



Council for Responsible Nutrition

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CITIZEN PETITION

June 1, 2021

Via Electronic Submission

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Re: Citizen Petition Requesting FDA Allow N-acetyl-L-cysteine (NAC) to be Marketed as a Dietary Supplement

Dear Sir or Madam:

The Council for Responsible Nutrition (CRN),¹ submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 requesting that the Food and Drug Administration (“FDA” or “the Agency”) reverse its recently adopted position that the Federal Food, Drug, and Cosmetic Act (FDCA) prohibits manufacturers from marketing products containing N-acetyl-L-cysteine (NAC) as dietary supplements. This policy—which represents a sudden and drastic departure from past Agency practice—is legally invalid. As such, FDA should revert to its longstanding policy of allowing manufacturers to market products containing NAC as dietary supplements.

CRN first raised concerns with the Agency about FDA’s questionable legal position in December 2020 through a letter to the Office of Dietary Supplement Programs (ODSP) Director, Steven Tave.² Since then, CRN has had several meetings with FDA leadership in which CRN raised this

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 180 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN’s Code of Ethics. Learn more about us at www.crnusa.org.

² Letter from S. Mister and M. Olsen, Council for Responsible Nutrition to S. Tave, Food and Drug Administration (Dec. 4, 2020) (hereinafter the “December 2020 Letter”).

issue, including meetings with the current ODSP acting director Cara Welch and acting FDA commissioner Janet Woodcock. FDA has represented that the agency is considering CRN's position, but has given no firm timeline for a response.³ CRN has stressed the need for quick resolution given marketplace reliance on FDA's public statements. While FDA reviews the legality of its policy reversal, NAC supplement manufacturers are experiencing significant negative economic impacts. For example, the largest U.S. ecommerce retailer and a significant distribution channel and source of consumer access to dietary supplements, Amazon, has removed NAC dietary supplements from its platform.⁴ As such, CRN believes formal action is needed through the Citizen Petition process to put a deadline on FDA's response.⁵ If FDA fails to respond within the 180 days required by the regulation, its failure to respond may be examined by the courts, unlike the agency's announcement in the July 2020 warning letters, which may not be considered final agency action that is ripe for judicial review. Otherwise, the information provided in this Citizen Petition is substantively similar to the information provided in CRN's December 2020 Letter.

For decades, manufacturers have safely marketed products containing NAC as dietary supplements in the United States. There are currently hundreds of dietary supplements containing NAC on the market,⁶ and thousands of consumers have come to rely on these products as a crucial source of nutrients. The safety of NAC has been widely recognized, including by authoritative government bodies, such as the National Institutes of Health.⁷ NAC is also naturally found in foods, like onions and garlic, and it is the precursor to the amino acid L-cysteine, which FDA considers to be generally recognized as safe (GRAS).⁸ The safety of NAC dietary supplements is not in dispute.

Until recently, FDA has consistently and affirmatively permitted manufacturers to market dietary supplements containing NAC. In fact, FDA has considered over 100 structure-function claim notifications regarding NAC and at least one qualified health claim petition for a dietary supplement containing NAC, and has not objected to the presence of NAC in any of these products.⁹ But, in July 2020, FDA enacted a sudden policy change by issuing multiple warning letters asserting that products containing NAC cannot be marketed as dietary supplements under

³ Letter from C. Welch, Food and Drug Administration to S. Mister and M. Olsen, Council for Responsible Nutrition (May 6, 2021).

⁴ See Josh Long, *Amazon confirms plans on removing NAC supplements*, Natural Products Insider (May 6, 2021), <https://www.naturalproductsinsider.com/regulatory/amazon-confirms-plans-removing-nac-supplements>.

⁵ See 21 C.F.R. § 10.30(e) (requiring that the FDA "Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition").

⁶ See NIH, *Dietary Supplement Label Database*, <https://dslid.od.nih.gov/dslid/lstIngredients.jsp?item=N-acetyl-L-cysteine>.

⁷ National Institutes of Health Office of Dietary Supplements, *Dietary Supplements in the Time of COVID-19*, <https://ods.od.nih.gov/factsheets/COVID19-HealthProfessional/> (noting that "[n]o safety concerns have been reported for products labeled as dietary supplements that contain NAC").

⁸ 21 C.F.R. § 184.1271 (promulgated March 15, 1977).

⁹ See Josh Long, *FDA Warning Letters on NAC Cause Stir in Supplement Sector*, Natural Products Insider (Aug. 11, 2020), <https://www.naturalproductsinsider.com/regulatory/fda-warning-letters-nac-cause-stir-supplement-sector>.

section 201(ff)(3)(B)(i) of the FDCA.¹⁰ Section 201(ff)(3)(B)(i) prohibits manufacturers from marketing products as dietary supplements if they contain an article that FDA has approved as a new drug under section 505 of the Act, unless that article was marketed in dietary supplements or food before it was approved as a drug (often called the “drug preclusion clause”). FDA’s July 2020 warning letters assert that NAC was approved as a new drug in 1963 and, to FDA’s knowledge, was not marketed as a dietary supplement prior to that date. As such, FDA claims that products containing NAC cannot be marketed as dietary supplements. FDA has failed to provide any rationale for this policy change other than the basic assertions made in these warning letters.

