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Dockets Management
Food & Drug Administration
Docket number 2004-N-0181
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **Critical Path Initiative**

VivoMetrics® is pleased to respond to the FDA's Critical Path Initiative. We have studied the March 2004 Innovation/Stagnation report and appreciate the opportunity to submit comments and provide information on ways to address the critical issue of improving the drug development process. Our response addresses the eight questions set forth by the FDA.

VivoMetrics, founded in 1999, provides ambulatory monitoring products and services for the collection, analysis and reporting of subject-specific physiologic data. Pharmaceutical companies use VivoMetrics' technologies to improve the speed and economics of clinical research. The company's offerings also enable academic researchers to discover new clinical signatures of disease, and U.S. Government agencies to research military and civilian first responders' physiological performance.

Our technology, the LifeShirt® System, is a non-invasive, ambulatory monitoring system that continuously collects, records and analyzes a broad range of cardiopulmonary parameters. Users wear a lightweight, machine washable garment with embedded sensors that collect pulmonary, cardiac, posture and activity signals. Data collected by integrated peripheral devices measure blood pressure, blood oxygen saturation, EEG/EOG, periodic leg movement, temperature, end tidal CO2 and cough. An electronic diary captures subjective user input and all physiologic and subject data are correlated over time.

1) "Hurdle Identification. Please describe the product development issue, the nature of the evaluation tool that is out-of-date or absent, how this problem hinders product development, and how a solution would improve the product development process. Please be as specific as possible."

Product development issue(s): There are three significant hurdles to the drug development process.

The first of these hurdles is related to the **quality and relevance of data** that is currently collected in clinical research. Many clinical trials still rely heavily on subjective patient self-report or discreet laboratory measures to assess drug effect and drug-disease interaction. These data are subject to substantial variability and discreet measures in a laboratory environment provide only 'thumbnail' detail of the patients' experience with the disease and the treatment. Limited or inaccurate information hinders decision making and may significantly lengthen the duration of clinical trials. A solution to this problem would allow objective data to be collected in a continuous manner from patients during their normal routine. Ideally, patient reported experience would be captured as well to provide the complete picture of the trial participants' physical and emotional experience of the disease and treatment. Data collection in this manner would lend itself to the development and use of novel endpoints that will more effectively reflect meaningful

2004N-0181

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improvements in treatment and the impact of these on the length and quality of patients' lives.

The second hurdle is related to **patient recruitment and retention** which has ramifications for trial duration and expense. Trial participation often involves substantial disruption in the lives of participants. This has two effects: First, the range of individuals willing to participate in clinical trials is limited to those who have the ability to meet participant requirements, often leading to trial sites having recognized lists of 'good subjects' which necessarily reduces the ability to generalize of the study results. Second, difficulty in recruiting or retaining enrolled subjects prolongs study timelines, delaying submission and evaluation of data packages, and increasing the expense of drug development which is inevitably passed on to patients and third party payers.

The final hurdle is the ability of clinical researchers to design trials that will allow both the evaluation of the use of a novel treatment in the general disease population while allowing appropriate stratification within the dataset to **evaluate variance in efficacy and safety risk across relevant subgroups**. The goal of the scientific process is to produce results that can be generalized to the population in general. In order to do this, a population with diverse characteristics within a target disease should be included in the trial. However, in relation to the development of novel pharmaceutical or biologic interventions, there are often subgroups within disease populations that respond significantly better or worse than others. The ability to collect appropriate stratifying variables allows a more refined evaluation of clinical trial data and more appropriate labeling and usage guidance. In this way, the benefits of products that are efficacious and safe in a subset of patients are identified.

2) "Please rank each hurdle identified in Question 1, above, in priority order according to which hurdles create the most severe product development problems. That is, which problems present the greatest opportunity for improving product development processes? Our goal is to identify those aspects of product development that would most benefit from new evaluation tools."

The priority of each hurdle described in point 1 is similar as these three hurdles are all integral to improving product development. However, the need to increase the quality and relevance of the data collected in clinical trials is the highest priority. The collection of improved data will enable more rapid review and, when appropriate, approval. Also, trial endpoints that are more relevant to the disease population will enable more rapid and targeted adoption rate, which will hasten return on the investment made by the research, pharmaceutical and biologic companies.

The second highest priority is the ability to improve trial subject recruitment and retention. Reevaluating the way that clinical trials are designed and conducted with the intent of making enrollment in trials more reasonable for a larger segment of the population will enable data collection time to be shortened. Additionally, this will allow a more representative sample of the population to participate in many trials.

Finally, increasing the scope of data collected in order to facilitate more refined stratification and subsequent analysis of the data collected throughout the drug development process will enable sponsors to better focus later stage trials. Increasing the number, accuracy, and relevance of stratifying variables will enable sponsors to better understand the safety and efficacy of their products in different populations. And, this increased information will facilitate appropriate decisions related to the continued clinical development of new molecules.

3) ***“For each problem identified, please indicate the type of drug, biologic, or device to which the hurdle applies.”***

The hurdles to new product development mentioned above relate to varying degrees to the development of all new drug and biologic product, and to many devices. The development of any drug, biologic, or device would be enhanced by overcoming the hurdles described above.

In addition, continuous ambulatory monitoring can be used to collect data on targeted populations, for example, to monitor patients in trials for drugs with long lasting side effects, to monitor pediatric patients while they are at home in their normal environments or to collect objective data on populations, such as autistic children, where it is not feasible to rely upon patient-reported input.

