To: U.S. Food and Drug Administration Docket No. FDA-2014-N-0233

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Subject: The competitive environment for technology-related approaches to combating opiate misuse is relatively un-populated. No contemporary approach has been meaningfully successful.

The Notice seeks commentary on packaging systems that could prevent misuse and abuse without reducing patient access. This document provides an **industry survey** of the current technologies that are known publicly, along with commentary.

Divert-X – the dispensing and behavioral monitoring system under development by Vatex – tackles the prescription drug abuse crisis directly by seeking to separate authentic patients from those who are exaggerating the intensity and duration of symptoms. Those who subvert the system to feed an addiction or sell their medications are far less likely to demonstrate the spectrum of dosing behaviors exhibited by compliant, authentic patients. A healthcare insurer has permitted Vatex to pilot Divert-X in a region it serves so that Vatex can demonstrate the efficacy of the intervention via robust science.

Analysis of remotely collected medication-use behaviors to infer motive is a novel approach to addressing addiction, misuse, and diversion, and the Vatex focus on a spectrum of patient-level data differs from all other strategies. While companies have attempted to use existing patient data to identify opiate misuse – demographics and pharmacy visits, for example – these systems are not broadly effective. For example, a patient who visits tens of clinics and tens of pharmacies per year will be flagged by state Prescription Monitoring Programs (PMPs) and private utilization-review systems, but many diverters purposely avoid becoming obvious (1-14). Conversely, PMPs are ideal for identifying criminal providers, according to the CDC (15). Instead, Vatex has chosen to rely on patient-level medication-use data that must be collected for each prescription cycle. Divert-X is the only technology-driven approach to differentiating between compliant patients and those abusing or diverting their medications. This recent statement by a retired DEA Administrator artfully summarizes the current national status: “We have been invaded by an army of casual doctor shoppers and drug diverters hidden among the 100 million pain patients estimated by the IOM to be in the US” (16). PMPs track paperwork whereas Divert-X tracks pills -- the two approaches and data sets are complimentary rather than competitive. Divert-X offers the advantage that its data will be delivered in real-time and will be integrated into pharmacy practice. Vatex has a unique IP position and complete freedom to operate in the area of behavioral scoring for misuse and diversion abatement

The competitive environment for technology-related approaches to combating opiate misuse is relatively un-populated. Many companies have developed “pill safes” where medications are rationed to the patient and locked up the rest of the time, for example Ramm Technologies PillGuard™. These devices restrict patient access to their medications -- which is a fundamental disadvantage and incompatible with “take-as-needed” regimens used to manage pain. Divert-X does not in any way restrict patient access to medication. Despite their presence in the marketplace for more than a decade, pill safes do not have any capability to identify diverters and no study indicates that they reduce diversion or misuse. The company developing PillGuard™ closed in early 2014, perhaps underscoring the reimbursement headwinds for the approach.

Several smart pill dispensers have been developed with the goal of improving adherence for key medications. For example with Vitality GlowCaps™ the pill container cap is the prompting device. Adheretech have developed an electronic device integrated to a pill bottle using capacitance to estimate the level of medication in the container, transmitting the data wirelessly with the capability of a feedback loop to send reminders. These types of adherence-improving products are not designed to identify diversion or to prevent subversion by opiate abusers and diverters or to

provide actionable behavioral assessment of patient motive. The company developing GlowCaps™ halted sales of the consumer product in 2013, perhaps underscoring the reimbursement headwinds for the approach.

Proteus Biomedical's "chip-in-a-pill" provides for the concurrent ingestion of a microchip embedded in each dose - when stomach acid contacts the chip a signal is emitted and detected by a patch worn on the abdomen, and then transmitted to a physician, indicating dose consumption. NIDA have recently financed an identical approach (eTect, Inc); given that Proteus has been exceedingly well financed ($130 million since its founding in 2001) and has no commercialized pharmaceutical product, this underscores the difficulties of the approach (17). From a practical standpoint, the approach is limited in requiring a factory-prepared formulation for each medication, necessitating pharmaceutical company partnerships and FDA approvals. Further, there is no reason to expect that abusers would both ingest the chip and wear the required receiver, so no data would be collected. Divert-X is specifically designed so that the device is filled at the pharmacy and is agnostic to pharmaceutical manufacturer, dose size and formulation -- making it of general utility to all solid-dose medications via the use of a small variety of single-use blister configurations stocked by pharmacies.