FDA’s sudden policy change is legally invalid on multiple grounds. First, it is not even clear, from FDA records, whether section 201(ff)(3)(B)(i) applies to NAC as a dietary supplement. The decades-old records for NAC drug approval contain unreliable information, such as handwritten dates, and unverifiable information. Second, NAC drugs approved prior to 2016 appear to be comprised of different forms of NAC from that which is found in a dietary supplement. Third, interpreting FDCA section 201(ff)(3)(B)(i) to prohibit the marketing of dietary supplements containing NAC violates the well-established presumption against statutory retroactivity. CRN’s review of the drug approval records for NAC, and subsequent discovery of unreliable and conflicting information, demonstrates one of the significant dangers of statutory retroactivity. FDA’s policy change also is an arbitrary and capricious agency action that is invalid under the Administrative Procedure Act (APA). And finally, the equitable defense of laches prevents FDA from enforcing its new policy. For these reasons, we urge FDA to reverse this policy change and revert to its longstanding policy of allowing manufacturers to market dietary supplements containing NAC.

A. Action Requested

FDA should revert to its longstanding policy of allowing manufacturers to market dietary supplements containing NAC and rescind the legally invalid position included in warning letters¹¹ that NAC is precluded by section 201(ff)(3)(B)(i) of the FDCA from being a legal dietary ingredient in dietary supplements.

¹⁰ See, e.g., FDA, Warning Letter to LES Labs, MARCS-CMS 593764 (July 23, 2020), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/les-labs-593764-07232020#:~:text=FDA%20is%20not%20aware%20of,in%20connection%20with%20your%20products.>

¹¹ See FDA Warning Letters to Vita Heaven, LLC dba Hangover Heaven (July 23, 2020), Happy Hour Vitamins (July 23, 2020), Les Labs (July 23, 2020), and Purple Bioscience, LLC (July 23, 2020).

B. Statement of Grounds

1. FDA's records do not reliably demonstrate that section 201(ff)(3)(B)(i) applies to NAC.

CRN reviewed numerous FDA records on NAC to determine whether section 201(ff)(3)(B)(i) would even apply, absent other concerns with FDA's retroactive application of this section and inconsistent policy in applying this section to NAC. The records contain a number of flaws that CRN believes make them unreliable to support an argument that NAC was approved as a new drug prior to NAC being marketed as a dietary supplement.

In the 2020 warning letters, FDA asserted that "NAC was approved as a new drug under section 505 of the Act [21 U.S.C. § 355] on September 14, 1963."¹² In the only other document, prior to the 2020 warning letters, that CRN could find alleging NAC was approved as a drug before it was used as a dietary supplement, FDA states that the agency "first approved N-Acetylcysteine (NAC) as a new drug in 1985."¹³ In fact, neither date appears to be reliable.

For the drug purportedly approved in 1963, CRN obtained the attached letter through a Freedom of Information Act (FOIA) request.¹⁴ The letter contains what appears to be a handwritten approval date of "1963". This handwritten notation raises a number of questions about the reliability of this record, not the least of which is whether the approval date was actually 1963 or sometime later, why was the approval date handwritten, when was the notation made, and who made it. This is not the type of document that should be regarded as authentic. The unreliability of a handwritten date is exactly the type of issue that FDA likely would raise for a dietary supplement company providing similar evidence that an ingredient was marketed as a supplement before being approved as a drug. CRN has been unable to verify whether an NAC drug was approved in 1985, as there appear to be no drugs with NAC as an active ingredient listed in FDA's Orange Book with a 1985 approval date.¹⁵

¹² See *supra* n. 10.

¹³ See Feb. 2, 2011 Letter from F. Hines, FDA Consumer Safety Officer, Division of Dietary Supplement Programs to Tira Pharmaceuticals regarding N-acetylcysteine (NAC) ethyl ester 75 Day Premarket Notification of New Dietary Ingredient.

¹⁴ See Attachment A.

¹⁵ Documents obtained through another FOIA search suggest that the 1985 date may be related to an approval for oral/intubation use for NAC as an additional indication for the drug purportedly approved in 1963, but the approval date is not included in the Orange Book as 1985. Even if this date is correct, CRN has concerns that the record does not reliably show that the NAC form of the drug approved prior to 1994 is the same "article" as NAC used in supplements, as described in more detail in this section.

2. FDA’s position fails to acknowledge that delivery form/route of administration must be considered to determine if ingredients are the same “article” under section 201(ff)(3)(B)(i).

