deterrant features of IPC Oxy is the blue dye, which is formulated to release if a tablet is physically manipulated. If a method of separation or degradation of the dye to provide near colorless solutions or white ground material could be discovered, this could make IPC Oxy more attractive to abusers. Consequently, a series of tests was designed to systematically study attempts to eliminate the dye from oxycodone with solvent extraction and photo and chemical degradation. Unlike large volume extraction studies that evaluated a wide range of different solvents of pH and polarity, the solvents and conditions used in the dye elimination studies were specifically chosen based on knowledge of the product's chemistry.

Table 2 provides the results from attempts at solvent extraction. Solvents 11, 13, 18 and 23 could not separate the blue dye from the oxycodone. Solvents 20 and 24 separated oxycodone from the dye, however, the yield of oxycodone was low, with 38% and 0% recovery in filtrate, respectively.

Table 2: Dye Elimination Results with Single Solvents IPC Oxy Tablet Form B at Temperature A

Solvent	Initial Color	Average Oxycodone Recovery (Color)	
		Filtrate	Residue
Solvent 11	Blue	89.6% (Blue)	8.8% (Light Blue)
Solvent 13	Blue	96.7% (Blue)	0.2% (Deep Blue)
Solvent 18	Blue	97.3% (Blue)	0.6% (Deep Blue)
Solvent 23	Blue	44.8% (Blue)	43.3% (Light Blue)
Solvent 20	Blue	38.0% (Colorless)	52.3% (Deep Blue)
Solvent 24	Blue	0.0% (Colorless)	76.8% (Deep Blue)

Based on the chemical properties of IPC Oxy, a variety of pre-treatments for the ability to eliminate the blue dye were also evaluated in Solvents 25, 26, and 27.

- With Solvent 25, Pre-treatments B and E did not eliminate the blue dye and yielded only 48% and 51% oxycodone, respectively (**Table 3**).
- With Solvent 26, Pre-treatments B and E eliminated the blue dye but only yielded 16% and 17% oxycodone, respectively (**Table 4**).
- With Solvent 27, Pre-treatments B and E did not eliminate the blue dye and only approximately 5% oxycodone was recovered in both conditions (**Table 5**).

Table 3: Dye Elimination Results with Solvent 25 IPC Oxy Tablet Form B with Pre-treatment

Tablet Form B Solvent 25	Initial Color	Average Oxycodone Recovery (Color)	
		Filtrate	Residue
Pre-treatment A	Blue	49.6% (Blue)	0.1% (Light Blue)
Pre-treatment B	Blue	47.7% (Blue)	0.1% (Light Blue)
Pre-treatment E	Blue	51.3% (Blue)	0.2% (Light Blue)

Table 4: Dye Elimination Results with Solvent 26 IPC Oxy Tablet Form B with Pre-treatment

Tablet Form B Solvent 26	Initial Color	Average Oxycodone Recovery (Color)	
		Filtrate	Residue
Pre-treatment A	Blue	19.2% (Colorless)	1.1% (Colorless)
Pre-treatment B	Blue	15.5% (Colorless)	3.6% (Colorless)
Pre-treatment E	Blue	16.8% (Colorless)	0.9% (Colorless)

Table 5: Dye Elimination Results with Solvent 27 IPC Oxy Tablet Form B with Pre-treatment

Tablet Form B Solvent 27	Initial Color	Average Oxycodone Recovery (Color)	
		Filtrate	Residue
Pre-treatment A	Blue	5.2% (Blue)	0.1% (Light Blue)
Pre-treatment B	Blue	5.1% (Blue)	0.1% (Light Blue)
Pre-treatment E	Blue	5.2% (Blue)	0.1% (Light Blue)

In order to test the dye to failure in accordance with FDA Guidance, a complex, multi-step process that took approximately 5 hours, several solvents, advanced laboratory equipment, and multiple modifications to temperature was attempted to separate out the blue dye. This process yielded 82% recovery of oxycodone salt with relatively high purity (84%). Due to considerable time, effort, advanced resources, and chemistry knowledge required, it is not anticipated that this procedure would be a feasible manipulation for abuse.

