

# Expanding hot-melt extrusion based abuse-deterrent formulation technology from extended release (ER) to immediate release (IR) application

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## Misuse and Abuse of Prescription Drugs

Prescription pain relievers are safe and effective when used correctly for a medical condition and under a doctor's supervision. But they can cause serious side effects if not used correctly. Incorrect use or use for non-medical reasons can lead to abuse, addiction and even death<sup>1)</sup>.

SAMHSA recently reported results from their 2014 Survey on Drug and Health<sup>2)</sup>. About 4.3 million people age twelve and older reported nonmedical use of prescription pain relievers including opioid-containing drugs such as hydrocodone (Vicodin®), oxycodone (OxyContin®, Percodan®, Percocet®), and fentanyl (Duragesic®) during the past month<sup>2)</sup>.

## Risks of Rx Opioid Abuse

Frequent non-medical use of prescription psycho-therapeutic medications can lead to aberrant behavior and addiction. Death from respiratory depression can occur from misusing or abusing prescription opioids<sup>3)</sup>. In general, risks from nonmedical use and abuse of these drugs can be even worse when they are combined with other drugs or alcohol<sup>4)</sup>.

Although the most common form of misuse and abuse of prescription drugs is swallowing the product whole, abusers frequently manipulate the products for non-oral routes of abuse and to increase the rate or extent of the drug release. This leads to a stronger euphoric effect when administering the manipulated form intra-nasally (IN) or intravenously (IV). Intranasal and intravenous abuse routes are associated with more severe consequences than oral administration. For example, they have been linked with larger proportion of moderate and major adverse events including overdose, and death<sup>5),6),7),8)</sup>. Intravenous opioid abuse is associated with human immunodeficiency virus (HIV) and hepatitis B and C infection risk<sup>9)</sup>, while intranasal opioid abuse has been associated with nasal, palatal, and pharyngeal necrosis<sup>5),6),7)</sup>.

## Abuse-Deterrent Technology for ER opioids

Over the past years different technology approaches have been developed aiming at reducing the amount of misuse, abuse, and diversion of extended release opioids. Formulations with increased resistance to mechanical manipulation demonstrated to have the potential to deter certain forms of illicit use because they cannot be easily crushed into forms that are readily snorted or injected<sup>10),11),12)</sup>. After the introduction of reformulated OxyContin® in 2010, the rate of abuse and death associated with the product have decreased<sup>13),14),15)</sup>. It was observed by abuse surveillance systems like RADARS®<sup>16)</sup> or NAVIPPRO®<sup>17)</sup> that abuse shifted away from products that utilize abuse deterrent technology towards other opioids that were easier to manipulate for the purpose

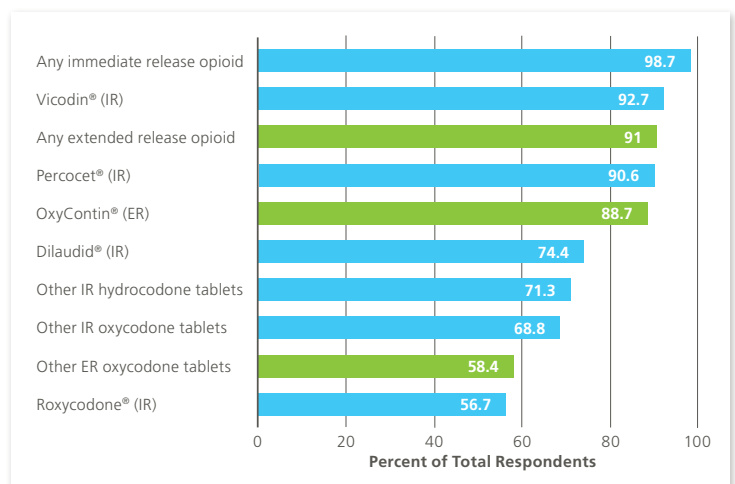
of abuse. As part of this shift, a substantial increase in the abuse of immediate release (IR) opioids was noted<sup>16),17),18),19),20)</sup>.

