KINSEY S. REAGAN
PETER R. MATHERS
ANTHONY L. YOUNG
ANNE V. MAHER
BONNIE A. BEAVERS
DANIEL R. DWYER
SCOTT M. LASSMAN
STACY L. EHRLICH
JENNIFER A. DAVIDSON
JAMES WILLIAM WOODLEE
CYNTHIA L. MEYER

LAW OFFICES
**KLEINFELD, KAPLAN AND BECKER, LLP**
1140 NINETEENTH STREET, N.W.
WASHINGTON, D.C. 20036-6606
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
www.kkblaw.com

OF COUNSEL:
WILLIAM J. HARDY

May 14, 2014

Via Electronic Submission and Overnight Courier

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Supplement to Citizen Petition
Docket FDA-2013-P-0070

Dear Sir/Madam:

The undersigned, on behalf of Ikaria, Inc. ("Ikaria"), submits this supplement to the Citizen Petition filed January 11, 2013 and assigned Docket Number FDA-2013-P-0070 ("Petition"). As detailed in the Petition, Ikaria's wholly owned subsidiary, INO Therapeutics, is the holder of NDA# 20-845 for INOmax® (nitric oxide) 100 and 800 ppm for inhalation, which is approved for use in the treatment of critically ill neonates suffering from a particular form of respiratory failure. Ikaria has also obtained 510(k) clearance for several specialized delivery systems necessary for the safe and effective administration of INOmax. In 2012, GeNO LLC received 510(k) clearance to market its own nitric oxide delivery system, the GeNOsyl™ MV-1000, citing an Ikaria delivery system as the predicate device. Also in 2012, GeNO announced that it has submitted a New Drug Application ("NDA") for a second generation product, the GeNOsyl™ MVG-2000.[1] In 2013, GeNO announced that it was developing two additional next generation products that manufacture and administer nitric oxide to patients.[2]

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[1] GeNO comments submitted to this docket state that the pending product is the subject of NDA 202860.

[2] *See* Form S-1, Registration Statement, GeNO LLC, available at: http://www.sec.gov/Archives/edgar/data/1359620/000119312513465262/d572802ds1a.htm.

## I. Inherent Safety Risks Require the GeNO Products to Incorporate a Dose-Counter-Like Mechanism to Assure Appropriate Reactor Cartridge Replacement and Avoid Potentially Catastrophic Consequences of Reactor Cartridge Degradation

### a. Background and Purpose of Supplement

GeNO touts its technology as superior to that of Ikaria, emphasizing the novel reactor cartridge component of its products.[3] According to GeNO, this component performs a critical function: chemical conversion of a toxic substance (nitrogen dioxide) into the finished pharmaceutical nitric oxide at the patient's bedside. To Ikaria's knowledge, no approved product generates an active pharmaceutical ingredient at bedside in a hospital for delivery to critically ill neonates on life support – circumstances where any product malfunctions or use errors can have the most serious clinical consequences, including death.

Ikaria's Petition requests that the Agency reconsider and rescind the 510(k) clearance for the GeNOsyl™ MV-1000, and in light of the claimed bedside manufacture of the finished drug product, nitric oxide, require approval of an NDA for the 510(k)-cleared product, as well as any other 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. The Petition also requests that FDA require any such NDA, including the NDA for the GeNOsyl™ MVG-2000, or subsequent revisions thereof, to incorporate appropriate current Good Manufacturing Practices, reflecting the novel and unprecedented bedside manufacture of nitric oxide, that assure that the finished pharmaceutical product administered to patients meets NDA specifications for identity, strength, quality, and purity.

