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Date: July 2, 2014
To: Scientific Management Review Board
From: John Archie Pollock, Ph.D.
RE: Public Comment • Pre-college Engagement in Biomedical Science

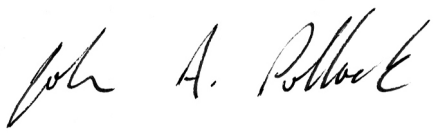
Since 1996 I have worked closely with museums to produce and install informal science education exhibits, displays and movies that teach children and the general public about a wide range of biomedical topics including cell biology, neuroscience, tissue engineering, regenerative medicine, diabetes, heart transplant, immune system, Charles Darwin and the fundamental principles of evolution, and stem cells among others. Several of the exhibits are in use in museums across the country and have also been adopted as components of standard curriculum by school districts. A pilot television show has been turned into a hour feature, which is currently in distribution to over 100 public television stations nation-wide reaching millions. Our first iPad/iPhone/Android App received over 600,000 downloads in the first 4 months, and was simply on the topic of broken bones. Collectively, my projects alone have touched tens of millions of people.

My team and I have taught museum educators, and public school teachers how to use these materials and have provided accessible teacher's guides, student workbook and English Language Learner resources. What my team and I do has been demonstrated to be effective as evaluated with children, teachers and parents and published in several papers and reports. What we do is scalable. Since the year 2000, the majority of the research, production and discovery work of how people learn from my creative products has been funded by two NIH R25 Science Education Partnership Awards (R25 5 RR15619 and R25 RR020403). These projects have also allowed me to train several waves of young professionals in how you can teach biomedically relevant fundamental principles of science to children and the general public. These young professionals are on their way to develop their own careers in this arena.

Of all the governmental agencies that support STEM education, the NIH is the only agency that has the depth and capacity to properly address topics as they relate to biomedicine and health. It is only the NIH that has the opportunity to not only inspires young people into realizing that these are topics that they can understand and appreciate, but that they can excel and master. This lets young people see themselves as the next generation of translational scientist and research physician. A fantastic secondary opportunity from SEPA projects done well is that health science literacy improves not only for the students, but also for the public at large. An informed electorate becomes invested in their own health.

Failing to support SEPA and other STEM related activities at the NIH will not only deplete the pool of potential new scientists and biomedical researchers, but will also further weaken our general public understanding of health, modern medicine and biomedical research.

Sincerely,



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NORTHWESTERN
UNIVERSITY

6 July 2014

Scientific Management Review Board
Pre-college Engagement in Biomedical Sciences (PEBS) Committee
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Committee Members,
I am writing to express my strong support for NIH's investment in K-12 education programs. As a NIH-funded investigator and PI of a Science Education Partnership Award (SEPA) award, I have seen first-hand the incredible difference that NIH funding can make in young people's lives, and for the teachers and community groups that support them.

As you're likely aware, the educational research literature clearly shows that interest in STEM and healthcare careers begins far before college. Robert Tai and colleagues at the University of Virginia have shown that the late elementary and middle school years are critical for shaping longer-term career attitudes and interests. The educational literature also highlights mentoring, educational support, and authentic science experiences during the K-12 years as important variables. Thus, if NIH is to fulfill its mission to prepare and diversify the biomedical workforce of tomorrow, investments in K-12 education today are essential.

Our NIH/SEPA-funded Science Club program uses a mentor-based approach to build science skills and foster interest in health careers among youth in grades 5-8 (summary attached). The program in partnership with a youth-focused community group, the Pedersen-McCormick Boys & Girls Club in Chicago. Northwestern STEM graduate students serve as small group mentors, with mentor-mentee groups persisting from quarter to quarter and year to year. Some kids have been associated with our program for 6 years!

Does it work? Absolutely. One of our first students back in 2008, Myles, just finished his sophomore year at the University of Kentucky. He is majoring in biomedical engineering. As an eighth grader he was not considering science at all - his mind was set on business or accounting (influenced by his mother). He had not had an authentic science experience in school, or ever met a practicing scientist.

Science Club completely changed Myles' mind. Based on the engaging health-related activities and mentorship he received, he decided to take more math and science courses in high school, which led to his career-changing decision. And this spring, I helped Myles secure a summer internship with an orthopaedic surgeon/biomedical engineer studying artificial joints. Without Science Club's support, none of this would have happened.

Two Science Club alumnae, Lucy and Sandra, just finished their freshman year in college, majoring in exercise science, and nursing, respectively. Another Science Club alumna will start at the University of Iowa this fall as a biology major.

Prior to Science Club's inception, the Boys & Girls Club had seen virtually zero interest in science & health careers – only one student in the past 10+ years had gone on to post-secondary training in a health-related career. The four students I listed above, as well as a strong pipeline behind, are evidence that our approach really works to engage, inspire, and support underserved youth to pursue health careers.

In fact, one of our former eighth grade students, Sandy, a first-generation American whose annual family income is less than $12,000, received a full-ride scholarship to attend high school at the Latin School of Chicago. Latin is the premier private high school in all of Chicago, with a tuition rate of more than $40,000 per year. Without Science Club's involvement in pushing her academically, helping bring this opportunity to her attention, working to help educate her mother about the opportunity, physically driving her to the school for a required pre-test, helping her assemble and submit her mother's financial paperwork, and paying for application fees, the opportunity would have been lost. This year, we provided similar support to two more Science Club youth, Alice and Jennifer, who also received full-ride scholarships. In fall 2014 they will matriculate as high school freshmen at Latin. That's three students in the last two years.

Beyond those students who do not choose a career in science, they learn valuable critical thinking, data, and scientific skills (designing experiments, reading data tables, use of control variables, experimental error, scientific vs non-scientific questions, etc.). We use two independent methods to evaluate scientific skills learning, both of which show a 30% increase in skills for Science Club youth compared to well-matched controls. A school principal recently posted our data on her office wall as goal for what schools should be accomplishing. This data will be published in the coming year.

Finally, I would be remiss not to mention the tremendous impact of Science Club on our graduate student and postdoctoral mentors - the lifeblood of Science Club. The average time of mentors in our program is approximately 1.5 years (and rising). We provide deep training in pedagogy, community engagement, program design, and evaluation. Case/control surveys reveal that our mentors are better able to design goal-oriented, rigorously evaluated outreach programs. Science Club dramatically improves graduate students' science communication skills, and helps them emulate good scientific practices in their own research. Many mentors report that Science Club reignites their interest in science - helping them remember why whey fell in love with science during their elementary and middle school years. These results, too, will be published in the coming year.

Finally, Science Club provides a much-needed opportunity for graduate students and postdocs to explore alternative career pathways. In the last three years, Science Club has produced three AAAS Science & Policy Fellowship winners. Many of our mentors have decided to pursue careers in teaching and science education. The Assistant Director of my office, Rebecca Daugherty, was a three-year mentor and made the switch to informal science based wholly on her Science Club experience. I know this is an important goal of NIH's, as your recent NIH-BEST program announcement attests.

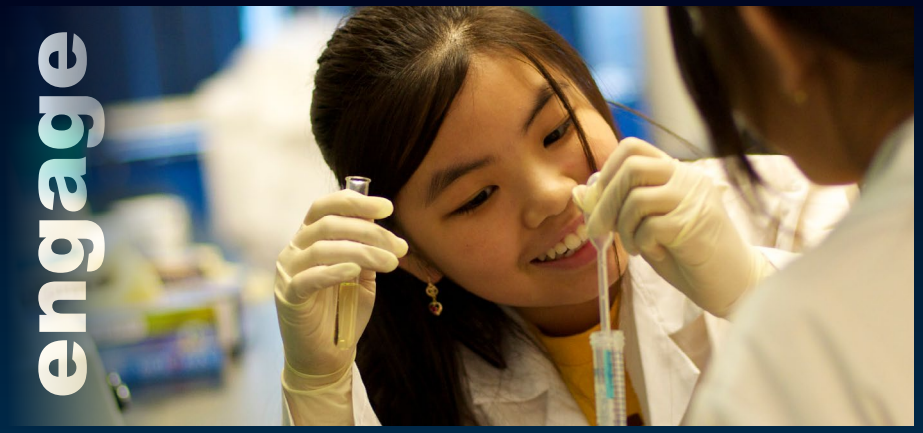
All of this is to say that SEPA programs like Science Club are of exceptional value. They inspire and educate underserved youth. They support teachers and educators in urban, high poverty schools. They train our graduate students how to be engaged and effective science ambassadors in their community. All of these amazing outcomes are consistent with NIH's mission to train and educate the biomedical workforce of tomorrow. I respectfully ask that NIH continue and even expand this support.

Please do not hesitate to contact me if you have any questions or would like hear more from our students and mentors.

Most sincerely,

Michael Kennedy, PhD
Director, Science in Society
Research Assistant Professor, Center for Genetic Medicine

engage



Science Club

A mentor-based after school program at the Pedersen-McCormick Boys & Girls Club

Science Club offers a new approach to urban science education, designed around long-term mentoring relationships. It integrates community expertise from the Boys & Girls Clubs of Chicago, dedicated teachers from Chicago Public Schools, and engaging scientist mentors from Northwestern University to form a powerful educational team.

On a weekly basis throughout the year, youth work in small groups with Northwestern scientists on fun, engaging curricula designed to foster creativity, critical thinking, writing, and analytic skills. Mentor-youth relationships persist from quarter to quarter and year to year, creating bonds and deeper learning that will last a lifetime.

