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THE PRESCRIPTION ABUSE EPIDEMIC: DESIGNING A SOLUTION

Aia Malik, Product Manager, Healthcare, and Gemma Budd, Director of Technology and Strategy, both of Lucideon, discuss the journey behind Lucideon's proprietary iCRT-deter technology, reviewing the escalating prescription abuse problem, abuse deterrent formulation (ADF) drivers and the factors that will shape the future of the iCRT-deter technology, which provides tamper-proofing and enhanced safety of pharmaceuticals. It has been used to give abuse-deterrent features to formulations of opioids and highly potent compounds.

Addictive compounds such as Hydrocodone and Oxycodone, both opioids, are regularly prescribed for the treatment of acute and chronic pain. Opioids work by tempering the perception of pain by the body. However they also boost dopamine levels in particular areas of the brain, resulting in euphoric feelings that may lead to addiction. Extended release formulations can contain up to three times the dose of immediate release products leading some abusers to try to extract the entire available drug to amplify this euphoric effect.

With the extensive effects that abuse can incur, from impacting the nervous and cardiovascular systems to the economic costs, it's unsurprising that the abuse of these compounds has drawn the attention of regulatory and governmental bodies. For manufacturers, reducing the risk of abuse associated with certain compounds has become both a regulatory and ethical issue.

TACKLING THE PROBLEM

Prescription drug abuse is currently considered an epidemic by the US Centers for Disease Control and Prevention (CDC). The levels of abuse, particularly in the case of opioids, are a key area of concern for public health, governmental and regulatory bodies such as the US FDA. Accordingly, vast investment in national programmes has been made to try and tackle the problem.

One such programme is the Prescription Drug Abuse Action Plan, which includes accelerating priority New Drug Application reviews by the FDA to develop analgesics with no abuse potential and abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential.

The FDA has been encouraging the development of opioid formulations with abuse-deterrent properties and has made clear that new and existing opioid medications should be made less susceptible to abuse. In support of this it has published two key guidance documents entitled *Abuse-Deterrent Opioids Evaluation and Labeling* and *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*. The documents offer guidance on how to prove abuse deterrence of opioid formulations and outline some key categories for abuse-deterrent features.

While regulatory pressures have helped form an emerging market for abuse-deterrent (or tamper-proof) technologies, other major drivers that have influenced the rapid uptake of such technologies include:

- Patents and generics development
- Corporate social responsibility
- Competitive advantage and differentiation
- Future-proofing of products.

More recently, the FDA surprisingly requested the withdrawal of one of the established supplies of oxymorphone, citing the risk of abuse as being the major cause. This was unexpected as it was thought that protecting the patients' supply of important medication outweighed reducing the abuse risk. This action further increases pressure on manufacturers to

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respond to this issue immediately and opens the door for new entrants.

ROUTES OF ABUSE

There are several known routes for abusing prescription drugs. These include:

- Intravenous intake
- Chemical tampering or crushing, followed by insufflation
- Oral abuse (ingesting a number of whole tablets greater than the prescribed dose).

To address these problems the FDA released a final guidance document highlighting several general formulation strategies that can be adopted to permit abuse deterrence marketing:

1. Physical/chemical barriers – e.g. preventing chewing, crushing, or grinding (physical).
2. Agonist/antagonist combinations.
3. Aversion – e.g. adding of nasal irritants to deter intranasal abuse, or unpleasant tasting chemicals released on crushing.
4. Delivery system – a drug release design or method of drug delivery that can offer resistance to abuse.
5. New molecular entities and prodrugs – a formulation that is activated by enzymatic activity in the body's metabolic process.
6. Combination – two or more of the strategies.
7. 1-5, in conjunction for abuse deterrent effects.
8. Novel approaches – new methods not covered in strategies 1-5.

