

## DART -- Novel Opioid Abuse and Resistance Technology

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### Purpose

Opioid abuse is a serious public health problem in United States. Laboratory studies of animals and humans indicate that with abuse of opioids reinforcing effects are generally increased by rapid onset with high intensity of drug effects. Intra-nasal and IV administration of Oxycodone and other opioids meet these criteria. Oxycodone cases responsible for all drug-related ED visits have risen between 2004 and 2008. Crushing Oxycodone was the major method of manipulation, while nasal inhalation was the major method of administration, followed by injection. "Abuse-deterrent" combination products have been developed with the intent to limit the abuse potential of the active opioid component.

### Method

DART is a patent pending novel technology platform for Divergence and Abuse Resistance of List 1 Chemicals and CII Controlled Substances. Alkaloid (ALK)/ Opioid utilized in pharmaceutical formulation is in a form of a proprietary complex with two GRAS ingredients: polyphenol such as Tannic Acid (TA) and a water soluble polymer such as PEG. Concentration of components in DART composition can vary depending on the intended use of formulation. Diversion and abuse resistance of DART formulations is imparted by a unique combination of chemical and physical properties of the three components. Tannic Acid undergoes auto-oxidation reaction when pH is altered and forms fine suspension that can not be separated with conventional methods (anti-diversion properties). Under conditions of abuse, the astringent ability of TA to shrink or constrict mucous membranes and blood vessels significantly decreases absorption of the API through the nasal and GI mucosa (anti-abuse properties).

### Results

If taken appropriately Tannic Acid, PEG and any Opioid (Alkaloid) form a soluble  $\pi$ -complex that produces expected bioavailability of an active opioid compound. Attempts to crush the medication for snorting will result in insoluble  $\pi$ -complex forming gelatinous mass that on contact with moisture of nasal mucosa further restricts opioid's uptake. Escalating the dose will only result in increased local vasoconstriction due to astringent properties of Tannic Acid and inability to achieve euphoria through peak systemic concentration by limiting bioavailability of the active compound.

Similarly, IV injection will be impractical with high viscosity of compound requiring excessive injection pressure, large needle size and increased volume of solvent. TA will also cause painful local vasoconstriction.

If one attempts to consume excessive quantity of the medication in an over-dose attempt or improper dose escalation that will result in tannic acid build up within GI. With a limited volume of GI fluid available, this will form an insoluble Tannic acid/opioid  $\pi$ -complex preventing reaching euphoric peak opioid concentration and potentially deadly respiratory depression. Gradual absorption and plateau of systemic concentration will be observed vs expected linear bioavailability. This was demonstrated in rats for non-narcotic alkaloids used in the technology development.

Various extraction techniques were previously demonstrated to be ineffective on DART/ephedrine formulations to isolate alkaloid for further conversion into methamphetamine. In-vitro experiments are currently underway in controlled laboratory setting for oxycodone and codeine to demonstrate resistance of DART formulations to various methods of abuse including crushing and snorting, syringability,

injectibility, temperature and physical manipulation, range of pH adjustments and follow-up extractions with different polarity solvents.

DART is a platform that can be used for reformulating any alkaloid opioids currently available. This will allow to file FDA form 505(B)(2) resulting in decreased time bringing it to the market.

### **Conclusions**

DART can be formulated into any suitable dosage form including tablets, soft and hard gelatin/HPMC capsules, gel, liquid and oral solution. There are no chemical modifications or special equipment required to manufacture the product resulting in decreased development cost.

Making opioid-containing pharmaceutical products diversion and abuse resistant is of critical importance to fighting the drug abuse epidemic. DART platform addresses all routes of real world abuse of prescription pain killers - extraction, pH manipulation, crushing and snorting, injecting and excess dosage. Ultimately DART platform can be utilized in other high risk over-dose medications such as sleep-aids and anti-depressants.