Mentors benefit tremendously from the experience, too. They learn advanced teaching skills, strategies to design curriculum, and evaluation techniques that prepare them to be engaged scientists and informal science education leaders.

Visit us online at scienceclub.northwestern.edu

Science Club is an educational research study made possible by a Science Education Partnership Award (SEPA) from the National Institutes of Health (#R25OD011033-05 IRB #STU13112)

BOYS & GIRLS CLUBS OF CHICAGO

NORTHWESTERN UNIVERSITY

COMMUNITY IMPACT

INSPIRING AND TEACHING URBAN YOUTH

- Science Club mentors have inspired and trained more than 200 middle school students in Chicago Public Schools
- Each child in Science Club receives 50 hours of mentor-led, engaging, and challenging science instruction throughout the academic year. In many cases, this doubles the amount of classroom science instruction received in school
- The average student's time in the program is over one year; some students have been in the program for more than five years
- Rigorous evaluation data collected over the last three years at three separate schools show a dramatic increase of 30% in science skills compared to well-matched controls
- Science Club plays a critical role helping 8th graders apply to selective enrollment high schools. Since 2012, three students have received full-ride scholarships to attend high school at Latin School of Chicago, valued at $130,000 each
- Science Club inspires youth to choose health careers. Alumni are pursuing college majors in biology, nursing, exercise science, physical therapy, and biomedical engineering

TRAINING GRADUATE STUDENT & STAFF MENTORS

- 80 Northwestern University science mentors - graduate students and staff - received training in advanced teaching skills, curriculum design, program evaluation, and community engagement. This not only makes them better scientists and teachers, but better citizens
- Average mentor time in the program is a year and a half and rising
- In the last four years, three Science Club Mentors have received prestigious AAAS Science & Policy Fellowships

SCHOOLS, COMMUNITY GROUPS, and JOBS

- Science Club supports science education at nine Chicago schools (Stewart, McCutcheon, Goudy, Bateman, Budlong, Nettelhorst, Thorp, St. Stans, Jahn) and two community sites (Pedersen-McCormick and General Wood Boys & Girls Clubs)
- Funding from the National Institutes of Health supports 9 jobs: three at Northwestern University, three at the Boys & Girls Club, and three at an evaluation firm

Science Club is supported by a Science Education Partnership Award from the National Institutes of Health

SEPA SCIENCE EDUCATION PARTNERSHIP AWARD
Supported by the National Institutes of Health

From: Jacque, Berri
To: SMRB (NIH\OD)
Subject: Dear Members of NIH"s SMRB subcommittee on pre-college STEM education
Date: Saturday, July 05, 2014 3:30:41 PM

Dear Members of NIH's SMRB subcommittee on pre-college STEM education,

I am co-investigator on an education project funded by the National Institutes of Allergy and Infectious disease to develop a support mechanism enabling high school teachers to teach effectively about infectious disease.

I would like to thank you for your support of NIH's continuing involvement in pre-college STEM education. It is a critical investment both in a STEM competent diverse US workforce and in health literacy, which is inadequate in many underserved communities.

I have been reviewing past meetings and would like to offer a comment on what seems like a misperception that may have arisen following the May meeting:

SEPA, NIAID and SEDAPA have always had unusually rigorous demands for evaluation of its projects. Evaluation is required to be logic-model based and at least 10% of the budget is required to be devoted to an external evaluator.
In fact the most current SEPA funding announcement PAR-14-228 has tightened the evaluation requirements even more. For classroom-based activities like our own, the PAR demands:

Classroom-based P-12 SEPA projects must have a rigorous evaluation plan,

Study to quantify project effectiveness.

This level of rigor is well-beyond what is required by either the Department of Education or NSF, neither of which state standards for evaluation in their requests for proposals. This needs to be taken into consideration as you determine the importance of NIH involvement in this work.

Sincerely
Berri Jacque

Berri Jacque PhD
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July 7, 2014

Science Review Management Board
Pre-college Engagement in Biomedical Sciences (PEBS) Committee
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Colleagues:

I commend the Working Group on Pre-college Engagement in Biomedical Science for their insightful analysis of the roles NIH can play in the realms of K-12 and public science education to bring about increases in science and health literacy among all US citizens.

As you consider how to move forward, please recognize that a high level, institutional change will be needed within the NIH to reinvigorate its science education efforts after the abrupt shutdown of programs and the Office of Science Education in 2013 and 2014.

Reinstating the Office of Science Education to oversee the Science Education Partnership Award program, the Science Education Drug Abuse Partnership Award program, and other R25 programs like there at other Institutes will be a signal that the NIH hierarchy takes seriously the job of promoting high quality, effective science education activities that bring scientists and real scientific experiences to K12 and public audiences. The quality control measures that your committee is charged with identifying will be best managed under the egis of this central office. Moreover, the Office of Science Education should resume its prior role as the "Go-To" resource for programmatic leadership in what constitutes best policies, practices and programs for educational engagement, workforce development and pipeline issues.

In our NIH funded Science Education Partnership Award (SEPA), BrainU, we provide high quality professional development to K12 science teachers combining neuroscience and investigative pedgagoy. I consider this a wholesale process, rather than a retail process wherein I, as a PI, might directly engage K12 students in my own laboratory's science endeavors. Over the past 15 year, the BrainU program has reached over 200 teachers and over 150,000 K12 learners. And yes, we have published multiple, documented measures of efficacy. These learners go on into diverse pursuits and professions; only a few become elite professional scientists. Therefore we are contributing to workforce development in the broadest sense. If I were to only bring top students into laboratories, the audience would be limited to a handful of students a year. Thus the design and reach of an educational program will determine how broad an impact might be expected. As you evaluate the programs that NIH promotes as satisfying its mission to build the scientific pipeline, consider how broad the programmatic reach truly is. Are these programs building scientifically literate citizenry, or just developing a special group of highly trained young investigators?

Moreover, please do not forget that education is a local, social, human, endeavor. Face to face interactions characterize the best educational experiences. Mentorship in mastering a body of knowledge or a professional set of skills is critical for success at all levels; K12, collegiate, professional and beyond into the workforce. Cost effectiveness and ability to scale up a program may not produce the same quality training and effective communication of scientific practices and reasoning as multiple, diverse, smaller programs spread throughout the country. Scaling up a program often requires diluting the content and spending lots of energy on administration and infrastructure. To this end, more locally tailored programs like those funded by SEPA, are needed, not a few big programs.

As scientists whose livelihoods are funded by tax dollars, we are obligated to both create new knowledge for the betterment of society and to communicate that new knowledge to the public that supports us. Ceding that responsibility to educational professionals who lack the scientific background isolates scientists, promotes misrepresentation as the science becomes oversimplified, and does not provide audiences with authentic scientific experiences. For NIH to demonstrate that it truly values the translation of new scientific knowledge to K12 and public audiences, SEPA, SEDAPA and related R25 programs should continue as ongoing, integral components of the NIH portfolio of programs.

Respectfully,

Janet M. Dubinsky, Ph.D.
Professor
Department of Neuroscience, University of Minnesota
2009 Science Educator Award, Society for Neuroscience
2011 Postbaccalaureate and Professional Development Award, UMN
Academy of Distinguished Professors, UMN

Taking Health Science out of the K-12 STEM Education Portfolio

Karina F. Meiri Ph.D.

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Abstract

Following a Presidential directive to develop a strategic plan for STEM education, the Office of Science and Technology Policy (OSTP) proposed to consolidate all K-12 programs at the Department of Education (D.Ed.), among which were NIH's entire K-12 education portfolio - the Science Education Partnership Awards (SEPA). In response NIH moved to divest itself of the SEPA programs. Here we present evidence of SEPA's unique discipline-specific functionalities focused on the biomedical K-12 STEM pipeline and health literacy that are not duplicative of any other federally funded efforts. We also discuss why transferring SEPA programs to the D.Ed. will impact critical SEPA functionalities: D.Ed. only proposes to fund school district-driven projects focused on model building, whereas SEPA projects are scientist driven and outcomes-oriented with a strong disciplinary focus and emphasis on program delivery. These caveats raise questions about how eliminating SEPA from NIH contributes to enhancing US K-12 STEM education.

'Science' has reported that in early September NIH divested itself of its scientist and physician driven K-12 health science education programs, namely the Science Education Partnership Award, administered through the Office of the Director, together with mission-specific siblings at the Institutes of Allergy and Infectious Disease (NIAID) and Drug Abuse (NIDA). Part of the motivation to eliminate the SEPA programs stemmed from a plan developed by the Office of Science and Technology Policy (OSTP) in response to a Presidential directive to '*make[s] disciplined choices to reorganize and cut back lower priority programs'* [1]. The plan attempted to identify duplicative programs, but the Government

Accountability Office (GAO) surveys on which the plan was based, indicates that the 3 NIH - funded programs (grouped together under the acronym SEPA) were actually unique in both objectives and scope [2,3]. Of the 11 'pre-secondary' (K-12) programs targeting biological sciences (the 3 SEPA programs, 5 programs at NSF and 3 programs at the Department of Education (D.Ed.)), the objectives of the SEPA programs did overlap with 2 programs at D.Ed., in that they too were designed to '*improve teacher (pre-service or in-service) education in STEM areas, and to improve or expand the capacity of K-12 schools or postsecondary institutions to promote or foster education in STEM fields'*. However, only the SEPA programs also targeted the pipeline to undergraduate STEM education. With respect to scope, the GAO survey characterized STEM fields with broad strokes: For instance 'biological sciences' did not distinguish between subsets of biology. However, applying the requisite granularity shows that of the K-12 programs targeting biological sciences, only SEPA focused on biomedical and health science. Hence the SEPA programs do appear to have unique functionalities. Thus whether they should be considered '*lower priority'* requires an assessment of their impact.