## Abuse patterns of IR opioids and the need for IR ADF technology

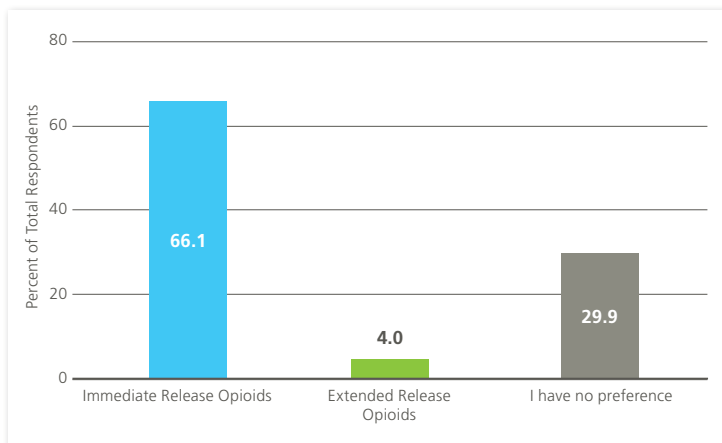
Manufacturers and regulators initially focused on technologies for ER formulations, since the release properties of conventional extended-release tablet formulations can be compromised easily making most, if not all, of the drug load readily available for swallowing, snorting or extraction. However, due to much higher availability of IR opioid products (both as single-entity and fixed-dose combination) in comparison to ER opioids, the population impact of the non-oral abuse of IR products is comparable given absolute numbers for abuse incidents.

A recent study investigated the abuse prevalence and preference of IR versus ER opioids in a population of individuals entering addiction treatment centers<sup>21)</sup>. The main findings according to the authors were:

1. Nearly all prescription opioid abusers have abused both immediate and extended release formulations (see Figure 1).
2. Non-oral routes of administration are used with similar, high frequencies for both immediate and extended release opioids<sup>21)</sup>.
3. Immediate release opioids are preferred by a wide margin over extended release opioids for abuse purposes, driven by the ease of which the immediate release products can be manipulated (see Figure 2).

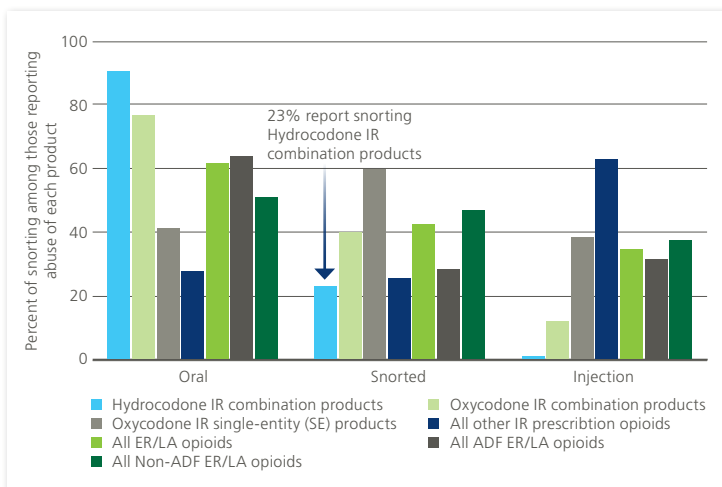


**Figure 1) Lifetime prevalence of opioid abuse**  
(reproduced from Cicero et al.)<sup>21)</sup>



**Figure 2)** Formulation preferences (IR versus ER opioids) of prescription opioid abuse (reproduced from Cicero et al.)<sup>21)</sup>

The results are consistent with findings from earlier investigations<sup>22)</sup>,<sup>23)</sup> by other authors which addressed the relevance of IR opioid abuse (single-entity and fixed-dose combinations) via non-oral routes and demonstrate the need and potential value of ADF technology for this product class (see Figure 3).



**Figure 3)** Route of administration for opioid abuse (reproduced from Cassidy et al.)<sup>22)</sup>

Consequently, manufacturers are working to develop technologies to make common forms of manipulation and abuse more difficult for IR opioid products as well.