VeriMed are developing a blister-based monitoring product VeriPak™ that provides a time-stamp of medication-dose access for subsequent USB-cable downloading at a prescriber's office. The system is not real time, provides no location or other information, is not cellular-based and is designed for factory or mail-order pharmacy fill. The product appears to occupy a business role which would put it in conflict with contracts PBMs establish with insurers. Furthermore its use requires active initiation and participation from physicians, but without a clear mechanism to reimburse them for the additional work without triggering Stark and related payment regulations. The VeriMed website exists, but all descriptive content has been removed (18), perhaps underscoring the headwinds for the approach.

Wireless systems to monitor patient access to individual doses of medications using smart-blisters such as Stora Enso's PharmaDDSi™ and MWV's Cerepak™ are designed as adherence-promoting products and are engineered only for factory-fill of the medication -- requiring a partnership with each pharmaceutical company and each packaging opportunity. They are insufficiently robust, in the measures monitored and in functional capabilities available, to provide the real-time service of behavioral assessment and communication that will be supplied by Divert-X.

Products that require factory assembly such as the "chip-in-a-pill" and previous versions of smart-blisters are not compatible with the Controlled Substances market. Branded manufacturers may view proven and effective measures to control diversion and abuse, unless mandated across all products and companies, to be contrary to their business aims. Many of the most abused and diverted medications have high sales volumes that have attracted multiple generic manufacturers. The generic drugs marketplace, comprised of multiple manufacturers fiercely competing on price, will not make manufacturing changes in the absence of broad governmental mandates because change is expensive. With the importance of generic Controlled Substances and the vast array of marketed doses and dosage forms, Vatex considers in-pharmacy packaging to be the only workable and broad solution.

A software system, NARxCHECK, has been developed that provides risk scores for narcotic users based on PMP reports. This is an important service because PMP reports can be quite complex. However, like PMPs, the system does not provide insight into patient medication-use behaviors, nor does it provide real-time inferences of diversion or possess preventative characteristics that would stop thoughtful diverters (1-14). A software system, SafeUseNow, has been developed to help streamline the identification of providers who become high-volume prescribers so that law enforcement can determine whether their prescribing is compatible with medical practice.

Reformulation of opiates to reduce the ease of abuse could be construed to be a competitive technology for Vatex. Despite decades of scientific endeavor, no FDA reformulation approval has resulted in a change of schedule for any Controlled Substance, despite this being a holy-grail business goal. Over 40 companies work in the abuse-resistant formulation arena (including the largest global pharmaceutical companies), so creating new strategies that can be patented without debilitating prior art is challenging. Professional diverters and drug abusers are adept at solving the challenge of any minor road block created by reformulation. For example, a workable method for extracting oxycodone from the abuse-resistant reformulation of Oxycontin™ was published in online chat rooms during the same month that it was available in pharmacies (stocking began August 9, 2010), and several contemporary methods are constantly refined online by competitive and creative people. As a measure of crowd acumen, the August 2010 "toaster" method is

still well regarded online. An FDA internal memo on the subject of Oxycontin™ reformulation describes two formal post-marketing studies (National Survey on Drug Use in Households; and Client Treatment Study Investigation) that show no decrease in nonmedical use or abuse after reformulation (19). FDA leadership have been direct regarding the current status of formulation strategies:

> *"I would love it if we had abuse-deterrent formulations that were actually meaningful and effective at deterring abuse in all instances."*
> *"Right now, unfortunately, the [all abuse-deterrent] technology is poor."*
> *"It [reformulated Oxycontin™] is, frankly, not where we need to be."*
> -- Commissioner Hamburg (20)

FDA and literature data show that the oral route is the most common route of abuse of prescription opioids, more prevalent than all other routes combined (21-22). Reformulation cannot address this problem because extraction is not used for oral abuse.

Once a drug has been reformulated to attempt to reduce abuse, history shows that (a) the new formulation will be quickly defeated, but (b) the defeated formulation is unlikely to be replaced because of the expense of the process. The Vatex approach does not suffer from a slow pace of change. The algorithms, hardware, and systems will be changed and upgraded in response to new system data and to keep ahead of attempts to subvert the behavioral inference and risk-scoring. Unlike a drug reformulation strategy, the hardware and analysis methodology within a Class I medical device can be changed much more quickly to respond to new modes of diversion and abuse – hence assisting Vatex to maintain its credibility and market.

The Vatex perspective is that the opiate and Controlled Substance problem is so corrosive to the U.S. healthcare system and so costly in terms of lives lost and dollars spent that all new, reasonable approaches to ameliorate the problem must be tested. We feel that the Vatex pilot may contribute important information needed to build a robust management system for medications with safety issues.

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