SEPA programs impact two critical areas of national interest: the biomedical workforce via the undergraduate STEM pipeline, and health literacy. Toward its goal to expand the STEM workforce both the American Association for the Advancement of Science (AAAS) and the National Research Council (NRC) have focused on elevating scientific literacy by reforming how science is taught to undergraduates, while NIH also addresses its mission-specific goal of enlarging the biomedical workforce by spending 90% of its education dollars on undergraduate and graduate education. Neglecting the pre-college population is short-sighted and negatively impacts the quality and diversity of the STEM workforce. For example, adolescents, particularly from underrepresented populations, steadily lose interest in science during their pre-college years [4]. As a result US high school students continue to display poor scientific literacy on the international benchmarks of achievement that assess readiness for college-level science studies with even lower levels of achievement by minority groups [5]. Worse, economically disadvantaged and underrepresented minority students and are more likely than higher income or white

students to drop out of school altogether, further compounding these problems [6]. Lack of a diverse and well- qualified work force particularly in mid-level jobs, has contributed to slow growth in the life science/biomedical sector, even in 'biotech powerhouses' like Massachusetts [7]. Yet the same studies demonstrating adolescent disenchantment with 'school' science show that when they experience 'real-world' science they value and which mirrors their real world experience their motivation and achievement increases [8]. This implies that emphasizing topics students find inherently interesting, such as their health and disease, could impact scientific and health literacy and ultimately the biomedical workforce pipeline. All 93 current and recent SEPA projects representing 40 states focus on engaging K-12 students with real-world biomedical and health science. The majority of SEPA projects address the needs of disadvantaged students for better teachers, rigorous curricula and authentic STEM research experiences, while more than 25% are specifically designed to enhance the STEM pipeline transition to undergraduate learning [9]. Additionally the working scientists and physicians who lead SEPA projects can call on close connections to research and clinical practice to model pathways to the biomedical workforce. SEPA's successes are well documented [10] and SEPA's impact on the biomedical STEM pipeline is therefore unique and would not seem to be '*lower priority'*. It would need to be reproduced were SEPA itself eliminated.

Another unique impact of SEPA is on fostering health literacy. More than half of the US population are functionally health illiterate meaning, in the words of the Institute of Medicine (IOM), they lack '*the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions'* [11]. Inadequate health literacy causes missed healthcare opportunities that cost the American taxpayer in the order of 200 billion dollars a year [12]. A patient's failure to process and understand basic health information has been traditionally considered as a failure in communication, largely dealt with by exhorting the medical team to communicate more clearly with their patients. Both the IOM and the Health and Human Services recognize that educating the K-12 cohort in health-related science is an underexploited opportunity to foster health literacy and has recommended that this avenue

be vigorously pursued [11,12]. But this presents a number of challenges: First, health in schools is usually taught from a physical fitness focus, so more health-related information is delivered in physical education than science classes. Second, even if science classes incorporated health science, science teachers are ill-equipped to teach it. Professional science teacher certification is unlikely to include courses in 21st century perspectives on biomedical and health sciences, because such topics are rarely on the undergraduate agenda, much less in education schools. More than half of all SEPA projects either address this problem by providing professional development for in-service teachers, or circumvent it by reaching the K-12 community and their parents directly, via after-school activities and museum experiences. SEPA's contribution to health literacy is therefore also unique and does not seem to be '*lower priority'*. It too would need to be reproduced were SEPA itself eliminated.

The magnitude of the science and health literacy crisis and its economic fallout suggests that, on the contrary, a SEPA-like approach bringing current health science to the classroom and community should be expanded. Perhaps recognizing this, NIH has supported the OSTP plan to consolidate K-12 programming, including SEPA, at the D.Ed. However, moving SEPA would not effectively reproduce its functionalities, even were the budget for a 'SEPA-like program' to increase significantly beyond the approximately $30M dollars per annum currently allotted. It is not merely that D.Ed. has no experience with health science education – this could be addressed by delegating suitable administrative support, which is NIH's proposal. Rather two confounding problems reflect a deep division between the education researchers who manage science education and the working scientists who drive projects like SEPA. The first is philosophical and lies in the question of what constitutes authentic science practice. Over the last 30 or so years, K-12 science education has been shepherded by education researchers who have embraced the idea that the methodology underlying science practice can be appreciated in isolation from the scientific content [13], a notion most professional scientists, particularly in rapidly evolving fields like biomedicine, find deeply flawed. Thus K-12 science education has had only peripheral involvement from scientists (SEPA, with its scientist-driven education projects has been an outlier). It is now evident that

this model has failed to sustain student engagement in learning science, or to promote scientific literacy. Furthermore adults educated in this environment appear to be weak in the problem-solving skills critical for the 21st century STEM workforce [14]. Since the mid 90's scientists, under the aegis of the National Academies, have been sounding the alarm that authentic science practice requires a solid foundation in content [15] and have recently begun to have an impact, as illustrated by the Next Generation Science Standards (NGSS) [16]. From past evidence it would seem likely that education researchers will need significant support from scientists to translate the NGSS effectively. Nonetheless, the D.Ed. response to proposed STEM consolidation does not include adding scientist-driven programs to its portfolio. Rather the D.Ed. will continue only to invite proposals from school districts that have acquired higher education partners. While there are many well-established partnerships between school districts and researchers from education departments, there are few precedents for partnerships with gatekeepers of biomedical knowledge like medical schools. It is difficult to envision school district and education research-*driven* partnerships effectively emulating SEPA-like approaches in an expedited time frame that would prevent critical functionality being lost were SEPA itself eliminated.

A second confounding problem lies in how the D.Ed. would deal with SEPA-like projects. In contrast with educational research that is largely concerned with the learning and teaching process, SEPA projects are largely outcomes-oriented with a strong disciplinary focus and emphasis on program delivery in addition to model development. As such they are obliged to spend at least 10% of their budget on external outcomes evaluation, and are expected to incorporate rigorous quasi-experimental or randomized hypothesis-driven methods including the randomized control trial (RCT) where appropriate. In contrast, even though the STEM education priorities for the FY2015 budget emphasize outcomes and indicate those methodologies as preferable for project evaluation [17], they are not appropriate for many education process research projects. Consequently few education journals publish outcomes-based research. This forces many SEPA projects to publish in the public health and health communication literature rather than the educational research outlets. Compounded with the philosophical differences outlined above, these

problems have conspired to limit SEPA's exposure to and impacts in the education research field, perhaps contributing to an apparent perception among the researchers that manage K-12 education that it is of '*lower priority'*.

Clearly none of the obstacles to reproducing critical SEPA functionality at D.Ed. are intractable: D.Ed. philosophy could be shifted to include authentic biomedical science practice; Program priorities could be adjusted to include outcomes-focused biomedical science education; Program design could be altered to incorporate scientist-driven projects; Program administration could be expanded to direct and evaluate outcomes focused biomedical science projects. The question becomes whether either eliminating SEPA or moving it from NIH will accomplish the '*Administration's comprehensive effort to improve STEM education'* [1]. The OSTP report indicated that criteria for success will be '*developed and refined through public and expert input'*. Clearly this input is needed before any further plans are developed.

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* This article benefited from input from many members of the SEPA community, particularly Rochelle Bloom, Jeanne Chowning, Berri Jacque, Dina Markowitz, Nancy Moreno, Scott Rawls, Patricia Thomas, Marilyn Winkleby and J. Michael Wyss.

Prepared Comments Presented By: James Harris, Ph.D.
On Behalf Of: Vatex, Developer of the Divert-X System
Presented To: NIH Scientific Management Review Board
During: The July 8, 2014 Meeting Regarding Grant Review Process Deficiencies

[Slide 1]

My name is Jim Harris. By way of background, I am ex-FDA, ex-pharma, and trained as a toxicologist. I am currently the Chief Scientific Officer of Vatex, a company founded to address the prescription drug abuse crisis, addiction caused by medical care, diversion, and the national black market for medications.

Before I begin, I'd like to thank Principal Deputy Director Tabak for making repeated requests that I present our case to you today. I appreciate the courage and wisdom needed to show the agency's ugly side rather than sweep it under the rug. No one should walk away from this presentation feeling good about America's prospects or our federal agency's abilities to solve emergent problems.

These arrest photos show the quick progression of a young lady just out of high school as she flows down the pipeline of addiction. Because pills diverted to the street are efficiently hijacking our youth – which she clearly represents -- we'll call her Miss America.