### Expanding an established ER ADF Technology to IR products

Building on its established abuse deterrent formulation technology INTAC<sup>®</sup>, applying a hot-melt extrusion (HME) process tightly embedding the active ingredient into a homogenous matrix formulation based on polyethylene-oxide (PEO) of high molecular weight, Grünenthal GmbH (Aachen, Germany) was successful to extend the application of this versatile approach to the immediate-release application space. Unlike with ER formulations, crushing and dissolving of IR tablets for oral abuse does not significantly alter their inherent fast-release profile. Therefore the focus in extending the INTAC<sup>®</sup> formulation platform is to impede preparation for non-oral abuse of IR products without impacting the desired IR functionality. Consequently, a multi-particulate based formulation has been developed that exhibits gelling properties leading to low

extraction rates and is expected to make the abuse via the intravenous route more difficult. The pronounced resistance against crushing of the pellets at the same time presents a barrier towards attempted preparation for nasal abuse. The multi-particulates (IR pellets) have a diameter of approximately one millimeter and are not considered suitable for abuse via snorting<sup>24)</sup>,<sup>25)</sup>,<sup>26)</sup>.



**Figure 4)** Process overview of INTAC<sup>®</sup> hot-melt extrusion manufacturing concept for ER and IR products (taken from Wening et al.)<sup>28)</sup>

The process for INTAC<sup>®</sup> IR deploys a similar HME process step as for INTAC<sup>®</sup> based ER products, but a different downstream process using a plurality of smaller dies and subsequent hot-phase cutting is applied (Figure 4). This delivers the multi-particulate pellets which exhibit immediate release properties and can be further processed into different dosage forms. For the manufacturing of the pellets a twin-screw extruder together with a pelletizer was used. Pellets were blended with granules or powder as outer phase for either tableting or filling into capsules.



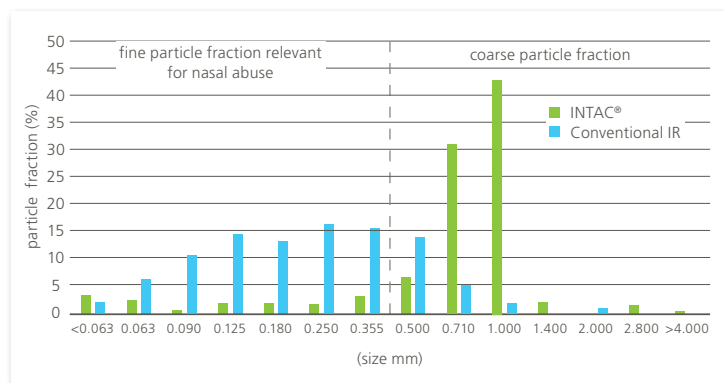
**Figure 5)** a) INTAC<sup>®</sup> IR pellets; b) IR tablet manufactured on rotary press; c) IR fixed-dose combination capsule (pellets colored for illustration purpose only); d) IR tablet with non-functional cosmetic coating (Wening et al.)<sup>28)</sup>

The blend for tableting was compressed into round shaped tablets using a rotary tablet press. Tablet cores were finally coated in a drum coating process with a non-functional coating. The Pellet blend for capsules was filled into capsules by a fully automated capsule filling machine<sup>26)</sup> (see also Figure 5).

### In-vitro ADF Characterization

The science of in-vitro characterization of abuse-deterrent technology is rapidly evolving as more and more products and approaches are being developed. As of today there is no universally accepted standard for in-vitro testing of ADFs that would honor the different aspects of abuse-deterrence for different approaches and products. Consequently, sponsors and FDA have to interact and iteratively discuss the testing strategies and methods and review the resulting data for a given product on a case-by-case basis. Nevertheless, there are commonly accepted and meaningful approaches which can be deployed early in development to initially characterize properties of the product and the formulation composition under consideration. In the following we present data from some of these initial in-vitro tests that have been applied to characterize different products under development in order to show the applicability of INTAC<sup>®</sup> IR as a broad platform. However, it should be noted that the data and tests presented here are not considered a comprehensive basis for regulatory approval of ADF labeling, but rather represent selected examples and feasibility results. A much larger set of tests under a variety of test conditions will be required in order to allow for an assessment of the abuse-deterrent characteristics of the product for the purpose of ADF labeling.