Despite the unique attributes of its products and the obvious risks associated with the vulnerable patient population on which they are proposed to be used, GeNO has taken the position that no additional or unique Chemistry, Manufacturing, and Controls, current Good Manufacturing Practice requirements, or robust verification and validation requirements apply to the GeNO products. In its Petition and May 3, 2013 Supplement, Ikaria established that all GeNO products employing a reactor cartridge to chemically convert nitrogen dioxide to nitric oxide *in situ* pose novel safety questions that must be addressed through additional CMC information and cGMP requirements. Ikaria also identified a number of particularly critical risks that are associated with any GeNO

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[3] Ikaria strongly disputes GeNO's claims of superiority. As demonstrated in Ikaria's submissions to Docket No. FDA-2012-P-1103, there is no basis to conclude that GeNO's products offer any therapeutic advantage over INOmax. Indeed, as discussed in this docket, there are serious questions about the safety of the GeNO products.

product using a toxic substance as a drug source, including the GeNOsyl™ MVG-2000, using nitrogen dioxide (or dinitrogen tetraoxide – $N_2O_4$) as the source gas. One such risk stems from the fact that the capacity of the reactor cartridge to convert nitrogen dioxide to nitric oxide degrades overtime, and the corresponding need for a mechanism to accurately identify when a used reactor cartridge must be replaced with a "fresh" reactor cartridge.[4]

Ikaria submits this Supplement to highlight the FDA's decision concerning applications relying on ProAir HFA (albuterol sulfate) Inhalation Aerosol as the reference listed drug. This decision further underscores the need for the GeNO products 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 (b) the importance of vigorous testing of that component in a actual use settings.

### b. FDA Precedent and Guidance Require Dose Counters for Interchangeable Drug Cartridges with Limited Life

In its ProAir HFA decision, FDA stated that generic versions of ProAir HFA must include a dose counter. FDA further confirmed that *in vitro* and in use studies are necessary to document the functionality, accuracy, and robustness of proposed generic dose counters.[5] The decision relies in part on FDA's guidance on incorporation of dose counting mechanisms into drug products for oral inhalation using metered-dose inhalers.[6] That guidance recognizes that an accurate dose counter prevents two adverse outcomes: (i) premature disposal of a drug product when doses remain, and (ii) continued use of a drug product after all doses are expended, risking administration of an incorrect (low) dose. While both outcomes are undesirable, FDA recognizes the second is potentially dangerous. For this reason, dose counters must be specifically designed to avoid undercounting, *i.e.*, signifying that more medication remains than is truly the case.[7] The guidance also describes FDA's risk-based rationale for determining which type of meter-dose inhalers require a dose counter:

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4 *See* May 3, 2013 submission to Docket FDA-2013-P-0070, at pp. 9-11.

5 Response to Citizen Petition, Docket FDA-2013-P-0850 (Dec. 9, 2013).

6 Guidance for Industry, Integration of Dose-Counting Mechanisms into MDI Drug Products (2003) ("Dose Counter Guidance"), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071731.pdf.

7 Dose Counter Guidance, pp. 2, 3-4.

> The recommendations in this guidance address primarily MDI products designed to deliver drugs to the lungs for any indication. This is because the consequences of not receiving an acceptable metered dose are more clinically important for oral inhalation drug products than for the current medications available in nasal MDIs. Medications delivered to the lungs often play a vital role in the treatment of airway diseases and are potentially life-saving. Nasally delivered drugs are more typically intended to treat bothersome, but non-life-threatening, conditions. However, if a nasal MDI were developed where the issue of dosing beyond the recommended label claimed number of doses were associated with a more serious consequence, this guidance would be applicable. [8]

Finally, the guidance states that dose-counter performance should be evaluated through *in vitro* testing (simulating use and potential abuse) and studies in clinical use. These studies should assess functionality, reliability, and accuracy.[9]

### c. Due to the Fundamental Safety Risks of the GeNOsyl™ Reactor, an Effective Dose-Counter-Like Mechanism is Essential to Ensure Patient Safety and Appropriate Use

FDA's regulatory approach to generic versions of ProAir HFA and other drug products for oral inhalation using metered-dose inhalers should also apply to the GeNO products. The toxic source material used by the GeNOsyl™ systems, nitrogen dioxide ($NO_2$ – obtained either from a pressurized $NO_2$ gas cylinder or derived from heating liquid $N_2O_4$, a powerful oxidizing agent commonly employed as a rocket propellant, within the GeNOsyl™ system, to generate $NO_2$ gas) is converted by a reducing agent (indicated by GeNO as aqueous ascorbic acid coated upon silica) residing within a reactor cartridge into gaseous nitric oxide (NO) for inhalation. As the product is used, the chemical conversion process eventually consumes the reducing agent and the cartridge is no longer able to convert $NO_2$ into therapeutic NO.