[Slide 2]

Prescription drug abuse has been declared an emergency, a crisis, and an epidemic by various federal agencies, notably the CDC. In early 2012, Vatex naively thought that NIDA would shepherd our initial application through the review process because NIDA staff were very complimentary of our new approach to the crisis – new mechanisms, new thinking, all new. Our first application was submitted in July 2012. As shown in the graph, this application – a Phase I of limited duration and funding level – received very low scores in review. The reviewers were making judgments on the Phase I submission based upon the information, activities, budgets, and timelines that would be expected as part of a subsequent Phase II application. It also became clear to us that the NIH review process was married to a mentality of slow-motion submit-edit-submit-edit-submit cycles such that the form of the application was more important than the function of the content or the urgency of the problem. Here, "perfect is the enemy of the good." When the plainly-obvious 'form over function' conclusion was reported to NIDA, we were startled to find that a senior NIDA official took this personally and became exceptionally emotional regarding our criticism. Our feedback – standard in the business world -- has surely had an impact on the outcome of this case.

Because NIH is among the few sources of R&D funds for pre-revenue companies and because we continued to naively think that NIDA wants to solve the crisis by acting quickly and testing many mechanisms simultaneously, we licked our wounds and prepared another application that smartly reacted to our initial failure. This time, we assembled a well-regarded clinical and technical team for a combined Phase I and Phase II application. The Fast-Track application format allowed us the budget, the time, and the room to describe our clinical plans, to delineate many important testable hypotheses, and to fully explain our business case. Meanwhile, during this same period, Miss America is devolving.

Our second application was a smashing success, highly regarded and strongly recommended by the Reviewers who read it.

[Slide 3]

Except that it was a failure. Along with these slides and text, I have submitted the annotated Summary Statement proving that one reviewer did not read our application but torpedoed it anyway. This is not surprising given that a majority of the reviewers recruited by NIDA for this panel receive funds from pharma and that Vatex, if successful, will harm pharma by reducing sales. What is inexplicable is that NIDA fought long and hard to subvert the opinions of the reviewers who read the application and, instead, to emphasize the opinion of the one reviewer who did not read the application. In ex plicable! Many details remain to be discussed, but you will need to ask questions so as to extend my 5-minute limit.

Vatex is likely dead in the water. We only have funds to last until approximately September, and we only have one potential source of oxygen on the horizon. These are tough times for pre-revenue companies that seek investment to solve problems that seem hard. Conversely, over one thousand fart apps are available in the Apple store.

[Slide 4]

NIDA will hardly talk to us, but they do tell us that we are free to submit a Phase I, putting us back where we began. More than 24 months have elapsed. Meanwhile, America and Miss America devolve further. I have so much more to tell you, so please ask questions to extend my time.

[Slide 5]

NIH must develop a separate set of rules for emergent healthcare crises declared by other agencies. Based on what we've seen, NIH cannot be trusted to declare its own emergencies. At minimum, these separate rules must address the fast repair of defective reviews. In our case presented here, throwing out Reviewer 1 for not reading the application is obvious and reasonable and – given the gravity of the crisis – expected. Currently, NIH has no repair mechanism for defective reviews that is in any way timely.

[Slide 6]

Based on the evidence we have in hand – again, please ask questions – I don't trust NIH as far as I can throw it. They have the money, but I suggest that these emergent reviews be outsourced to an external organization.

[Slide 7]

NIDA is sick. The details and outcome of our case are inexplicable, and the public must be cautioned to avoid giving NIDA the benefit of the doubt. Specifically, we have found conditions within NIDA that make it ripe for malfeasance. For example, we possess documentation of an undiscovered felony perpetrated by a key senior NIDA official involved in this case. Next, NIDA have taken extreme measures to deflect the COI and process gaps we discovered. Again, please ask questions so that we can extend my time beyond 5 minutes and provide more details. If OIG, anyone with whistle blowing advice, or concerned citizens viewing the replay would like to reach me, my number is 276-633-0099.

[Slide 8]

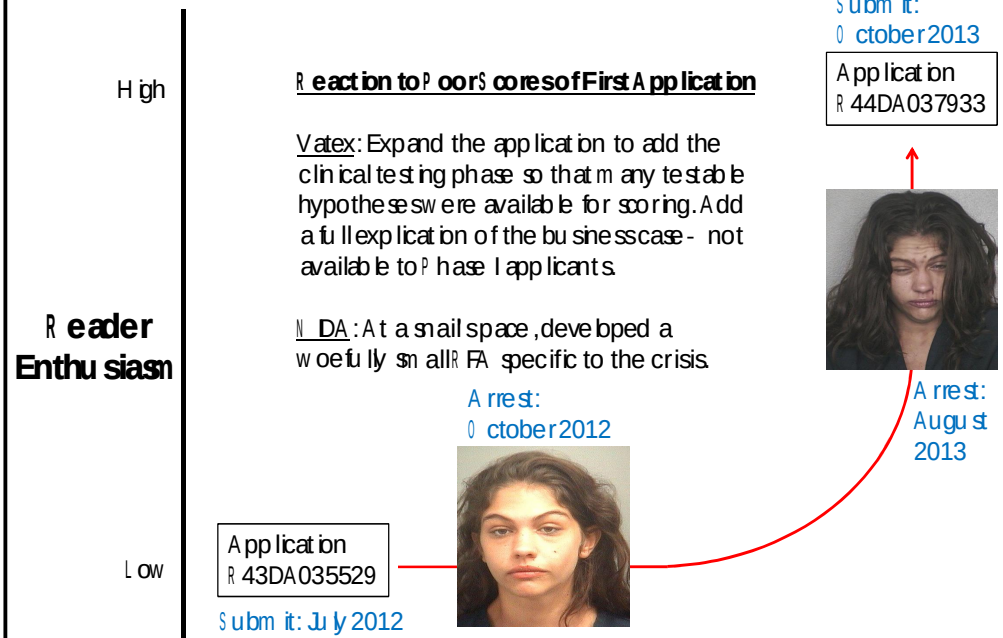
I am not sure that Miss America can be saved. For all we know, she will die an early and tragic death. Others are joining her now. Criminals and addicts have infiltrated our medical system to supply the black market and bleed our economy. This quote from Vermont's Governor Shumlin says is better than I can: "We've all got to roll up our sleeves and get involved because in the most industrious, productive, and imaginative democracy in the world, I maintain that this particular healthcare crisis is the one that can destroy America's quality of life if we keep doing business the way we are doing it." I shall be eager to answer your questions, to stay here as long as there is interest, and to turn over evidence to external investigators with subpoena powers. Please note that bad behavior within NIH is rarely reported with a level of detail that is actionable because scientists are unwilling to risk their funding -- this is a go-along-to-get-along culture. Vatex is taking this first of several go-public steps because we agree with Governor Shumlin. Thank you.

Pipeline of Addiction:

1) Pills to Heroin, and NIDA's Shameful Response
2) Absence of accountability in NIH grant review system
3) Hypothesis: Was: incompetence; Now: malfeasance

