CITIZEN PETITION

December 10, 2019

The undersigned submits this petition under Title 21 of the Code of Federal Regulations and the provisions of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to amend or otherwise withhold action on the proposed "Amendments to the Bulk List of Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act" (the "Amendment") to the extent set forth below.

A. Action Requested

Petitioner requests that the Amendment be modified such that Nicotinamide Adenine Dinucleotide ("NAD") remain included on the 503A list of bulk drug substances permitted to be used in compounding for a period of not less than 5 years to enable completion of additional studies as may be needed to satisfy The U.S. Food & Drug Administration ("FDA") of its safety and efficacy.

B. Statement of Grounds

The FDA on September 5, 2019, published in the Federal Register (ID: 2019-18951) a proposed amendment listing those drugs to be included on the 503A "bulks list" – those chemical products from which drugs are permitted to be compounded by a community compounding pharmacy (a 503A pharmacy).

Among other chemicals, the list as published removes from permitted use Nicotinamide Adenine Dinucleotide ("NAD") which has for many years been well-accepted in the medical profession and demonstrated clinically to be beneficial to patients.

NAD is present in every cell of the body. Without it the Krebs Cycle which fuels the cells could not function; the body would have no means of conversion of food energy into the chemical energy necessary to sustain life; death would result. We are unaware of any adverse reactions associated with the administration of NAD over many years of use. Accordingly, it would seem that NAD does not present any inherent danger in use.

NAD, a derivative of Niacin (Vitamin B-3) was discovered to provide substantial benefit to those persons suffering from addiction to alcohol and other drugs in the 1950's and 1960's and was patented in 1966 (US Patent 3,266,989) for use in alcohol addiction at that time. It subsequently fell out of favor with the introduction of Methadone.

Methadone is only a long-term substitute for the addictive drugs it replaced; it does not alleviate the root cause of the addictive behavior – the craving for drugs or alcohol. Many patients consider it "liquid handcuffs" because they feel that they must have it, and cannot survive without it. For this reason, many of those addicted become trapped into long-term treatment and are dependent upon Methadone and support groups to maintain sobriety because, though the abuse may have been curtailed, the craving for the abused substance remains indefinitely.

NAD has been clinically demonstrated to have significant benefit in the detoxification of those addicted to opiates, alcohol and other drugs. It has been demonstrated to substantially eliminate the craving for the addicted substance. (see "Intravenous Administration of Nicotinamide Adenine Dinucleotide Significantly Reduces Self Report Craving Ratings Associated with Opiate and Alcohol Withdrawal" S. L. Broom et al., – **Attachment 1**) This was further supported by additional work detailed by Dr. Broom

in "Therapeutic Effect of BR+NAD on Opioid and Alcohol Withdrawal: Implications for Clinical Populations" (Susan Broom Gibson, PhD. William Carey University, October 1, 2019 – **Attachment 2**). The substantial reduction or elimination of the craving for the abused substance enables the patient to make better lifestyle decisions and minimize or avoid relapse if accompanied by appropriate aftercare programs. Thousands of patients have been successfully treated using NAD.

A recent double-blind peer-reviewed study indicates that there is significant uptake of NAD at the cellular level when administered in an IV. (A Pilot Study Investigating Changes in the Human Plasma and Urine NAD+ Metabolome During a 6 Hour Intravenous Infusion of NAD+ by Ross Grant[1,2,3]*, Jade Berg[1], Richard Mestayer[4,5], Nady Braidy[6], James Bennett[5], Susan Broom[7] and James Watson[8] published: 12 September 2019 doi:10.3389/fnagi.2019.00257 – **Attachment 3**) This supports the contention in the Broom study that it is NAD that would appear to be the causative agent responsible for the reduction in the craving for the addicted substance. This is a very significant finding that merits further study.

It is clearly understood that the drug abuse epidemic currently confronting this nation is a significant risk to the health and well-being of the country. Proceeding with the proposed Amendment as drafted would make NAD unavailable to physicians and would be a major step backwards in drug addiction therapy.

In its previous review of NAD+ (FDA Briefing Document, Pharmacy Compounding Advisory Committee (PCAC), Meeting May 8-9, 2017) the FDA staff remarked that the molecule is a fragile molecule. While this may be true with respect to exposure to heat and light, the compounded sterile product for infusion, if kept refrigerated, has an indicated 100% potency and sterility beyond 100 days (See ARL BioPharma test results, – **Attachment 4**). The standard associated with these results has been confirmed in a study conducted by ARL BioPharma (Beta Nicotinamide adenine dinucleotide+ Method Validation Final Report, January 2019, copy attached of pages 1-28 – **Attachment 5**). This excludes 228 pages of supporting charts and data which is available upon request.

Because NAD was previously patented for use in addiction therapy, there is no protection of intellectual property available that would provide any measure of commercial protection necessary to support the cost of an Investigational New Drug Application. For that reason, compounding is the only available means of access to these products that is both commercially and economically feasible.

Those who favor NAD in treatment of this disease state are not large corporations with unlimited research and development and legal budgets. They are medical doctors and clinical practitioners who have learned of the product over many years of peer-to-peer education. They do not have the budgets to fund the research necessary to support the FDA's IND process. Even if they did, the cost of the process could never be recovered in the marketplace since the molecule can no longer be patent protected and thus the intellectual property that would be created would have no market protection, rendering this approach economically infeasible.

Thus, for the lack of large research budgets and the work this would support, FDA through its proposed Amendment has effectively determined to terminate the availability of an important therapeutic aid to clinicians treating the difficult disease of drug and alcohol addiction.

It is in the public interest that the FDA grant this petition in order to facilitate the additional study needed while in the interim, not depriving prescribers and therapists a valuable tool to aid in the recovery process for those addicted to drugs and alcohol.

C. Environmental Impact

We claim categorical exclusion under 25.30, 25.31, 25.31, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Economic Impact

Economic impact information will be submitted upon request of the commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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