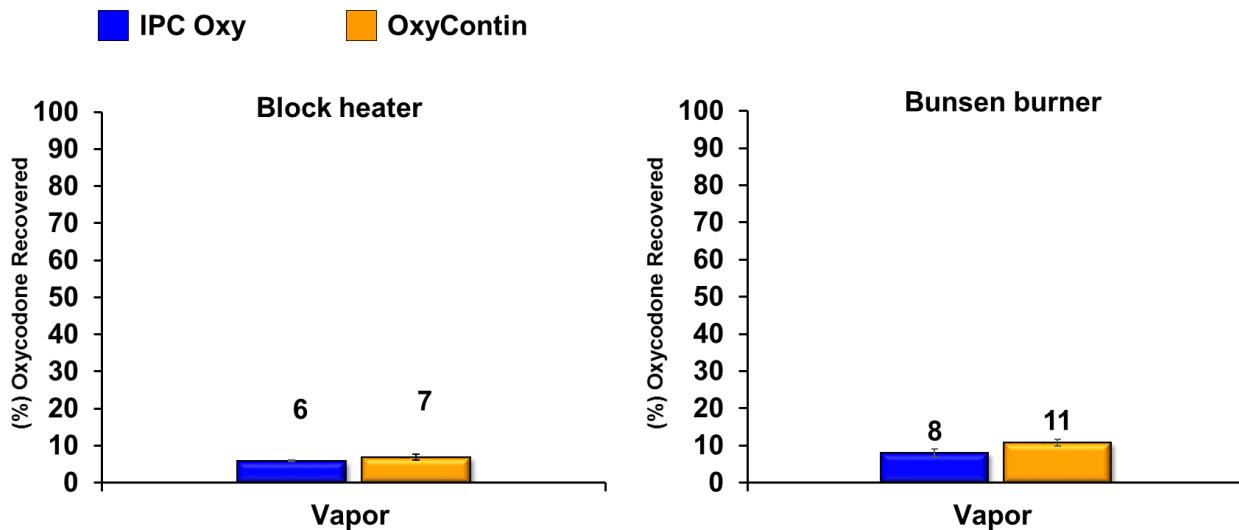
5.8 Simulated Smoking/Vaporization Studies

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 IPC Oxy and OxyContin. The temperatures and times selected for these studies were based on exploratory study with pure API to determine the optimal heating time and temperature.

Vaporization of IPC Oxy and OxyContin using optimal conditions with a block heater produced approximately 6% and 7% oxycodone in vapor. Applying direct heat with a Bunsen burner yielded 8% oxycodone recovery from IPC Oxy and 11% from OxyContin. Neither method would be considered an efficient route of abuse for either product (**Figure 33**).

Figure 33: Simulated Smoking Using Optimal Temperature (Block Heater) and Extreme Temperature (Bunsen Burner)



6 CLINICAL PERSPECTIVE ON IPC OXY

6.1 Bioequivalence of IPC Oxy to OxyContin

The clinical PK program has demonstrated that IPC Oxy is bioequivalent to OxyContin at the highest and lowest dosage strengths, in fed and fasted states, and at steady state. Together, these data provide evidence that IPC Oxy 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 IPC Oxy without regard to meals. Therefore, IPC Oxy 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.

6.2 Incremental 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 abuse-deterrent formulations, which can be found easily on drug abuse websites. IPC Oxy has demonstrated superior resistance compared to OxyContin against these procedures to defeat abuse-deterrent formulations, which represents an important incremental improvement in abuse-deterrent technology. Therefore, IPC Oxy has also met the standard outlined in the 2015 FDA Guidance for abuse-deterrent labeling for the IV route of abuse.

6.3 Post-Marketing Plans

If IPC Oxy is approved, IPC would become an active member of the Extended-Release/Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Companies (RPC). As such, IPC would fulfil the post-marketing study requirements of the Opioid Post-marketing Consortium (OPC) regarding the safe use of ER/LA opioid analgesics.

In addition, if IPC Oxy is approved, IPC would work with the FDA to design a series of Category 4 post-approval epidemiologic studies to evaluate the effect of IPC Oxy on abuse in the real world. Concurrently, IPC would complete Category 2 and 3 pharmacokinetic/pharmacodynamic studies to evaluate the human abuse potential of IPC Oxy for the oral and nasal routes of abuse. Upon completion of the HAP studies, IPC would submit a supplemental NDA to the Agency to request Category 2/3 labeling if results supported abuse deterrence for additional routes of abuse.

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