DESIGNING A USABLE PRODUCT

Through our research we gained some critical insights from manufacturers and practitioners about concerns around tamper-resistant and abuse-deterrent products or technologies. Of those the biggest issue was usability for non-abusing patients, which consequently impacts compliance. As such our technology, iCRT-deter, had to be designed to factor in the following:

- Usability for regular use
- Small, easy to swallow tablets (consider geriatric/paediatric population)
- Crushing may be required for administration
- Compatibility with other technologies
- Ease of processing/formulation
- Versatility to accommodate other delivery routes, e.g. oral, sublingual.

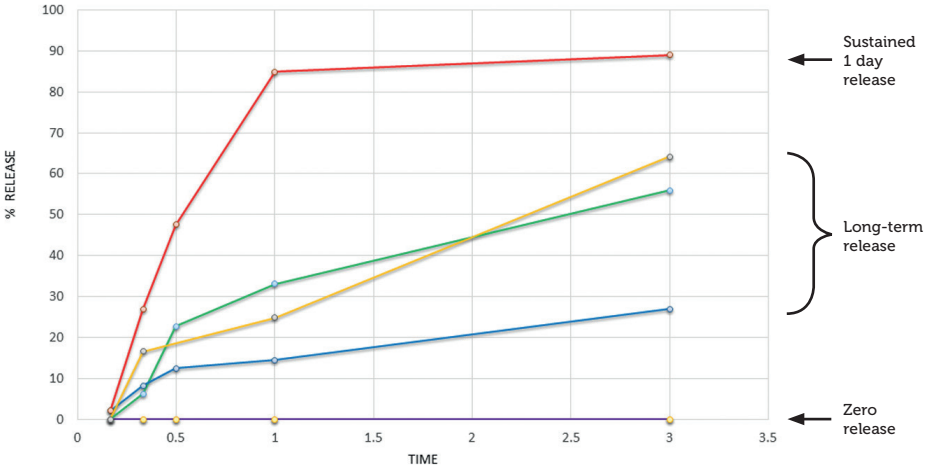

Figure 1: A range of release profiles controlled by rate of carrier dissolution.

INTRODUCING iCRT-DETER

Lucideon's iCRT-deter technology is a smart carrier that has been designed to give critical abuse-deterrent features to addictive or high dose formulations, without compromising ease-of-use for, and thus compliance of, non-abusing patients. In addition to being a controlled release technology that aims to boost compliance, the carrier has tamper-resistant features built in to tackle three key routes of abuse:

- Crushing in order to snort
- Dissolving in order to inject
- Extraction in order to access the raw drug.

Key Features

At its core Lucideon's iCRT-deter is a controlled-release platform. The technology incorporates active molecules within its nano-porous silica matrix, offering superior, adaptable release profiles. The technology also utilises a range of triggers such as time, pH and moisture to achieve more specific drug delivery profiles, such as pulsatile and delayed release.

The platform was designed to tackle difficult molecules and uses inorganic materials, such as silica, to avoid common issues caused by polymeric carriers and excipients. These problems can include unpredictable drug release and swelling/absorptive behaviours, and unwanted degradation products, which can impact the active pharmaceutical ingredient (API) stability and affect local tissues.

The platform has also been tailored for injectable dose forms and is being developed to address critical issues such as large molecule instability and bioavailability challenges for poorly soluble compounds. Its powder form makes it ideal for incorporation into, and enhancement of, existing formulation technologies – essentially replacing the API powder with the iCRT powder.

There is a range of release profiles (Figure 1):

- **Immediate release** – employing triggers such as pH or moisture
- **Delayed release** – using coatings or triggers
- **Extended release** – hours to weeks depending on the dose form and profile required
- **Bi-phasic release** – various rates of release for one compound or combining different compounds that have different optimal release requirements.

KEY FEATURES OF THE TECHNOLOGY

No single technology will completely prevent abuse, but a benefit of Lucideon's technology is its versatility and relative simplicity – it can be readily combined with other ADF technologies. It is intrinsically a controlled-release technology as well as being abuse deterrent, so this dual benefit is appealing from both a manufacturing and end-user perspective.