As mentioned in the previous section, the first focus of in-vitro characterization in the development setting is on the preparation for intranasal and intravenous abuse. The example in Figure 6 shows the resistance to manipulation for intranasal abuse preparation for an INTAC<sup>®</sup> IR product where samples were milled for two minutes in a coffee grinder. Afterwards the particle size distribution (PSD) was determined by sieve analysis<sup>25)</sup>. The PSD analysis shows that the majority of the particles are larger than 500µm. This is expected to make intranasal abuse less attractive as particles exceeding 500µm show increasingly unpleasant effects based on literature data<sup>24), 25)</sup>.



**Figure 6)** Particle size distribution after tampering for a conventional IR tablet and INTAC<sup>®</sup> based tablet (taken from Bartholomäus et al.<sup>24)</sup>

When exposed to liquid the pellets form a highly viscous gel that makes abuse via the intravenous route difficult. To simulate IV preparation in a development test setting samples were placed into 5ml water, heated until boiling and kept boiling for 5 min. The resulting supernatant was attempted to be drawn into a syringe (Figure 7). The amount of liquid in the syringe was determined and tested for assay of API by HPLC measurements<sup>25)</sup>.

INTAC<sup>®</sup> IR multiparticulate tablet after attempted preparation for i.v. abuse



Substantially restricted availability of resulting extract for i.v. abuse



**Figure 7)** Result of an attempt to prepare INTAC<sup>®</sup> IR pellets for intravenous abuse (taken from Bartholomäus et al.<sup>24)</sup>

A number of initial feasibility studies, including assessment of stability, dissolution properties, and in-vitro manipulation resistance have demonstrated that the technology can be applied to a broad range of opioids (see Tables 1 and 2). The release profiles comply with the USP specifications for immediate release products<sup>25), 26)</sup>.

Comparing the results from Tables 1 and 2 conveys that although INTAC<sup>®</sup> provides as a platform technology each opioid formulation requires individual attention and optimization during development. The formulations used for the testing of the different opioids as shown in Tables 1 and 2 had the same composition within the series but the compositions were different between the series presented in Table 1 versus those in Table 2. In regard to the results from the initial screening tests for IV extraction (boiling for 5 minutes in 5mL of water) it becomes apparent that different opioids require different compositions for optimized in-vitro results.

Formulation "B"	Batch	Test battery IV (5ml H <sub>2</sub> O)	Dissolution after 30 minutes
Morphine	CD13002	9%	83%
Oxycodone	BY13002	40 %	90 %
Hydromorphone	BR13002	29 %	87 %
Hydrocodone	CA13002	0 %	91 %

**Table 1)** Results from IV preparation tests (n=3) of INTAC<sup>®</sup> IR pellet batches with same composition but different opioids. (taken from Schwier et al.<sup>25)</sup>

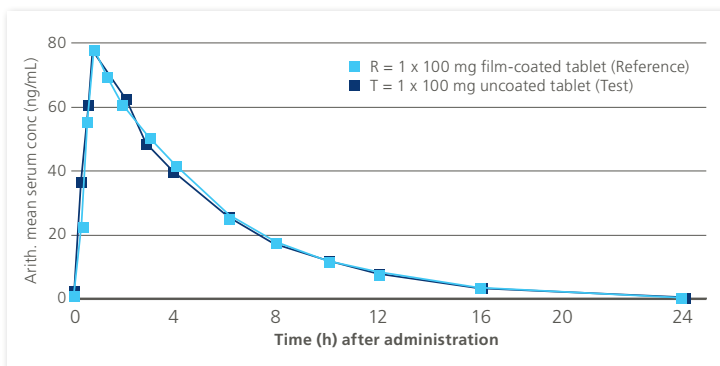
Drug product	Intact Hydrocodone bitartrate (10 mg)/ Acetaminophen (325 mg) ADF pellet Tablet	Intact Hydrocodone ADF pellets (10 mg)	Intact Oxycodone ADF pellets (10 mg)	Intact Morphine Sulfate ADF pellets (10 mg)	Intact Hydromorphone ADF pellets (8 mg)	
Amount extracted						
Amount extracted (% / mg)	1	4.05	10.98	1.34	-*	12.25
	2	-*	8.60	3.07	-*	4.47
	3	5.05	13.19	1.26	-*	3.10
	mean (%)	4.55	10.92	1.89	0	6.61
	mean (mg)	0.46	1.09	0.19	0	0.66

\* = no value: no material could be drawn up into syringe for testing

**Table 2)** Example results from initial IV extraction tests (n=3) of several ADF IR dosage forms for four different opioids having same composition (taken from Wening et al.<sup>26)</sup>

## Bioequivalence Testing

A bioavailability study comparing the INTAC® based test product to a marketed standard formulation demonstrated excellent congruence between the pharmacokinetic profiles (Figure 8).



