DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

SEP 11 2014

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."[2]

This letter responds to issue 3 raised in the Petition and the issues raised in the Supplement because those issues pertain to products regulated by FDA's Center for Drug

[1] Petition at 3.
[2] Supplement at 3.

Evaluation and Research. FDA's Center for Devices and Radiological Health will address issues 1 and 2 in the Petition separately at a later date.

I. Background

A. Current Good Manufacturing Practices

Section 505(d)(3) of the FD&C Act requires FDA to refuse to approve an NDA if "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity." These requirements are further described in our regulations on cGMPs at 21 CFR parts 210 and 211. NDAs and supplements to approved applications are required to include information regarding chemistry, manufacturing, and controls, as specified at 21 CFR 314.50(d)(1). This requirement includes specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product.

Specifications are generally quality standards proposed and justified by the applicant and approved by FDA as conditions of drug approval. The term *specification* means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, and materials used in the production of a drug substance or drug product.[3] For the purpose of this definition, the term *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described. The acceptance criteria are generally the same from product release throughout shelf life. An applicant, however, may choose to have tighter in-house limits at the time of release to provide increased assurance that the product will remain within the regulatory acceptance criteria.

B. FDA Guidance for Industry

In March 2003, FDA issued a guidance for industry on *Integration of Dose-Counting Mechanisms into MDI Drug Products* (Dose Counter Guidance) that reflects the Agency's recommendations regarding the integration of dose-counting mechanisms into metered-dose inhaler (MDI) drug products for oral inhalation.[4] The Dose Counter Guidance recommends that MDIs under development for oral inhalation include an integrated dose-counting device.[5] As explained in the Dose Counter Guidance, the purpose of a dose counter is to allow the patient to reliably track the number of actuations used from an individual MDI, which helps prevent the patient from discarding an MDI unnecessarily or using it beyond the labeled number of actuations.[6] The Dose Counter Guidance recommends that dose counters:

> should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible. However, if some low frequency of

[3] See 21 CFR 314.3(b).
[4] This guidance is available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Clinical/Medical.
[5] Dose Counter Guidance at 3.
[6] Id.

error is unavoidable, the device should be designed to specifically avoid undercounting (i.e., the metered-dose inhaler sprays, but the counter does not advance). Undercounting could result in patients assuming they have medication left in their MDI when they do not, a circumstance that is potentially dangerous.[7]

II. Discussion

A. cGMP Request

The Petition requests that FDA "refuse to approve any NDA for a GeNO drug manufacturing/delivery system that does not propose adequate means of assuring the identity, strength, quality, and purity of the drug product, taking into account the unique site of manufacture."[8] You contend that adequate means would be achieved in two ways:

- First, you assert that because GeNO's system manufactures nitric oxide at bedside, a location that is not conducive to quality control, GeNO must in any NDA validate alternative procedures and controls to assure the identity, strength, quality, and purity of the nitric oxide produced by its system.[9]
- Second, you state that GeNO must verify and validate a number of variables related to ensuring the quality of the cartridge/reactor portion of its product.

In addition, you claim that quality assurance for GeNO's product necessitates a high degree of monitoring in the field and that GeNO must develop procedures to ensure the cartridge/reactor is properly replaced and continues to produce nitric oxide of the "requisite identity, strength, quality, and purity" upon replacement.[10]

We do not agree with your assertion that the location of nitric oxide administration would make it "difficult, if not impossible, to adhere to . . . traditional procedures for complying with cGMPs."[11] However, we do agree that for a nitric oxide manufacturing/delivery system that converts nitrogen dioxide as a source material to nitrogen oxide using a cartridge/reactor (NO system), a number of variables would need to be validated to ensure the quality of the finished drug product. We also agree that in such a nitric oxide delivery system, a monitoring system would be essential to ensure quality of the finished drug product, as would procedures to ensure that the cartridge is properly replaced.

Given that we do not agree that using an NO system at bedside would change the quality control requirements for approval, your request that GeNO be required to validate alternative procedures to assure the quality of the nitric oxide delivered by its product is denied. However, FDA agrees that an NO system employing nitrogen dioxide as a source material would need to meet quality control measures similar to the basic control measures described in the Petition. Therefore, your requests that the submitter of an NDA for such a product be required to verify and validate the cartridge/reactor portion of

[7] Id.
[8] Petition at 18.
[9] Id.
[10] Id.
[11] Id.

its product, develop an appropriate quality assurance program, and develop procedures to ensure that the cartridge/reactor portion of the system is replaced and continues to perform properly are granted.

B. Dose-Counter Request

The Supplement contends that FDA's "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."[12] The Supplement requests that to prevent under dosing or overdosing, FDA apply a dose-counter requirement to the GeNO products to help 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."[13] In addition, you ask that FDA require not just a dose counting mechanism based on time, but rather a "sophisticated system" that can accurately track usage of a reactor cartridge.[14] You also ask that FDA require both in vitro and in-use studies to "document the functionality, reliability, and accuracy of the mechanism."[15]

While we agree that an NO system employing nitrogen dioxide as a source material would need to employ a mechanism to prevent unnecessary patient exposure to nitrogen dioxide, a dose-counter is not the most appropriate mechanism to achieve that result. There are many different mechanisms that can be added to such an NO system to prevent patient exposure to dangerously high levels of nitrogen dioxide. For any proposed mechanism, FDA would evaluate the data supporting the use of the mechanism and determine whether it adequately mitigates the risk of nitrogen dioxide exposure. We do not agree that such a mechanism would, necessarily, need to be "sophisticated," as you contend. In addition, we do not agree that in vitro and in-use studies should be required to validate such a mechanism. However, any mechanism added to such an NO system to prevent unnecessary patient exposure to nitrogen dioxide should be adequately studied to demonstrate its reliability and to demonstrate that it can detect and stop toxic exposure in time to protect the patient from danger. This would require testing that represents actual use conditions for the product, covering the extreme ranges of potential use. For these reasons, the requests in the Supplement are denied.

[12] Supplement at 4.
[13] Supplement at 5.
[14] Id.
[15] Supplement at 6.

III. CONCLUSION

For the reasons described in this response, the requests in the Petition regarding cGMP requirements for an NDA for an NO system are granted in part and denied in part, and the requests in your Supplement are denied. FDA will continue to evaluate the other issues raised in the Petition and will provide a response at a later date.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research