The abuse-deterrent drugs on the market offer aversion features, physicochemical barriers such as gelling when crushed or immersed in water or crush resistance. iCRT-deter offers a combination of strategies including resistance to crushing or manipulation via solvent extraction to avert insufflation or intravenous abuse. It can also protect patients from unintentional misuse through parallel alcohol consumption. Alcohol-induced dose dumping not only affects clinical efficacy, but also poses a major safety risk for modified-release products in general that can dose dump in the presence of alcohol, resulting in increased exposure.

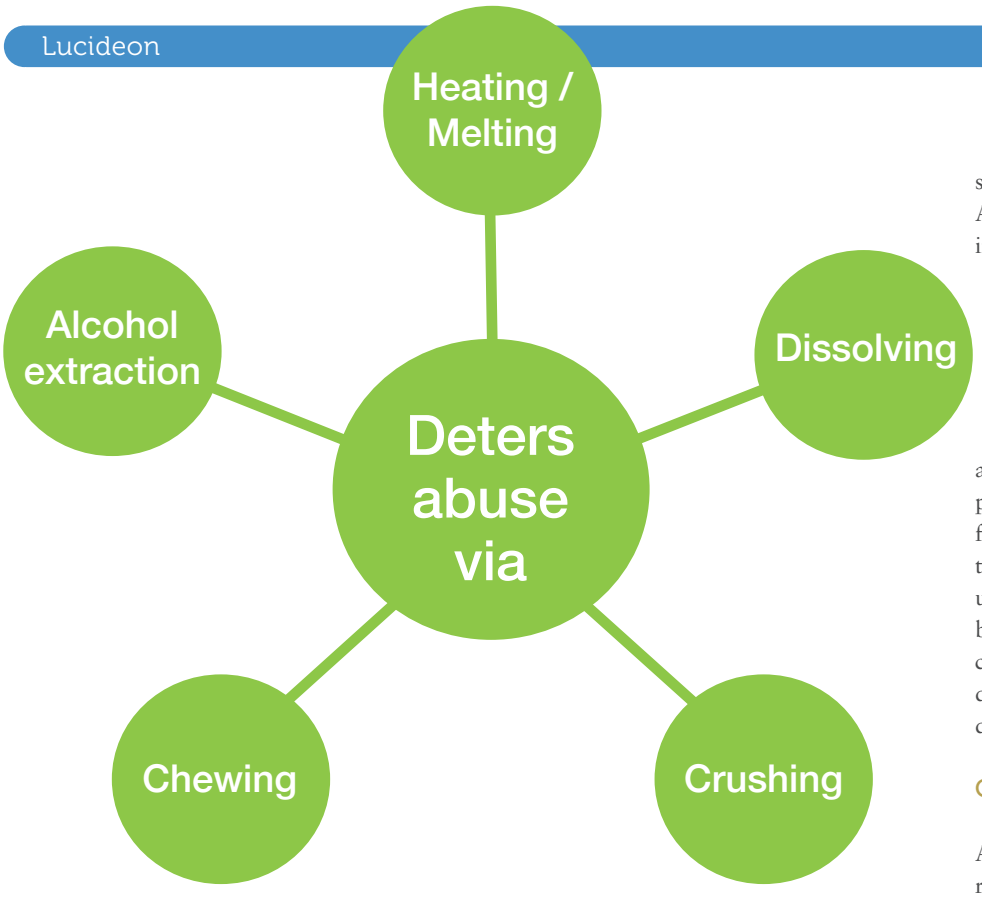

Figure 2: The key abuse deterrent features of iCRT-deter.