**Figure 8)** Arithmetic mean concentrations of analgesic drug [ng/mL] vs. time [h] following single dose oral administration of Test and Reference (taken from Stahlberg et al.)<sup>27)</sup>

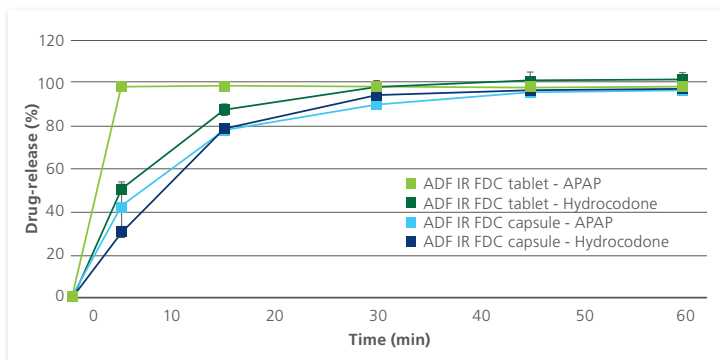
The 90% confidence intervals (CI) calculated for the ratios of the mean  $AUC_{0-1}$ ,  $AUC$ , and  $C_{max}$  for the Test formulation were within the range commonly accepted for demonstrating in-vivo bioequivalence (Table 3)<sup>27)</sup>.

Pharmacokinetic parameter	ANOVA CV [%]	Point estimate of ratio T/R [%]	90% Confidence interval of ratio T/R [%]
$AUC_{0-1}$	13.73	101.80	94.24 - 109.97
$AUC$	13.52	101.69	94.25 - 109.72
$C_{max}$	24.06	102.61	89.74 - 117.32

ANOVA = analysis of variance, random effects model with carry-over; CV = coefficient of variation

**Table 3)** Intra-individual variation, point estimates and their 90% CI for selected single-dose PK parameters of the investigated analgesic (taken from Stahlberg et al.)<sup>27)</sup>

In the meantime, the pellet-based approach has been expanded to include further single-entity and fixed-dose combination (FDC) tablets and capsules<sup>25),26),28)</sup>. Based on the technology, prototypes for opioid/APAP combination products have been developed and successfully screened for feasibility and in-vitro ADF properties<sup>25),26)</sup>. Results of dissolution and extraction studies in comparison with non-TRF tablets are depicted in Figure 9 and Table 4, respectively.



**Figure 9)** Dissolution profiles for INTAC® based FDC products (taken from Wening et al.)<sup>26)</sup>. Dissolution studies were performed using dissolution apparatus II (paddle, 75rpm, 0.1N HCl, 600 ml).

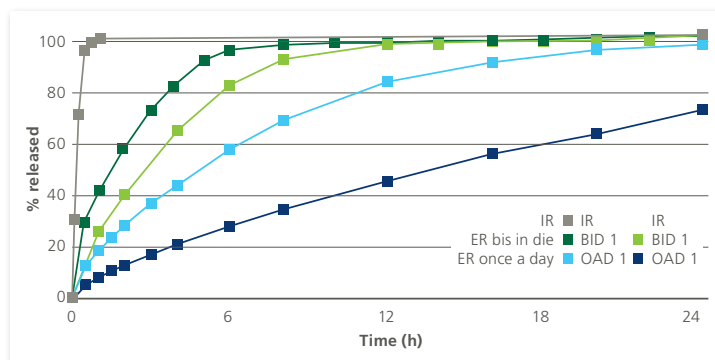
Drug product	Hydrocodone bitartrate TRF IR pellets #CA14010-1000	Hydrocodone bitartrate / Acetaminophen TRF pellet tablets #CA14010-1100	Comparator Vicodin® # 120459A
<b>Amount extracted</b>			
Amount hydrocodone extracted [mg]	1.09	1.8	7.05
Amount hydrocodone extracted [%]	10.92	17.99	70.47
SD [%]	3.06	1.66	7.64