4) ***“For each problem identified, if a solution would facilitate the development of drugs, biologics, and/or devices for a particular disease or categories of disease, please indicate which diseases would be affected?”***

Specific diseases that would be affected include: asthma, diabetes, obesity, cancer, congestive heart failure, hypertension, depression, sleep disorders, COPD, cystic fibrosis, depression, bipolar disease, neuromuscular disorders, pain, rheumatoid arthritis, osteoarthritis, and any disease with a respiratory, cough, sleep, or activity component.

5) ***“Nature of the Solution. For each problem identified, please describe the evaluation tool that would solve the problem and the work necessary to create and implement the tool/solution. For example, would a solution come from scientific research to develop a new assay or validate a new endpoint? If the solution involves biomedical research, please specify the necessary research project or program. Would a tool be developed through data mining or computer modeling? Would the right tool be a new FDA guidance or industry standard? If work on a solution is underway, what steps remain? Are there other innovative solutions that could be explored?”***

Continuous ambulatory monitoring tools that measure multiple physiologic parameters, can be used to help compress the critical path of new drug development and are available today. Gathering objective physiologic data in a patient's normal environment improves both the quality and relevance of data. Synchronizing objective data with patient self-report provides a complete picture of the trial participants' physical and emotional experience. Monitoring patients in their normal environment minimizes disruption and enhances patient recruitment and retention. Stratifying patient populations allows a more refined evaluation of clinical trial data.

The LifeShirt System from VivoMetrics is a non-invasive, continuous ambulatory monitoring system that captures physiologic data from subjects in clinical research. The LifeShirt has received marketing clearance (K011903 and K031550) and is being used in the United States, Europe, and Canada. The LifeShirt System is composed of core and peripheral physiologic sensors and data analysis software. The core data streams are respiratory inductance plethysmography (RIP), electrocardiography (ECG) and accelerometry. Peripheral inputs include electroencephalography (EEG), arterial oxygen saturation (SpO₂), skin or core temperature, limb movement, blood pressure and throat sound. An electronic patient diary allows the collection of subject-reported information such as symptoms, emotions, activities, medications taken and programmed survey data, all fixed in time with the physiologic state of the individual wearing the shirt. Data collected by the LifeShirt System are encrypted and stored on a data card, processed by trained technicians using VivoLogic® software in the VivoMetrics 21 CFR part 11 compliant data center, and securely stored and transmitted to clinical trial sponsors or research sites for use in clinical trials.

The combination of core and peripheral inputs with sophisticated software has enabled data analysis time to be reduced substantially while enabling a variety of lab based or patient self-reported outcomes measures to be made objectively. For instance, cough can be objectively quantified as can sleep time and quality. Additionally, activity and posture can be quantified with the accelerometer, and all of the physiological data can both enhance and be enhanced by electronic patient diary input.

The LifeShirt System improves the quality of data collection while increasing comfort and convenience for clinical trial subjects thereby improving patient recruitment and retention and ultimately increasing the speed, quality, and efficiency of clinical research.

6) "For each solution identified, please indicate which could be accomplished quickly, in less than 24 months, and which require a long-term approach?"

The LifeShirt has received marketing clearance from the FDA, is in use in the marketplace and can be implemented in clinical trials immediately.

7) "For each problem identified, what role should FDA play and what role should be played by others? Should FDA play a convening role, bringing the relevant parties together to discuss an approach or solution? If so, who else should participate? Should FDA coordinate scientific research, the results of which would be publicly available? We are seeking input on ways to target FDA scientific and collaborative activities to help industry bring more safe and effective medical products to us for review."

The FDA can play a valuable role by bringing together drug developers and technology providers, and by coordinating scientific research and pilot projects.

Meetings between drug developers, the FDA and technology providers will provide a forum for discussion on new and innovative technologies and their applications, and be educational and informative for all involved.

Scientific research and pilot projects will provide objective evaluation of the contributions technologies can make to compress the critical path of drug development. Pilot studies are an effective way to establish best practices and show outcomes and economics of new approaches. Results should be easily and publicly accessible to encourage wide spread dissemination of the information.

The Center for Drug Evaluation and Research and Center for Devices and Radiological Health can play pivotal roles in bringing innovative technologies and pharmaceutical companies together. CDER could proactively identify investigational new drug approval applications that would benefit from capturing objective physiologic data in patients' normal environments, consult with CDRH regarding devices that capture this data and facilitate a meeting between interested parties.

8) "What factors should guide FDA in setting priorities among the hurdles and solutions identified?"

The FDA should focus on those areas where pilot projects and prototypes can be used to quickly evaluate the contribution a technology or approach can make to improving public health by compressing the critical path for new drug development. Therapeutic areas for study can address a broad spectrum of the population, such as obesity, diabetes, asthma and cardiovascular disease, providing benefit for a large population.

Thank you for identifying the problems surrounding new drug development and taking the lead role in addressing these critical issues. Members of the VivoMetrics team are available and would welcome the opportunity to discuss these issues and our response during a conference call or meeting. Please call me on (805) 275-5814 if you have any questions or would like additional information.

Very truly yours,

A handwritten signature in black ink, appearing to read "Paul Kennedy". The signature is fluid and cursive, with a large initial "P" and a long, sweeping underline.

Paul Kennedy
President & CEO

cc: Larry Kessler, MD