Ms. Jennifer A. Davidson
Kleinfeld, Kaplan and Becker LLP
1140 19th St., NW
Washington, DC 20036-6606

Re: FDA-2013-P-0070

Dear Ms. Davidson:

This letter partially responds to your citizen petition received on January 14, 2013 (Petition). You request that the Food and Drug Administration (FDA or the Agency):

(1) Reconsider and rescind the 510(k) clearance for the GeNOsyl MV-1000, dated May 16, 2012; and

(2) Require approval of a new drug application (NDA) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) before marketing of any GeNO LLC (GeNO) nitric oxide delivery system that manufactures any portion of the finished pharmaceutical at bedside (in situ) by chemically converting nitrogen dioxide into nitric oxide for patient administration, including the GeNOsyl MV-1000.

(3) Refuse to approve any NDA for a GeNO nitric oxide delivery system that chemically converts nitrogen dioxide into the finished pharmaceutical nitric oxide at the patient's bedside unless it incorporates appropriate current good manufacturing practices (cGMPs) that provide the requisite assurance that the nitric oxide administered to patients meets NDA specifications for identity, strength, quality, and purity, per 21 U.S.C. 355(d)(3).[1]

In addition, you filed a supplement to the Petition, which was received on May 14, 2014 (Supplement). The Supplement requests that FDA require GeNO "to incorporate an appropriately sophisticated dose-counter-like mechanism to assure the reactor cartridge component is replaced at the appropriate time before its performance begins to degrade," and require "vigorous testing of that component in actual use settings."

This letter responds to issues 1 and 2 raised in the Petition because those issues pertain to products regulated by FDA's Center for Devices and Radiological Health. FDA's Center for Drug Evaluation and Research already responded to issue 3 and the issues raised in the Supplement on September 11, 2014.[2]

[1] Petition at 3.
[2] See Letter Response from Dr. Janet Woodcock to Ms. Jennifer A. Davidson, FDA-2013-P-0070-0012 (Sep. 11, 2014).

I. Background

A. *The Ikaria InoMAX DS*

On December 14, 2006, FDA cleared the Ikaria INOmax DS delivery system (INOmax DS) to deliver INOmax (nitric oxide for inhalation) nitric oxide therapy gas into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of nitric oxide (NO), as set by the user, to the patient throughout the inspired breath. The INOmax DS provides continuous integrated monitoring of inspired oxygen (O_2), nitrogen dioxide (NO_2), and nitrogen oxide (NO), and a comprehensive alarm system.

The INOmax DS uses a "dual-channel" design to ensure the safe delivery of INOmax to the patient. The first channel has the delivery CPU, the flow controller and the injector module to ensure the accurate delivery of NO. The second channel is the monitoring system, which includes a separate monitor CPU, the gas cells (NO, NO_2, and O_2 cells) and the user interface including the display and alarms. The dual-channel approach to delivery and monitoring permits INOmax delivery independent of monitoring but also allows the monitoring system to shutdown INOmax delivery if it detects a fault in the delivery system such that the NO concentration could become greater than 100 ppm.[3]

B. *The GeNO GenoSyl MV-1000*

On, May 16, 2012, FDA cleared the GeNOSyl MV-1000 (MV-1000) to deliver nitric oxide (NO) for inhalation therapy gas into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of nitric oxide (NO), as set by the user. The device provides continuous integrated monitoring of inspired oxygen (O_2), nitrogen dioxide (NO_2), and nitrogen oxide (NO), and a comprehensive alarm system.

The MV-1000 adds NO to gases that are to be inhaled by the patient. The MV-1000 maintains an approximately constant concentration of NO during the inspiratory flow regardless of the variation in flow rate within the inspiratory portion of the respiratory cycle. The concentration of inspired NO will or must be set by the user, typically in the range of 0 to 80 parts per million (ppm). The user can set upper and lower measured NO concentrations. If the concentration deviates from these limits, an alarm will be activated. In addition, if upper concentration limit is exceeded, a shutdown condition will stop the NO injection.