**Table 4)** Example results for amount of hydrocodone bitartrate extracted after 5 minutes in boiling water from INTAC® pellets formulation, intact pellet-based FDC tablets, and a standard comparator (taken from Schwier et al.)<sup>25)</sup>

## Conclusion

By extending the INTAC® platform into the IR space it is now possible to tailor the release profiles from minutes up to about 24 hours (see Figure 10).

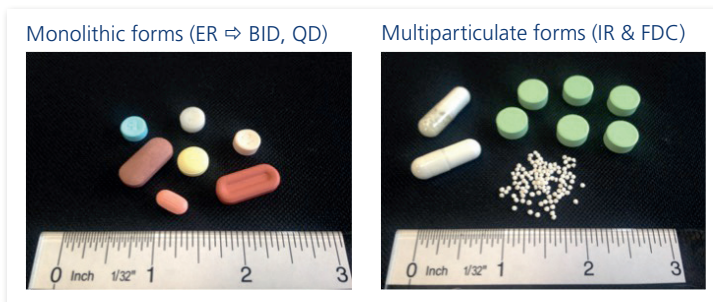
Based on its flexible release characteristics and scalable process INTAC® offers a broad range of abuse-deterrent solid oral dosage options for various products and applications based on a single proprietary hot-melt extrusion platform (Figure 11).



**Figure 10)** In-vitro release profiles utilizing INTAC® (taken from Bartholomäus et al.)<sup>24)</sup>

## Outlook

Grünenthal is currently implementing a comprehensive program to demonstrate the versatility and robustness of different INTAC® based product options. This will include category 1, 2 and 3 testing according to the FDA Guidance for Industry on Abuse-Deterrent Opioids – Evaluation and Labeling<sup>29)</sup>, clinical food-effect studies for INTAC® IR opioid products, and exploratory investigation of INTAC® IR formulations designed to provide exposure limitation characteristics after ingestion of multiple dose units by the oral route.



**Figure 11)** INTAC® offers a broad range of abuse-deterrent solid oral dosage form options for various product categories and needs based on a single highly flexible HME platform.

## Further Information and Contact Details

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## References and Resources

1. <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MisuseofPrescriptionPainRelievers/default.htm> (accessed January 12, 2016)
2. <http://www.samhsa.gov/data/sites/default/files/NS-DUH-FRR1-2014/NSDUH-FRR1-2014.pdf>
3. <http://www.drugabuse.gov/publications/research-reports/prescription-drugs/what-prescription-drug-abuse> (accessed January 25, 2016)
4. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm220112.htm> (accessed January 12, 2016)
5. Alexander D, Alexander K, Valentino J, Intranasal Hydrocodone-Acetaminophen Abuse-Induced Necrosis of the Nasal Cavity and Pharynx. *The Laryngoscope*. 2012; 122:2378-2381.
6. Degenhardt L, Bucello C, Mathers B, et al. Mortality Among Regular or Dependent Users of Heroin and Other Opioids: A Systematic Review and Meta-Analysis of Cohort Studies. *Addiction*. 2011; 106:32-51.
7. Katz N, Dart RC, Bailey E, et al., Tampering With Prescription Opioids: Nature and Extent of the Problem, Health Consequences, and Solutions. *The American Journal of Drug and Alcohol Abuse*. 2011; 37:205-217.
8. Silva K, Schragger SM, Kecojevic A, et al. Factors Associated With History of Non-Fatal Overdose Among Young Nonmedical Users of Prescription Drugs. *Drug and Alcohol Dependence*. 2013; 128:104-110.
9. CDC. Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services. *Morbidity and Mortality Weekly Report*. 2012; 61: 1-40.
10. Vosburg SK, Jones JD, Manubay JM, Ashworth JB, Benedek IH, Comer SD. Assessment of a formulation designed to be crush-resistant in prescription opioid abusers. *Drug Alcohol Depend*. 2012; 126:206-215.
11. Fishman SM, Papazian JS, Gonzalez S, et al. Regulating opioid prescribing through prescription monitoring programs: balancing drug diversion and treatment of pain. *Pain Med*. 2004; 5(3):309-324.
12. Grudzinskas C., Balster RL, Borodetzky CW, et al. Impact of formulation on the abuse liability, safety and regulation of medications: the expert panel report. *Drug Alcohol Depend*. 2006; 83(suppl 1):S77-S82.
13. Green JL. The impact of tamper resistant formulations on prescription drug abuse. National Association of State Controlled Substance Authorities (NASCA) Conference. Scottsdale, AZ. October 2012. <http://www.radars.org/home2/research/research-publications>
14. Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. (2014). Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiol Drug Saf*; 23(12):1238-46.
15. Havens JR, Leukefeld CG, DeVaughn-Geiss AM, Coplan P, Chilcoat HD. (2014). The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. *Drug Alcohol Depend*; 139:9-17.