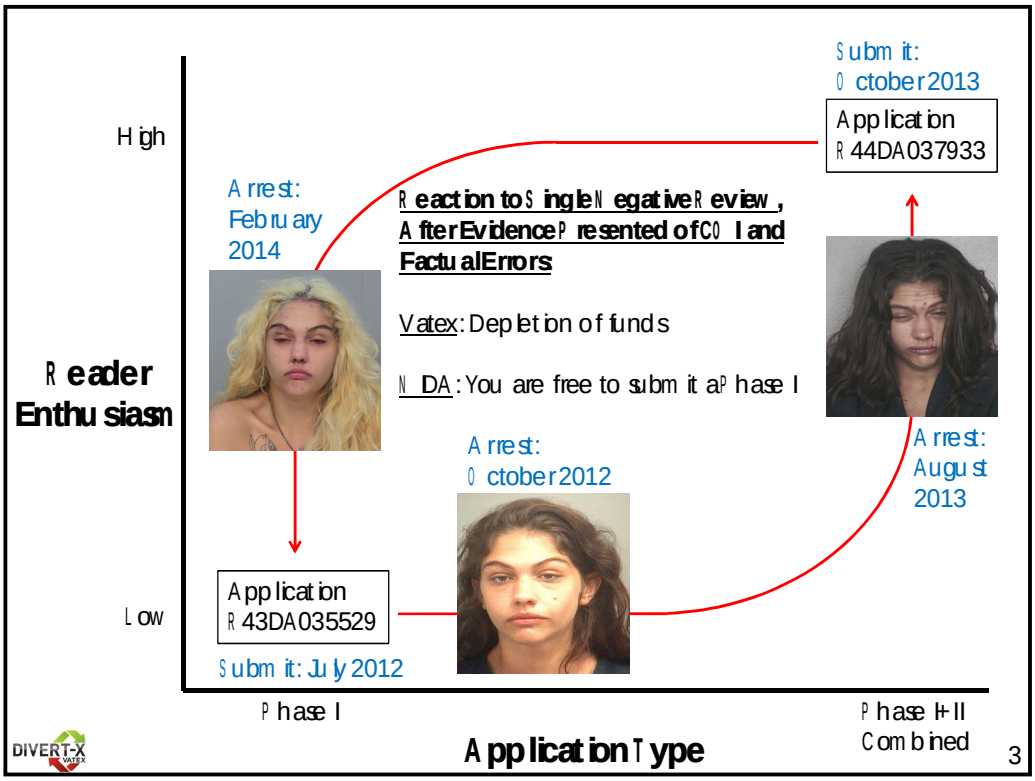
DIVERT-X VATEX

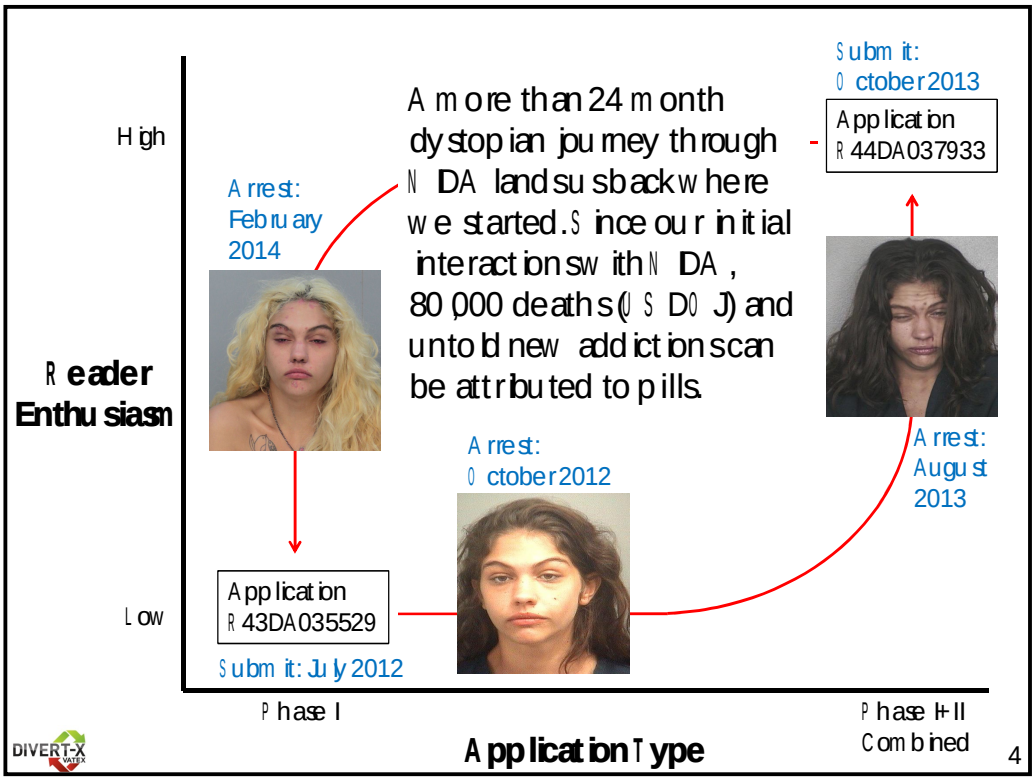
86% of Heroin users begin with pills (averaged results of 4 studies) 1



DIVERT-X VATEX

2


High
Reader Enthusiasm
Low
Arrest: February 2014
Reaction to Single Negative Review, After Evidence Presented of COI and Factual Errors:
Vatex: Depletion of funds
NDA: You are free to submit a Phase I
Submit: October 2013
Application R44DA037933
Arrest: October 2012
Arrest: August 2013
Application R43DA035529
Submit: July 2012
Phase I
Phase I+II Combined
Application Type
DIVERT-X VATEX
3


High
Reader Enthusiasm
Low
Arrest: February 2014
A more than 24 month dystopian journey through NDA land sus back where we started. Since our initial interaction sw ith NDA, 80,000 deaths (US DOJ) and untold new addiction scan be attributed to pills.
Submit: October 2013
Application R44DA037933
Arrest: October 2012
Arrest: August 2013
Application R43DA035529
Submit: July 2012
Phase I
Phase I+II Combined
Application Type
DIVERT-X VATEX
4

Ask #1

Design a separate set of rules or exceptions for declared national emergencies. Declarations by third parties (e.g., CDC, WHO) should trigger rules that provide a mechanism to repair defective reviews. Current NIH rules only allow for a very slow response. Emergencies cannot be mixed with plodding science.

DIVERT-X VATEX

5

Ask #2

For emergent healthcare challenges, consider funding via NIH appropriations but reviewing using external bodies. NIH too hidebound to do anything quickly?

DIVERT-X VATEX

6

Ask #3

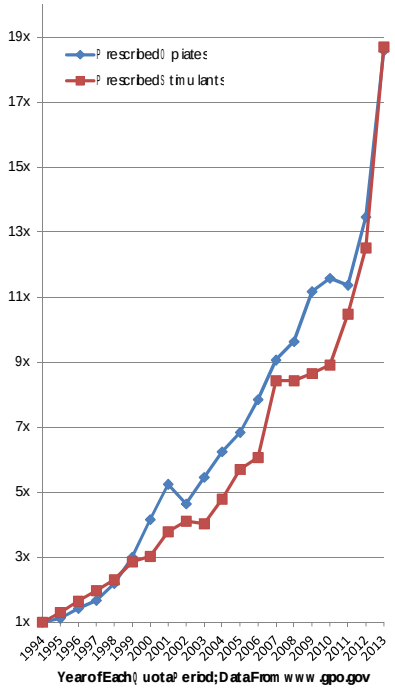
Consider bringing in OIG to investigate the review of the Vatex application. Chronic incompetence was the early explanation. Instead, malfeasance may be at the root: 1) undiscovered felony by a senior NIDA official involved in this fiasco (dishonesty established); 2) concerted effort to avoid review conflict-of-interest details (cover-up); 3) NIDA Council not independent and not alerted (purposeful).

DIVERT-X VATEX

19 Fold!

Help get pills out of her middle and high schools. NIDA leadership have failed. Change. Investigate.

U.S. Production, Normalized to 1994



DIVERT-X VATEX

SUMMARY STATEMENT

PROGRAM CONTACT:
Will Aklin
301-443-3207
aklinwm@mail.nih.gov

(Privileged Communication) ***Release Date:*** **03/14/2014**

Application Number: **1 R44 DA037933-01**

Principal Investigator

HARRIS, JAMES WAYNE PHD

Applicant Organization: VATEX

Review Group: **ZDA1 GXM-A (06)**
National Institute on Drug Abuse Special Emphasis Panel
Abuse-Resistant and Abuse-Deterrent Formulations and Devices to Avoid the Abuse, Misuse and Diversion of Prescription Opioids by Patients (RFA-DA-14-013; R43/R44 SBIR)
Meeting Date: **02/25/2014** ***RFA/PA:*** **DA14-013**
Council: **MAY 2014** ***PCC:*** **CX/WMA**
Requested Start: **07/01/2014**

Project Title: **Impact of opioid-access monitoring in identifying misuse and diversion**

SRG Action: **Impact Score: 50**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **44-Human subjects involved - SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	134,638	156,671
2	752,075	875,150
3	283,950	330,418
TOTAL	1,170,663	1,362,239

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R44DA037933-01 Harris, James

PROTECTION OF HUMAN SUBJECTS UNACCEPTABLE (See comments below)

RESUME AND SUMMARY OF DISCUSSION: In this fast track SBIR application from Vatex, Dr. Harris describes a plan to develop an integrated medical device IT system that monitors medication access and incorporates behavioral science to address opioid misuse and diversion, and to evaluate the system in a limited pilot study involving drug court subjects. Significance is supported by potential to develop a closed-loop dispensing and monitoring system and to gain insights into the population, although the system's goals might be compromised by subjects accumulating unused pills; the commercial potential seems limited due to costs (Reviewers 2 and 3 refute this because they read the application. Why were their presentations ignored? For example, Reviewer 3 understood our pricing model and indicated that we are likely under-pricing the service relative to its value; given that Reviewer 3 was present and spoke after Reviewer 1 and given that this section was written by an NIH employee to reflect the discussion, how can the NIH review process be so non-functional that glaring errors are not corrected on the spot, prior to releasing the Summary Statement?) (The cost position is stated in detail below- Divert-X will generate economic benefit to medical insurer-customers if it reduces the consequences of medication misuse by any more than only 5%); acceptance by multiple stakeholders seems necessary; and there seems moderate relevance to prevention (On the contrary there are at least two different modes of action of the system which are preventative. The use of the technology will have inherent properties of deterrence towards misuse. Secondly the data will enable the detection of the development of dependence, which will lead to intervention and the prevention of iatrogenic addiction). Dr. Harris is well-qualified as is the team which offers appropriate complementary and integrated expertise relevant to both Phase I and Phase II studies. Although somewhat similar technologies are being developed (Reviewers 2 and 3 describe the technology as unique. Vatex is not aware of any closely similar concepts in development), there is innovation in the proposed system, notably in the behavior modification approach which may represent a valuable alternative to the established policing approach, in the real-time data on dose timing and location, and in centering the technology in pharmacies. The approach is generally sound although it is at early stage development, the methodologies, timelines and schedule are appropriate, and the system has some potential to both abuse and behavior issues. However, how data analysis may be used relative to intervention remains unclear; initial pilot studies with a drug court population and with a limited set of types and doses of drug formulations, may lead to a less generalizable system (The Drug Court environment has been selected for the study because it will represent a concentrated pool of 'bad behaviors'. The data will be used to refine the behavioral algorithms. One of the great challenges of the prescription drug epidemic is that there are no methods to identify misusers from compliant patients. The evolved algorithms generated by this SBIR will be fully generalizable to the normal patient population- albeit that behaviors identified will be exhibited at lower incidence). The environment includes appropriate institutional and collaborative arrangements for the project, although resources necessary for later development are not evident (Why does the NIH employee who wrote this section repeatedly parrot factual errors made by Reviewer 1? Why are the views of Reviewers 2 and 3 -- who read the application -- ignored? Two letters of support from potential investors were provided in the application). A human subjects concern is noted (See comment below). Overall, this is a very good to good SBIR application.

