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TO: Janet L. Scudiero, Neurological Devices Panel of the Medical Devices Advisory Committee.
FROM: Dr. Leon M. Silverstone, NeuroMed Devices, LLC.
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I am enclosing a list of twenty questions for the Neurological Devices Panel of the Medical Devices Advisory Committee. The answers to these important questions will enable my team and I to get a feel for both the thinking and direction of the panel with respect to the potential introduction of new treatment devices in the near future. Clearly, these are not questions to which we do not already know some of the answers, rather they are designed to illuminate the panel paradigms and any latent positive and negative prejudices before we commit to protocols and studies that will cost enormous sums. I would like to express my gratitude to panel members in advance for their efforts and time in considering these questions.

I give my permission in advance to authorize the public release of my questions and subsequent answers.

Introduction

Reports have shown that 100,000 Americans die each year in U.S hospitals as a result of taking drugs and two million non-fatal drug reactions occur yearly, not due to mistakes in prescribing by doctors, nor mistakes using them by patients. All drugs can have adverse side effects. Thus, the use of a non-drug approach to alleviating symptoms of a variety of diseases is highly desirable not only because of eliminating adverse drug effects but also to control ever spiraling healthcare costs which approached \$2 trillion in 2005. One important question to ask is that in view of rising healthcare costs, has there been a corresponding reduction in disease levels that plague mankind on a daily basis?

Chronic Pain costs Americans more than a \$100 billion annually. Chronic Pain Syndromes such as low back pain, carpal tunnel syndrome, fibromyalgia, complex regional pain syndrome and others affect a large percentage of the U.S. population and are responsible for much pain and suffering with only palliative approaches to treatment.

Chronic long-term sleep disorders affect at least 40 million Americans and left untreated interferes with work, driving, and have negative effects on physical and mental well-being.

Obesity in children is now epidemic with 1 child in 5 being overweight, and 30 percent of U.S. adults are obese, greatly increasing the risk of heart attack, stroke and other debilitating diseases.

About 20 million Americans suffer from depressive illness which causes extreme pain and suffering. In December 2006 an FDA Advisory Panel warned that the risk of suicide linked to antidepressants be extended from children and adolescents to include adults up to age

25 since the risk for suicide attempts doubled. The American College of Obstetricians and Gynecologists recommended, also in December 2006, that pregnant women and those wishing to become pregnant refrain from taking the antidepressant Paxil because of the risk for birth defects.

Genital herpes is a sexually transmitted, incurable disease that according to the Centers for Disease Control & Prevention has now infected 1 in every 5 Americans over the age of 12 years, that is about 50 million Americans, with 500,000 new cases occurring every year in the U.S. "Neonatal Herpes" can cause blindness, brain damage and even death in newborns by transfer of the herpes virus during birth.

Alzheimer's disease is a degenerative disease of the nervous system and is the fourth leading cause of death among American adults. It afflicts at least four million Americans and about 2,000 patients die each week in the U.S. as a result of the disease. There is no treatment to effectively arrest or cure the disease.

Obviously in spite of increasing healthcare costs there is still much to be accomplished which is a major challenge facing those involved in healthcare research at all levels and especially the FDA as the premier regulatory body.

Questions:

1. Are there any major innovations underway in neurological devices? What are they?
2. What are the current concerns with therapeutic neuromodulation.
3. What are the known side-effects of neuromodulation for Chronic Pain?
4. What other patient risk factors are associated with neuromodulation?
5. What are the most successful methods for mitigating these risks?
6. Has there been any successful non-invasive device to breach the blood/brain barrier?
7. What are the perceived risks of non-invasive neuromodulation?
8. How would the panel view an anti-depression claim for a non-invasive neuromodulation device?
9. What might comprise satisfactory endpoints for clinical studies for such a device?
10. Could a neuromodulation device that is non-invasive and truly therapeutic be regulated as a Class II device?
11. How might the panel decide on a De Novo 510(k) submission for a Genital Herpes indication for a non-invasive therapeutic neuromodulation device?

12. How might the panel decide on a De Novo 510(k) submission for an indication of Clinical Depression?
13. Could indications for Chronic Pain or Fibromyalgia be added by means of a Special 510(k) with data?
14. What particular clinical study requirements might be required by the panel to support claims of therapeutic benefit for indications for Multiple Sclerosis, Parkinson's disease and Alzheimer's disease?
15. What study endpoints would best serve to allow claims for the above indications in question 14?
16. Would any foreign data be acceptable insofar as they were under GCP?
17. Would a STED submission format for a PMA and/or PMN be considered at this time?
18. If a non-invasive therapeutic neuromodulation device were cleared by a De Novo 510(k) submission, what would constitute the least burdensome approach for any new indication?
19. How many patients might the panel require for a clinical depression study, and could Bayesian statistical methods be applied?
20. Could a humanitarian device exemption be issued for a non-invasive device treating clinical depression?

Dr. Leon M. Silverstone obtained his sciences and pre-medical education at Queen Mary College, University of London, UK, and his professional degrees from The Royal College of Surgeons of England and the University of Leeds School of Dental Surgery. He obtained his Ph.D. in pathology from the University of Bristol, UK, while working for the Medical Research Council of Great Britain. He then became the first recipient of the D.D.Sc. degree by thesis from the Faculty of Medicine, University of Leeds, UK, for his work on experimental remineralization. He was a Reader and Hospital Consultant at The Royal London Hospital Medical College, and in 1976 left England to come to the U.S. where he held appointments as Professor and Head of the first Division of Cariology in the USA, at the Dows Institute for Dental Research, University of Iowa Medical Center in Iowa City, and then a Dean of Research at the University of Colorado Health Sciences Center. In 1989, after 26 years in full-time academia, he joined the private sector where his research has focused on neurosciences in the development of unique electronic devices for the non-invasive treatment of pain syndromes, neurological disorders and viral diseases. He has been a Consultant to The Medical Research Councils of Great Britain and Canada, and The Pan American Health Organization branch of WHO. He is past President of ORCA, the European Organization for Caries Research, and the first to be appointed from the U.S. He is a past member of the Oral Biology and Medicine Study Section of NIH, and past Chairman of the NIDR Programs Advisory Committee at NIH.