16. Sellers et al. Do Pre-Marketing Studies Anticipate Post-Market Consequences? A Case Study of Reformulated Oxycontin® (2013) Oral presentation at the Abuse Deterrent Formulation Science Meeting, Rockville, MD, <http://nebula.wsimg.com/d6cc8ab4956d00ab6a-fa601e0c10e196?AccessKeyId=7B2DBB1E2E28C2F11192&disposition=0> (01 Oct 2013).
17. Cassidy TA, DasMahaptra P, Black RA, Wieman MS, Butler SF. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. *Pain Med.* 2014; 15: 440-451.
18. Dart R, Adams EH, Baker GM, Pitner JK, Vorsanger G. Trends in Nonmedical Use of Nucynta by college students. 2012a. AAPM Annual Meeting July 29 – August 2, 2012. Abstract 27.
19. Dart R, Cicero TJ, Surratt HL, et al. Assessment of the abuse of tapentadol immediate release: The first 24 months. *J Opioid Manag* 2012b; 8:395-402.
20. Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, Coplan PM. Abuse Rates and Routes of Administration of Reformulated Extended-Release Oxycodone: Initial Findings From a Sentinel Surveillance Sample of Individuals Assessed for Substance Abuse Treatment. *J Pain.* 2013; 14 (4): 351-358.
21. Cicero TJ, Ellis MS, Harney J (2015), Abuse prevalence and preference of immediate release versus extended release opioids. RADARS® System Technical Report, 2015Q4.
22. Cassidy TA, Thorley EM, Daily T, Butler SF (2015), Abuse prevalence and patterns for immediate-release hydrocodone combination products; presented at PAINweek 2015, September 8-12, 2015, Las Vegas, NV.
23. DeVeauugh-Geiss A, Sessler N, Chilcoat H, Coplan P (2015), Non-oral Abuse of Immediate-release Hydrocodone; presented at CPDD 77th Annual Scientific Meeting June 13-18, 2015, Phoenix, AZ.
24. Bartholomäus J, Schwier S, Brett M, Stahlberg H-J, Galia E, Strothmann K, New Abuse-Deterrent Formulation (ADF) Technology for Immediate-Release Opioids, *Drug Development & Delivery*, October 2013, Vol 13, No 8.
25. Schwier S, Wening K., Stahlberg H-J, Comparison of in-vitro test characterization of immediate and extended release products with abuse deterrent features; presented at PAINweek 2015, Las Vegas, NV.
26. Wening K, Lehrach I, Schwier S, Novel Abuse Deterrent Immediate Release Tablets and Capsules for Opioids Containing Hot-melt Extruded Pellets Based on the INTAC® Technology; presented at AAPS Annual Meeting 2015, Orlando, FL.
27. Stahlberg H-J, Brett M, Ossig J, Philipp AA, Schwier S, Bridging from conventional marketed immediate release formulations to new tamper resistant alternatives; *J Pain* 2013; 14(4), Supplement 1, S70.
28. Wening, K, Barnscheid L, Abuse Deterrent Formulations for Fixed-Dose Combinations and Products with Multi-Modal Release Properties for Opioids and Stimulants using INTAC® Technology; presented at AAPS Annual Meeting 2015, Orlando, FL.
29. FDA/CDER Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, 2015 (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>)