DESCRIPTION: The Fast-Track proposal would fund major steps required to commercialize an integrated medical device-IT system (Divert-X), designed to leverage established behavioral science to combat opioid misuse and diversion. Divert-X monitors in real time patterns of patient access to individual doses

of medications and creates objective information flow that will enable evidence-based intervention by healthcare providers. Divert-X has uniquely broad modalities that will contribute to the reduction of prescription drug abuse- including preventative, deterrent, educational, diversion-identifying and street-supply reduction characteristics. The Divert-X system is designed to be filled and dispensed at pharmacies. The dispensed portion consists of a smart-blister pack and wireless module that communicates dose-access events in real time to analytics in the cloud. Divert-X is an open system that allows patients to access their medications as needed. To have the broadest impact and eliminate any requirements for commercial cooperation by pharmaceutical companies, the blister packaging is designed to be agnostic to dose, formulation and manufacturer. Phase I of this proposal includes the development and testing of blister-designs to result in child-proof certification- essential for product introduction. Child mortality from accidental opiate overdose is a prevalent mode of poisoning. The completion of all Phase I Specific Aims will enable a Phase II clinical evaluation of Divert-X in a population of buprenorphine patients nominated by Drug Courts. This opiate-dependent population is chosen for study because it is a concentrated group of patients expected to exhibit drug misuse and diversion more often than the general population. It represents a capital-efficient approach to generating behavioral data, directly applicable to the general population because most opioid addictions begin with medications. The study will compare inference of patient behavior determined by Divert-X versus saliva bio-analysis, medication inventory, and patient survey results collected during assessment visits. The data will be used to refine the Divert-X algorithm to improve its capability to detect drug noncompliance and diversion and to determine whether Divert-X reduces buprenorphine misuse-studied as a proxy for all opiates. Because of the national importance of the crisis, Vatex has recruited partners for the study with expertise in Drug Court clinical investigation and addiction (Dr. Brown), pharmacology (Dr. Fennell), evaluation and drug diversion research (Dr. Novak), and health-economic outcomes (Dr. Aldridge). The goal of the Fast-Track is to complete critical tasks required prior to Divert-X commercialization. Adoption of Divert-X for dispensing of Controlled Substances will be driven by cost-savings to insurers through reducing their spiraling costs from prescription drug abuse. Divert-X will enhance patient outcomes and access, identify and reduce diversion and trafficking, and save lives. The long term goal of Vatex is for the Divert-X drug-safety system to become standard-of-care for dispensing all Controlled Substances.

PUBLIC HEALTH RELEVANCE: The epidemic of opiate and prescription drug abuse continues to accelerate in part because the medical system has few tools to objectively identify patients who abuse or divert medications. Vatex is developing an integrated system to enable evidence-based protocols of intervention and counseling to be delivered to the right patients at the right times. The system will identify medication misuse and diversion and create accountability in the healthcare system from both patient and provider- combating misuse and diversion, improving patient outcomes and reducing the excess healthcare costs that are a consequence of abuse.

CRITIQUE 1:

Significance: 5
Investigator(s): 5
Innovation: 6
Approach: 7
Environment: 5

Overall Impact: The overall impact/priority score of 6/9 reflects my assessment of the likelihood for this project to exert a sustained, powerful influence on the research related to abuse-resistant (AR) device or system to avoid the abuse, misuse, addiction and diversion of prescription opioids by patients. The conceived product (system) is somewhat novel and might have an improvement over the current abuse-resistant strategies but that would require a change in current dispensing and practice behaviors (The magnitude of the epidemic and the associated mortality and fiscal burden shows that current approaches need to change. Vatex is targeting our system to payers because they have the power and motivation to make major changes if they are convinced by evidence to do so). The investigator has the necessary experience and expertise to successfully direct the project (Yet this reviewer assigned a 5 to Investigators). The proposed research strategy is adequately designed, but it is not clear if the data obtained will be generalizable to a broader population. This questions if it is actually actionable and if it can achieve the specific aims (Like all research, this is ultimately a chicken-and-egg concern. Although Vatex has robust expectations of the impact of Divert-X, naturally until the system impact is quantified in a clinical environment we have no proof of compelling merit.). The listed principals add value to the company's potential of achieving success but the current company would benefit from a strategic partner with IT, medical, manufacturing, and commercial depth. (Vatex has formed deep partnerships with companies in our supply chain- who will contribute engineering acumen and manufacturing expertise to the project.) The cost of the device limits the potential commercial success ($1500/unit) (A severe factual error on the part of Reviewer 1. See comments below). Furthermore, implementation and scalability of this system will require a drastic change in practice and buy in from many stakeholders, which diminishes the chances of success and reduces the value proposition (A severe factual error on the part of Reviewer 1. See comments below).

Significance:

Strengths

There is a need to have a closed loop multidimensional AR dispensing system or product readily available in the market. The proposed method incorporates behavioral modeling which is novel.

The successful completion of the aims could provide insight into the specific population tested. The application makes a modest case for the significance of the proposed research (The expectation and goal of Vatex is for Divert-X to reduce Controlled Substance misuse and diversion by 30%. This is clearly stated in the Commercialization section and surely must be considered to be a significant contribution.).

Weaknesses

The proposed project has limited commercial potential. Implementation and scalability of this system will require a drastic change in practice and buy in from many stakeholders, which diminishes the chances of success and reduces the value proposition (The system was described in the Commercialization section. To recap, implementation requires pharmacists to fill a blister rather than a pill bottle and for stakeholders-pharmacist, clinician and payer- to act upon the real-time behavioral assessment. There are multiple drivers for adoption including significant new revenue to the pharmacy and large overall cost savings to the insurer. A new treatment paradigm, 'Active MTM' has been designed to create communication pathways to facilitate leverage of Divert-X data -- this is described in the Commercialization section. Overall, for

Divert-X to be deployed widely insurers will mandate its use and we believe that this will happen once the economic value of Divert-X has been demonstrated).

Investigator(s):

Strengths

The investigative team (PD/PIs, collaborators, and other researchers) has FDA experience and has demonstrated the necessary skills to adequately perform this phase of the experimentation.

The PI has created a team with complementary and integrated expertise. He has held a leadership project role in the past and there appears to be the necessary governance and organizational structure appropriate for the project.

Weaknesses

There is no decisive evidence that the existing team has the necessary clinical, IT, nor manufacturing experience to execute the products to a viable commercial position (It is clear that Vatex will add personnel as the company grows. Manufacturing will be by third parties and Sellers has a 20-year history in custom manufacturing in regulated environments. Extensive IT and other resources will be added as required -- as is normal in the evolution from a start-up to a commercial company).

The development strategy is not clearly defined (This is a puzzling comment. To recap, examples of the development tasks described in the proposal include: quantify the impact of Divert-X, implement a new care model- 'Active MTM' to facilitate use, register with the FDA, present economic value to customers -- all of which are described in detail in the application.).

Innovation:

Strengths

This novel proposed system challenges to seek to shift both the current research and clinical practice paradigms.

Weaknesses

There are other somewhat similar technologies being developed (Vatex is not aware of any other product in development with such a broad array of modalities to combat medication misuse or that integrates patient behavior to patient motive). The necessary efforts to accomplish wide spread adaption is material (Is this not true with any innovative product development program?).

Approach:

Strengths

The proposed overall strategy, methodology, and analyses seem appropriate to accomplish the specific aims of the project. However, benchmarks for success are not clearly described.

The proposed study is scientifically rigorous but the investigative team has the necessary experience to perform the required tasks. The program schedule is rational and adequate timelines have been presented.

The study design utilizes acceptable methodologies.

Weaknesses

The investigative team has not identified the weakness of the approach adequately in the potential limitations and difficulties section of the proposal.

The project is in the early stages of development and the investigative team has not fully described a strategy to establish feasibility or how risky aspects are to be managed.

The costs are unreasonable in relationship to the size of the project and allocation of funds. The device costs contribute to this. Costs of units is a likely limiting factor for commercialization: $1,500/unit (This is a severe error on the part of the reviewer. Reviewer 3 read the application and states that Vatex is under-valuing the service. The cost of the Divert-X units does equate to roughly $1500 for the few-hundred devices required for the clinical evaluation which is the focus of this SBIR proposal. This pricing reflects the initial setup, design and re-tooling of precision manufacturing equipment required to manufacture to Vatex's specification. Subsequent production volume in the tens of thousands is projected to be $50 per unit. Upon full commercialization Vatex expects tens of millions of units to be produced, and that the cost will trend to $20. The Divert-X wireless module clearly has less capability than a cell phone so it is perplexing that a Reviewer would adopt the value of $1500 per unit as any guideline of future cost. Although the issue of the cost of the device is not explicitly described in the application, the Commercialization section does provide discussion of full service pricing and economic value. At a per prescription price of $20-30 for the integrated system, Vatex projects generating a net return of $150 to our customers. Reviewer 3 states that Vatex is under-valuing the service. This may well be correct but Vatex is motivated to drive the rapid adoption of Divert-X in order to turn the tide of the epidemic as quickly as possible.)

Environment:

Strengths

The scientific environment in which the work will be done shall positively contribute to the probability of success as these centers have vast depth and experience.

The institutional support, equipment and other physical resources available to the investigators are more than adequate for the proposed project.

The project will benefit from unique features of the scientific environment and collaborative arrangement.