The MV-1000 minimizes the time that NO is mixed with O_2 and thus minimizes the concentration of NO_2 in the gas inhaled by the patient. In the presence of O_2, some conversion of NO to NO_2 will occur. The MV-1000 includes an ascorbic acid cartridge that serves a dual purpose: a mixing chamber and conversion of any transient nitrogen dioxide to nitric oxide prior to inhalation by the patient.[4]

[3] See 510(k) summary available at http://www.accessdata.fda.gov/cdrh_docs/pdf6/K061901.pdf.
[4] See 510(k) summary available at http://www.accessdata.fda.gov/cdrh_docs/pdf12/K120216.pdf.

C. Combination Products

Section 503(g)(1) of the FD&C Act states that the Secretary of the Department of Health and Human Services[5] shall assign an Agency center to regulate products that constitute a combination of a drug, device, or biological product. Section 503(g)(1) further specifies that the primary mode of action of the combination product determines which Agency center will have primary jurisdiction over the product. For example, if the primary mode of action is that of a drug (other than a biological product), the Agency center charged with premarket review of drugs shall have primary jurisdiction.

II. Discussion

1) You request that FDA reconsider and rescind its 510(k) clearance of the MV-1000. After you submitted your petition, on September 26, 2014, the United States Court of Appeals for the District of Columbia Circuit ruled that FDA could not rely on inherent reconsideration authority to rescind its initial substantial equivalence determination for a surgical mesh device. *Ivy Sports Medicine, LLC v. Burwell*, 767 F.3d 81 (D.C. Cir. 2014), *reh'g en banc denied*, 2015 U.S. App. LEXIS 4140 (D.C. Cir. Mar. 13, 2015). Based on that decision, FDA denies your request to rescind clearance under the circumstances presented here.[6]

2) You also request that the Agency require approval of a new drug application (NDA) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) before marketing of any GeNO LLC (GeNO) nitric oxide delivery system that manufactures any portion of the finished pharmaceutical at bedside (in situ) by chemically converting nitrogen dioxide into nitric oxide for patient administration, including the GeNOsyl MV 1000.

   We do not believe that a decision regarding the appropriate premarket regulatory pathway for these products as a group is warranted at this time. Accordingly, FDA will determine the appropriate premarket regulatory pathway for the GeNO products you describe based on the statutory definitions and requirements set forth in the FD&C Act, as applied to the scientific data and other relevant facts concerning a particular product that are available to FDA when it receives an application for a particular product.

[5] The Secretary has delegated this authority to the Commissioner of Food and Drugs.

[6] The *Ivy Sports* court determined that it was "unnecessary to decide" whether FDA may rescind a 510(k) clearance "'obtained through fraud, ex parte contacts, or other misconduct tainting the original record and thereby affecting the integrity of an agency's proceedings.'" See *Ivy Sports Medicine*, 767 F.3d at 88 (quoting *American Methyl Corp. v. EPA*, 749 F.2d 826, 834 n.51 (D.C. Cir. 1984)). But you have not asserted that such issues or other similar circumstances exist here.

III. CONCLUSION

For the reasons described in this response, your request that FDA require approval of an NDA before marketing of any nitric oxide delivery system that manufactures any portion of the finished pharmaceutical at bedside (in situ) by chemically converting NO_2 into NO for patient administration is denied. Your request that FDA rescind the 510(k) clearance of the MV-1000 and require approval of the device under an NDA is denied. Thank you for bringing these matters to our attention.

Sincerely,

Ellen J. Flannery -S
Digitally signed by Ellen J. Flannery -S
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Ellen J. Flannery, JD
Deputy Center Director for Policy
Center for Devices
and Radiological Health

Douglas C. Throckmorton -S
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Patrizia Cavazzoni, M.D.
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