As noted in FDA's Dose Counter Guidance, under-dosing is dangerous, especially for medications delivered to the lungs. In the case of inhaled nitric oxide, this concern is particularly acute: unintended, abrupt discontinuation can lead to worsening oxygenation and increasing pulmonary artery pressure, *i.e.*, rebound pulmonary hypertension syndrome. [10]

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[8] Dose Counter Guidance, pp. 2-3.

[9] Dose Counter Guidance, pp. 3-4.

[10] *See* Section 5.1 of the professional labeling for INOmax® (nitric oxide) 100 and 800 ppm for inhalation.

Of even greater significance, if the volume of nitrogen dioxide entering the reactor cartridge exceeds conversion capacity limits for the reactor, nitrogen dioxide will pass through the reactor and to the patient unconverted. Accordingly, failure to replace the reactor cartridge in a timely fashion risks exposing patients to unmeasured, ever increasing levels of nitrogen dioxide, unbeknownst to the user. The consequences of administration of $NO_2$ to a critically ill patient would be catastrophic. Accordingly, it is imperative that the user recognize when to replace a reactor cartridge prior to any exhaustion of the reducing agent to avoid any pass-through of toxic $NO_2$.

**d. The Unpredictable Lifespan of the GeNOsyl™ Reactor Necessitates a Sophisticated Dose-Counter-Like Mechanism to Communicate Reactor Cartridge Capacity Under Varying Conditions of Use**

In light of the serious, inherent risks described herein for the GeNOsyl™ systems, and FDA's established approach to metered-dose inhalers, it is clear that the GeNO products must incorporate a robust dose-counter-like mechanism to assure reactor cartridges are replaced *before* any degradation of capacity to convert nitrogen dioxide into nitric oxide. Significantly, the rate at which the reducing agent is expended will depend on many variables associated with individual patient therapy. In particular, administration of inhaled NO occurs at various doses in conjunction with oxygen and through a large and variable array of mechanical ventilation systems. Differences in patient type (adult, pediatric, and neonate) and hospital protocols (drug, dose, and ventilator brands) further compound variability of ventilator settings, such as flow, volume, and pressure. These common and well known differences among inhaled NO treatment paradigms will likewise cause variation in consumption of the reducing agent within the GeNOsyl™ reactor cartridge. Even exposure to air will deplete the capacity of the reactor cartridge because the reducing agent will react (*i.e.*, oxidize) with any oxygen source with which it comes into contact, including oxygen in air. Because of the variables impacting consumption of the reducing agent, a dose counting mechanism based solely on time of use would be useless, as it would not account for the varying rates at which the reducing agent is consumed within the reactor cartridge under the widely varying expected conditions of use. Instead, only a sophisticated system that can accurately track reducing agent consumption and monitor the actual remaining reactor cartridge capacity would be appropriate for the GeNO products.[11]

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[11] While INOmax does not present the same risks as the GeNO products using a toxic substance as a source material, it is nevertheless important for healthcare practitioners to know when a cylinder of INOmax must be changed. As with the GeNO products, the useful life of an INOmax cylinder depends on nitric oxide dose and flow. The INOmax $DS_{IR}$ delivery system regulator contains a pressure gauge that indicates the cylinder pressure. Per the user manual, therapy should not be initiated with a cylinder containing less than 500 psig and cylinders should be changed at 200 psig. In addition to a visual display of the cylinder pressure, an alarm will sound if the pressure is low. Finally, the INOmax "cart" is designed to support two cylinders, so

**e. Because of the Critically Ill Nature of the Intended Patient Population, and the Inherent, Severe Danger Reactor Cartridge Depletion Poses to Patient Safety, *In Vitro* and In Use Studies are Necessary to Confirm the Functionality, Accuracy, and Robustness of any GeNO Dose-Counter-Like Mechanism**