Weaknesses

Vatex has limited resources (staff and money) to complete the project (This is an assumption without any verifying data. In any case it should not be presented as a weakness -- capital and personnel are added only as required by any frugal young company). No evidence of additional funding was presented (Two letters of support from potential investors were provided in the application).

Fast Track (Type 1 R42 and Type 1 R44 applications):

Unacceptable

The Phase I application states clear, appropriate, and measurable goals (milestones) that should be achieved prior to initiating Phase II. The applicant did not provide evidence of letters of interest, additional funding commitments, and/or resources from the private sector or non-SBIR/STTR funding sources that would enhance the likelihood for commercialization (The Reviewer completely missed the two letters of support from the financial institutions and two from medical insurers/ future customers. Reviewers 2 and 3 support the Fast Track).

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

IRB review pending

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Select Agents:

Acceptable

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Unacceptable. The costs are unreasonable in relationship to the size of the project and allocation of funds. The device costs ($1,500/unit) contribute to this (See comments above).

CRITIQUE 2:

Significance: 4
Investigator(s): 1
Innovation: 1
Approach: 4
Environment: 1

Overall Impact: This Fast Track SBIR application seeks to continue the development of Divert-X in Phase I and conduct a small pilot study in Phase II that can further refine the product. As a new dispensing device for prescription medications, Divert-X can be clearly differentiated from other products on the market and is highly innovative. It has the potential to identify patterns of prescription misuse, at least with regard to aberrant times and locations of doses being accessed; it is less clear the likely impact on diversion, particularly for the medication (buprenorphine) to be tested in the drug court pilot study. The methods for Phase I are very strong and the milestones for Phase I are clearly defined. There are no concerns regarding the feasibility of Phase I, but there are some concerns about the design of the drug court pilot trial proposed for Phase II. The commercialization plan may oversimplify the market potential, but there are clear plans for moving the product forward in a logical way. Taken together, this project has some potential for resulting in a device that may have some positive impacts on reducing prescription drug misuse.

Significance:

Strengths

New devices are needed to address the prescription drug epidemic, and this application proposes a dispensing device that is novel and would potentially offer an improved way to measure prescription drug misuse beyond current methods of self-reports.

The argument that adding monitoring can change human behavior (irrespective of whether the monitoring results in actual consequences) is somewhat persuasive regarding the potential value of Divert-X in reducing prescription drug misuse/abuse.

Weaknesses

Divert-X, as a product, will provide information on where and when a dose is accessed, but a major element of diversion—particularly for buprenorphine—is that patients convince prescribers to prescribe a high dose (which requires multiple tablets or films), and then they only use some of the tablets/films and save the rest for diverting to others. This aspect of diversion is unaddressed by the product, which does limit its impact on diversion (We concur that Divert-X will not stop all misuse and diversion.

We think of Divert-X as a methodology to 'de-industrialize' diversion and misuse, with an overall goal of 30% reduction).

Beyond the general impact of monitoring, it is less clear how and when health care providers and other stakeholders will access the real-time data in clinical decision-making. Although perhaps some of the clinical decision-making tools may be developed in later phases, the absence of a general overview makes it difficult to fully gauge the full impact of this product on reducing prescription drug abuse (An implementation protocol termed 'Active MTM' is described in detail in the Commercialization plan. Vatex intends to work with stakeholders to develop this concept to provide an easy way for clinicians, pharmacists and payers to take advantage of the Divert-X data stream).

Although reducing diversion and misuse may save insurers money, the financial argument (i.e., that the cost-savings will prompt adoption) for adoption by insurers may be overly simplistic. There are ample examples of cost-effective interventions that have gained little traction with insurers. For example, many major insurers are attempting to limit the duration of buprenorphine treatment even when the scientific evidence indicates that long-term buprenorphine treatment is cost-effective. This example points to the complexities within the adoption process. Notably, of the two letters of support from insurers that are included about interest in the product, only one of which makes a specific commitment about potentially adopting Divert-X (Vatex certainly acknowledges that introducing new products, even those both innovative and cost-effective, is challenging).

Investigator(s):

Strengths
PI has lengthy history of research, invention, and successful navigation of the patent process.

Other members of the team bring important expertise: IT/computing (Wylie), clinical expertise in substance use disorders and drug court research (Brown), epidemiology & statistics (Novak), health economics (Aldridge), and pharmacokinetics (Fennell).

Innovation:

Strengths

This research will yield a product that offers much more real-time data related to medication dispensing that is more objective than simple self-reports of medication compliance.

A compelling case is made regarding how Divert-X differs from existing dispensing technologies that have attempted address prescription drug misuse/diversion, particularly with regard to the novelty of having a pharmacy-based (rather than drug manufacturer-based) system and the innovation of having real-time data on dose access (i.e., timing & location).

Approach:

Strengths

The Divert-X system has many attractive features: >month-long battery life, real-time wireless transmission of data, feasibility for implementation in the pharmacy setting (e.g., limited interruption of workflow and not requiring capital equipment), consideration of patient privacy (i.e., no identifiable data within Divert-X—that information stays with the pharmacy records), methods to prevent tampering in the device itself, and methods to monitor potential tampering (i.e., having patient return device at end of the month). These aspects of the product are key strengths.

The approach (Phase I) to ensuring that the Divert-X packaging is child-safe and yet accessible for older adults is very strong, and complies with requirements of the Poision Prevention Packaging Act.

The approach to considering costs in the economic analysis of the Drug Court Pilot is appropriate and will be useful for key stakeholders.

The approach to using data from the Drug Court Pilot to improve the predictive algorithm within Divert-X seems reasonable.

Weaknesses

How Divert-X provides actionable information regarding patient motives is unclear. Furthermore, the description of how real-time data on location will be used is not clearly articulated (One use of the location data is to identify the aggregation of medications in the device, as is commonly the situation with organized diversion rings. This aspect is mentioned in tabulated form in the Commercialization plan. Many other, more subtle aspects of location will be scrutinized by the algorithm- such as use of medications from a location not registered by the patient).

The eliding together of diversion with medication misuse is troubling. Diversion is typically defined as moving a medication into the illicit marketplace. Neither outcome measure in the Drug Court Pilot truly captures diversion—at best the outcomes (one that is a medication inventory, and the other integrates multiple pieces of information to determine medication compliance) may indicate misuse (i.e., not taking the medication as directed) (Full clarity of diversion practices would seem impossible without institutionalized patients. The system will generate information which if it indicates questionable practices will lead as a first step to increased scrutiny).

It is not clear whether the statistical analyses for the Drug Court Pilot will be intent-to-treat, and the analysis plan lacks sufficient detail about how compliance data collected at multiple time points (i.e., 4 visits) will be analyzed.

Details regarding recruitment and eligibility criteria for the Drug Court Pilot are limited in the main application (and some details are only presented in Human Subjects, which should not be used as a method for circumventing page limits). It appears that participants are newly-diagnosed individuals with opioid dependence who then will be initiating buprenorphine treatment as part of the study. It is not entirely clear (based on the Approach) where subjects will receive their buprenorphine treatment (particularly those recruited outside of Dane County), and whether those providers have the capacity to take on additional patients—this is an important issue because prescribers are limited in the number of patients (30 patients, or 100 patients depending on their X-license) who they can treat with buprenorphine at any given time.

It is not entirely clear whether Divert-X can accommodate the range of buprenorphine-naloxone products currently on the market. Many patients use the Suboxone® films, and it is unclear whether the blister packs can accommodate the films. Furthermore, the newest product, Zubsolv® is already manufactured in individual blisters—how likely would pharmacists be willing to open each Zubsolv® blister and move each tablet into Divert-X? Even for patients taking the generic tablets, most will need to take more than 1 for their —dose in the morning, and it is not entirely clear how these are packaged in Divert-X. (A key item in the proposal work schedule is developing the full evaluation protocol; the description in the application is not intended to be complete. The study will focus only on pills/tablets -- users of the film formulation will be excluded. This is known and accepted by our clinical and judicial partners. Over the long term, Vatex will develop a version of Divert-X that can accommodate films and other dosage forms; this breadth of applicability is one of the strengths of the Divert-X approach.)

Environment:

Strengths

Vatex has developed Divert-X, and thus has the intellectual resources to support the project; they are renting space from NTEC which has adequate space and other shared equipment to support the project.

University of Wisconsin and RTI have ample resources to support their aspects of the project.

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

Milestones for the Phase 1 study are very clear. The criteria for demonstrating achievement of the milestones should be easily interpreted by program staff at the end of the Phase 1. Milestones also appear to be feasible given the state of development of Divert-X and the proposed timeline.

Protections for Human Subjects:

Unacceptable Risks and/or Inadequate Protections
In Phase I, protections of human subjects are largely mandated by the requirements of the Poison Prevention Packaging Act. Participation in the Phase II Pilot Study will be voluntary and data will not be shared with drug court program. Data security procedures are acceptable. Certificate of Confidentiality will be obtained. However, the Pilot Study proposes to use either buprenorphine or buprenorphine-naloxone with participants; given that pregnant women are excluded from participating, the rationale for using the mono buprenorphine product is unclear. Mono buprenorphine lacks the abuse deterrent (i.e., naloxone) which increases its abuse potential (e.g., injecting the medication) and related risks are not well addressed (The study will only recruit buprenorphine-naloxone subjects).