The key abuse deterrent features of iCRT-deter include (Figure 2):

- **Solvent extraction** – Equal or significantly reduced drug dissolution in alcoholic media and other household solvents as a result of its tuneable surface chemistry, charge and microstructure.
- **Crushing** – The material used is an extremely hard inorganic structure which is very hard to crush beyond its primary particle size without specialist grinding equipment. Importantly the control of release is dictated by the powder – not the tablet – so crushing back down to powder does not significantly accelerate the drug dissolution. This outperforms other "crush-resistant" tablets – often significantly larger than normal – that compromise the ability for normal patients to take the drug, resulting in reduced compliance and reluctance to prescribe.
- **Heating** – The carrier has a very high melting point (1000°C+), which deters injection because melting the carrier will destroy the drug. Furthermore, heating the carrier will densify the nanoporous network, further trapping the drug within the powder.
- **For injection** – Lack of powder solubility, relatively large, angular particles and poor flow properties make it unsuitable for injection through suspension – it clogs up even large gauge needles.
- **For insufflation or oral abuse** – Recalling that the control of drug release is dictated by the powder, not the tablet, snorting the drug-loaded powder will not result in a "hit", and most of the drug will be cleared by the body before it is able to release from the carrier.

Further, as the technology results in a one powder material with built in abuse-deterrent features, it can be easily combined with other deterrents. Colour leaching in liquids can be employed to deter spiking of drinks and antagonists that only release on manipulation can be added, as is currently used in some marketed opioids. As the technology can be used to give abuse-deterrent features to the active ingredient selectively, the products can be readily combined with antagonists whilst still allowing them to perform as required.

OTHER DRUG USES

Although opioids have taken centre stage in the development of the technologies, a market is emerging for the abuse deterrence of other potent and addictive drugs, mainly from Schedule II controlled substances, such as prescription amphetamines. Anti-depressants, sleeping aids and Attention Deficit Hyperactivity Disorder (ADHD) treatments all have high abuse potential. To future-proof products and gain larger market share, some companies are already employing ADF strategies for these compounds. It is inevitable that more will follow.

iCRT-deter has been developed as a platform technology so that it can be applied to other compounds. As most of the abuse-deterrent features are inherent in the material, the reformulation would simply focus on adjusting the microstructure of the carrier powders to achieve the drug-release profiles for the chosen compound. Lucideon has the expertise to achieve this through its understanding of the chemistry and physics behind the materials and knowing how to control and modify its technology for the different physicochemical properties of the drugs in question.

CONCLUSION

Abuse deterrence is becoming increasingly relevant for not only opioids but also other addictive or high-dose formulations. As the regulatory landscape is becoming clearer and the US government and policymakers continue to place pressure on the industry this will no doubt continue to accelerate the uptake of ADF solutions. Other key factors, including differentiation and market share protection, will also continue to drive development in this area. However the challenges facing the ADF market are many, amongst them are some key issues including product usability for non-absuing patients and, of course, costs of development.

Lucideon's iCRT-deter aims to strike a balance between tackling abuse, serving non-abusing patients and the manufacturer's requirements. It offers a controlled release solution with a range of ADF strategies built in, as well as other formulation benefits to reduce manufacturers' costs and complexity of development, all without compromising usability.

ABOUT THE COMPANY

Lucideon focuses on delivering competitive advantage for pharmaceutical manufacturers using novel technologies and development support. Lucideon's solutions are borne out of materials expertise and ability to cross-fertilise ideas and knowledge across sectors.

Lucideon believes that true innovation is achieved via partnership – scientists working closely with analytical teams, chemical engineers and process engineers in the US and the UK to develop tailor-made solutions for every client.

When off-the-shelf just won't do

Drug Delivery & Formulation Solutions

At Lucideon, our focus is on delivering competitive advantage for you through our unique drug delivery and formulation platform technologies.

What makes our materials unique?

We manipulate them to give you tailored properties – expertise and flexibility that is just not available with off-the-shelf excipients.

Visit **www.lucideon.com/icrt-pharma** to find out how we can help you to develop the products and applications of the future.

MODIFY RELEASE

IMPROVE SOLUBILITY

DETER DRUG ABUSE

INCREASE LOADING

ENHANCE STABILITY

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insight creating advantage

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