Evaluation of the GeNO dose counter-like mechanism should also be consistent with FDA's approach to applications relying on ProAir HFA as the Reference Listed Drug and other oral inhalation drug products administered with metered dose inhalers. Specifically, both *in vitro* and in use studies should be required to document the functionality, reliability, and accuracy the mechanism. *In vitro* studies should simulate use and potential abuse/misuse of the mechanism. Consistent with current use of INOmax, in use studies should assess performance of the mechanism in the real world setting of the critical care environment, which typically involves three shifts, rotating personnel, frequent staff turnover, and the use of medical residents, all in a fast-paced environment where gravely ill patients are being administered multiple therapies. These studies should document that, in a real world setting, users appreciate and react to information communicated by the GeNO dose counter, change reactor cartridges appropriately, and thereby avoid potentially catastrophic consequences. The in use studies should also evaluate performance of fail-safe mechanisms intended to prevent tardy change of depleted reactor cartridges, such as alarms to notify user of reactor failure and continuous monitoring of $NO_2$ levels to inform of gradual reactor depletion or failure.[12] Finally, in use studies should encompass use in the NICU in term and near-term neonates with hypoxic respiratory failure, and also reasonably foreseeable uses outside of the NICU.[13]

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As documented in the Petition and May 3, 2013 Supplement, GeNO's proposed bedside synthesis of a finished pharmaceutical from a toxic source gas raises a host of novel questions bearing directly on the safety and efficacy of the GeNO products. In order to satisfy applicable statutory and regulatory standards, and demonstrate that its

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that when cylinder pressure is low, the healthcare practitioner can easily switch to the adjacent cylinder.

[12] *Guidance Document for Premarket Notification Submissions for Nitric Oxide Delivery Apparatus, Nitric Oxide Analyzer and Nitrogen Dioxide Analyzer,* Section 3.1.3, available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073767.pdf.

[13] As noted in Ikaria's Supplement of May 3, 2013, p 10, more than half of all inhaled nitric oxide administered in hospitals is for uses other than term and near-term neonates with HRF and inhaled nitric oxide is the standard of care for many of these conditions.

products are safe and effective for the gravely ill patients to whom nitric oxide is administered, GeNO must carefully consider and address these questions, developing and validating alternative procedures and controls that provide the requisite assurance of the identity, strength, quality, and purity of the nitric oxide produced at bedside.

One such essential control is a dose-counter-like mechanism. Consistent with FDA's decision concerning applications referencing ProAir HFA, the GeNO products must incorporate an appropriately sophisticated mechanism that accurately tracks reducing agent consumption and monitors the actual remaining reactor cartridge capacity. FDA already recognizes the need for dose counting mechanisms within drug-device therapies wherein failure to replace an interchangeable component of the drug-device combination can result in little or no drug delivery to the patient. The risk associated with the GeNOsyl™ system is much greater. Not only will failure to timely change a GeNO reactor cartridge cause limited or no drug delivery to a critically ill patient, but further, the patient will receive express delivery of a highly toxic, potentially deadly material, $NO_2$, directly into the breathing passages. Clearly, there is little or no room for error. Therefore, FDA should require any GeNO system incorporating such reactor cartridges to employ a reliable, easy to understand, dose counting system to monitor and communicate available reactor capacity. The functionality, accuracy, and reliability of the system should be demonstrated through both (a) *in vitro* data, and (b) in use testing demonstrating its effectiveness in reliably prompting users to replace the reactor cartridge in a timely manner, well before any instance of reactor failure or reducing agent conversation. Further, because reactor cartridge degradation rate is not constant, allowing individual reactor lifespan to fluctuate greatly based on variable settings of flow, volume, pressure, and dose, in use testing must encompass the wide variety of ventilator settings and doses administered to patients receiving nitric oxide therapy within and outside of the NICU.

Respectfully submitted,

Jennifer A. Davidson
Counsel to Ikaria, Inc.

**Verification**

"I certify that, to my best knowledge and belief:

(a) I have not intentionally delayed submission of this document or its contents; and

(b) the information upon which I have based the action requested herein first became known to me on or about December 19, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making this certification on behalf of Ikaria, Inc. as part of my responsibilities as an employee and officer of Ikaria, and will not be separately compensated for contributing to the contents of this petition or making this certification.

I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

May 14, 2014

Jonathan N. Provoost
Associate General Counsel/Chief Compliance Officer
Ikaria, Inc.
Perryville III Corporate Park
53 Frontage Road, 3rd Floor
P.O. Box 9001
Hampton, NJ 08827-9001
Direct phone: (908) 238-6392