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

- Procedures for monitoring and reporting of AEs and SAEs are included.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Both genders and all racial/ethnic groups are eligible to participate in the Phase II Drug Court Pilot. It is estimated that 47% of subjects will be female, 18% will be Hispanic, and 22% will be African American. Children aged 18-20 will be eligible to participate. Children will also participate in the Phase I packaging testing.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 3
Investigator(s): 2
Innovation: 2
Approach: 3
Environment: 2

Overall Impact: Divert-X is designed to leverage established behavioral science to combat opioid misuse and diversion by monitoring in real time patterns of patient access to individual doses of medications and creating objective information flow that will enable evidence-based intervention by healthcare providers. This technology addresses a significant problem in the field, the redirection and misuse of prescription drugs, especially opioid drugs. Estimates indicate the problem leads to societal disruption and $125-150 billion in excess medical spending in the United States each year, and the number of deaths per year exceeds auto related deaths per year. The ability to use —pill use tracking (for Buprenorphine) and data based tools to monitor drug abuse behavior and intervene clinically appears to be a novel approach in this space, inasmuch that such quantitative tools do not exist on a large scale today. The positive aspects are that knowledge of the monitoring is open to both the monitor and the user, so it's a very transparent approach and there is evidence from related approaches (e.g., gambling, pornography use) that compliance visibility is helpful. The concern is that the system can only affect abuse through post abuse intervention (i.e., not preventive in nature) (There are strong preventative aspects to the approach- tabulated in the Commercialization section. Deterrence towards misuse and an ability to generate data that can be used to prevent patients developing iatrogenic addictions are two examples).

Significance:

Strengths

The ability to use data based tools and behavioral modification algorithms to monitor drug abuse behavior and intervene clinically appears to be a novel approach in this space, inasmuch that such quantitative tools do not exist on a large scale today. The positive aspects are that knowledge of the monitoring does both the monitor and the user, so it's a very transparent approach and there is evidence from related approaches (e.g., gambling, pornography use) that compliance visibility is helpful.

Weaknesses

The negative aspect is that the system will affect primarily through post abuse intervention. The concept is not preventative in nature, with the exception of the "known observation" the users will experience (See comments elsewhere).

Investigator(s):

Strengths

The combination of the Vatex team, with RTI and UW Madison provides a strong, well academically qualified multidisciplinary team, especially in terms of data collection approach, abuse algorithm development, and Phase II clinical evaluation approaches.

Weaknesses

Omission of some details regarding regulatory issues suggests some additional expertise may be warranted (see Comments to Applicant)

Innovation:

Strengths

The primary innovation appears to be in the behavior modification approach, a recognition that working with drug abusers in early intervention is a realistic approach that will make a significant long term difference. I feel this is important because it provides a valuable alternative to the —policing approach" that is highly worthy of evaluation. The development strategy is clearly defined, with a Phase 1 approach to define the smart blister packs and develop abuse detection algorithms.

Weaknesses

There should be a focus early in the program on risk management, a process failure modes and effects in analysis to identify and mitigate process risks in the approach and software mitigations for those risks.

Approach:

Strengths

The development of the blister pack and data tracking services appears to be well thought out. The development of the abuse detection algorithms involves experts and the development of clinical protocols and involvement of the Drug Court participants appear to be a robust approach for monitoring and intervention. The use of data cloud based analytics and regional device tracking appear well thought through, however data security will be a concern and there should be a robust approach based on expert input.

Weaknesses

The pilot use of the drug Buprenorphine and the Drug Court participants may lead to algorithms that are too focused for general drug abuse use later (The Divert-X algorithm will be large and complex. The specific aspects incorporated from the Drug Court study will form only a portion of the algorithm. As is the norm in other healthcare-analytics applications, it will be constantly modified as additional data and experience is generated).

Environment:

Strengths

The Vatex and RTI teams appear well experienced to enable development of the behavioral modification algorithms.

The UW Madison team appears well positioned to support the clinical data analysis form the Phase II studies.

Weaknesses

There may need to be increased experience and support in the team on the development of the smart blister pack in order to achieve cost and functionality goals (we have vendors in place who are expert in this field).

Fast Track (Type 1 R42 and Type 1 R44 applications):

Acceptable

There appear to be clear goals, letters of support and adequate preliminary data to support the proposal.

Commercializability: recommend developing detailed requirements and risk mitigations for potential abuse scenarios for the blister pack (traceability feature) and its interaction with the monitoring software. At least 1-2 prototype iterations should be planned based on learnings to improve product launch success. If leading experts can provide white papers on the behavior modification approach, it will assist in the launch promotion until published, statistically appropriate, clinical evaluations are completed.

Manufacturing: recommend soliciting proposals from 3 potential suppliers for the blister packs based on price and quality targets. In addition, consider manufacturing options for the blister pack and a roadmap for future improvements in design and manufacturing.

Potential market size: The market size would appear to be significant, however the following potential limitations should be considered (patients without access to the data communication required to support the software integration, patient sub-populations for which regular knowledge of abuse patterns has not provided a useful remediation strategy).

Pricing: To the extent that the behavior modification approach is largely successful, or at least in that patient sub-population, pricing can be extended upward to reflect a significant portion of the cost avoidance of opioid abuse recidivism.

Protections for Human Subjects:

Unacceptable. There is not a specific clinical protocol attached to describe the protection of test subjects for evaluating behavioral modification algorithms (The development of the protocol is a project task, and will be addressed with rigor as part of Phase I).

Inclusion of Women, Minorities and Children:

M1A – Minorities included, Acceptable

G1A - Both Genders, Acceptable

C1A - Children and Adults, Acceptable

Additional Comments to Applicant (Optional):

The ability to use data based tools and behavioral modification algorithms to monitor drug abuse behavior and intervene clinically appears to be a novel approach in this space, inasmuch that such quantitative tools do not exist on a large scale today. The positive aspects are that knowledge of the monitoring does both the monitor and the user, so it's a very transparent approach

The investigators should incorporate a medical device regulatory review within their development cycle. I'm not sure that the assumption regarding the development process for a Class 1 medical device is correct, in that it will only require a "light" development process based on FDA requirements. In my experience a Class I devices requires following design controls per 21 C.F.R. §820 and because the device is primarily software. A strong regulatory position paper should be in the development plan. The investigators should incorporate a medical device regulatory review within their development cycle ("Class I device category NXB (131) while the database falls outside the boundary of products FDA chooses to regulate (132)"). I'm not sure that the assumption regarding the development process for a Class 1 medical device is correct, in that it will only require a "light" development process based on FDA requirements. In my experience a Class I devices requires following design controls per 21 C.F.R. §820

and because the device is primarily software. A strong regulatory position paper should be in the development plan. Potentially applicable references:

- FDA **Medical Device Data Systems (MDDS)** are hardware or software products that transfer, store, convert formats, and display medical device data. An MDDS does not modify the data or modify the display of the data, and it does not by itself control the functions or parameters of any other medical device. **MDDS are not intended to be used for active patient monitoring.**

- Food and Drug Administration (FDA), Quality System Regulation, 21 CFR Part 820.

- "Guidance for Industry and FDA Staff - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" published by the U.S. Department Of Health And Human Services, Food and Drug Administration Center for Devices and Radiological Health, Office of Device Evaluation.

- ANSI/AAMI/IEC 62304:2006 "Medical device software – Software life cycle processes"

- "Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices" published by the U.S. Department Of Health And Human Services, Food and Drug Administration Center for Devices and Radiological Health, Office of Device Evaluation

- IEC TR 80002-1:2009 Medical device software –guidance on the application of ISO14971 to medical device software; IEEE Std 1016-1998 IEEE Recommended Practice for Software Design Descriptions; IEEE Std 1012-2004 Standard for Software Verification and Validation.

Content of Premarket Submissions for Management of Cybersecurity in Medical Devices - Draft Guidance for Industry and Food and Drug Administration Staff, DRAFT GUIDANCE, issued on: June 14, 2013.

Data security will be a concern and there should be a robust approach based on expert input (Vatex appreciates these helpful comments which will be investigated thoroughly. We maintain that Divert-X is Class 1. The term 'light' was not meant to be pejorative -- rather it reflects our comfort with this level of regulation when compared to our experience gained in the drug development industry).

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): UNACCEPTABLE. In Phase I, protections of human subjects are largely mandated by the requirements of the Poison Prevention Packaging Act. Participation in the Phase II Pilot Study will be voluntary and data will not be shared with drug court program. Data security procedures are acceptable. Certificate of Confidentiality will be obtained. However, the Pilot Study proposes to use either buprenorphine or buprenorphine-naloxone with participants; given that pregnant women are excluded from participating, the rationale for using the mono buprenorphine

product is unclear. Mono buprenorphine lacks the abuse deterrent (i.e., naloxone) which increases its abuse potential (e.g., injecting the medication) and related risks of addiction are not well addressed (The study will only recruit buprenorphine-naloxone subjects). Also, there is not a specific clinical protocol attached to describe the protection of test subjects for evaluating behavioral modification algorithms, and this should be specified (This will be a section in the fully-developed protocol).

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.
The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

National Institute on Drug Abuse Special Emphasis Panel
NATIONAL INSTITUTE ON DRUG ABUSE
Abuse-Resistant and Abuse-Deterrent Formulations and Devices to Avoid the Abuse, Misuse and Diversion of Prescription Opioids by Patients (RFA-DA-14-013; R43/R44 SBIR)
ZDA1 GXM-A (06) R
February 25, 2014

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.