Another, even larger issue, appears to have been overlooked in the 2020 warning letters when FDA cited the 1963 approval as evidence that NAC is precluded from being a dietary supplement due to section 201(ff)(3)(B)(i). The 1963 approval, according to the document obtained by CRN, was for an inhaled drug.¹⁶ For section 201(ff)(3)(B)(i) to apply, the dietary supplement ingredient must be the same “article” as the approved drug. An inhaled substance should not be treated as the same article as an orally consumed substance. To do so would go against FDA’s own significant precedent and guidance. For example, for drug approval FDA would not consider an inhaled drug to be “the same” as an orally ingested drug, as the route of administration and dosage form, among other requirements, are considered by the agency.¹⁷ Further, a dietary supplement, by definition, must be “a product that . . . is intended for ingestion.”¹⁸ Because of this limitation, a dietary supplement would, by its very nature, differ significantly in the route of administration and dosage form from an inhaled drug. Such significant differences, which will affect a substance’s impact on the human body, must preclude an inhaled ingredient from being considered the same “article” as an orally ingested ingredient.

The NAC drug approval record indicates that no NAC drug was approved for oral use only until 2016 – well after dietary supplement companies had been marketing NAC as a supplement. The Orange Book shows that NAC drugs were approved for “inhalation, oral” as early as 1982, however, the earliest that an NAC drug was approved for “inhalation, oral” form and route of administration and that has not been discontinued is August 1994. It is not clear (1) whether these inhaled/oral drugs could even be considered the same “article” as NAC used in a dietary supplement due to their dual route of exposure; and (2) whether the approval date of discontinued drugs may be used to determine the date of preclusion for dietary supplement use.

With regard to discontinued drugs, section 201(ff)(3)(B) does include a clause precluding supplement use where a drug is approved for investigation, substantial clinical investigations are actually conducted, and those clinical investigations made public. But, to invoke such a clause, to determine a specific preclusion date pre-1994 would require a record that those criteria were all met before NAC was marketed as a dietary supplement (in addition to the drug and dietary supplement being the same article) – likely a difficult task for FDA to demonstrate on records that are over 25 years old. As discussed in Section II below, NAC was being marketed as a dietary supplement well before October 1994. The conflicting nature of information in FDA documents and the difficulty in obtaining accurate information as to when NAC was in fact approved as a drug that could be considered the same “article” as an NAC supplement also underscores CRN’s significant concern that section 201(ff)(3)(B)(i) was never intended to be applied retroactively.

¹⁶ See Attachment A, pg. 4 (the approved drug is a “mucolytic agent” intended to be taken “via face mask or mouthpiece (aerosolized) or . . . into a tent or croupette . . .”).

¹⁷ FDCA § 505(2)(A)(iii).

¹⁸ FDCA § 201(ff)(2)(A).

The court's holding in *Pharmanex v. Shalala*¹⁹ is not dispositive of this matter either. In that case, the Tenth Circuit concluded that Congress's use of the term "article" as used in section 201(ff)(3)(B) was not intended to limit that provision's application to finished drug products, but included individual ingredients as well. However, it did not consider the current situation in which the route of administration for the drug (inhaled) was different than the delivery form of the supplement (ingested). Additionally, the dispute in *Pharmanex* involved two products that were essentially marketed for very similar health outcomes (the reduction of cholesterol) and thus the marketing of the supplement could conceivably serve as a disincentive to conducting further research for the pharmaceutical use. In this situation, the long-established structure-function claims for dietary supplements containing NAC (*e.g.*, maintain cellular health, boost cellular glutathione levels, antioxidant support) are vastly different than the disease claims made for the NAC products considered by the agency prior to 1994 to which FDA points for establishing NAC's pre-existing use as a drug (as a mucolytic).

3. FDA's interpretation of section 201(ff)(3)(B)(i) violates the well-established presumption against statutory retroactivity.

Even if FDA records reliably demonstrated drug approval before 201(ff)(3)(B)(i) was enacted, it is a well-established canon of statutory interpretation that legislation shall not be read to have a retroactive effect on private rights unless Congress expresses a clear, unambiguous intent to the contrary.²⁰ This "presumption against statutory retroactivity" ensures that Congress has "affirmatively considered the potential unfairness of retroactive application and determined that it is an acceptable price to pay for the countervailing benefits."²¹ Courts have long held that this presumption is particularly important in the context of property rights, for which "predictability and stability are of prime importance."²²

FDA's interpretation of section 201(ff)(3)(B)(i) is wholly inconsistent with the presumption against statutory retroactivity. Congress enacted section 201(ff)(3)(B)(i) as part of the Dietary Supplement Health and Education Act of 1994 (DSHEA),²³ which took effect on October 25, 1994. Thus, the definitional exclusion established by section 201(ff)(3)(B)(i) should be read to have *proactively* prohibited products containing articles that were approved as new drugs *after* October 25, 1994 from being marketed as dietary substances, unless such articles were marketed in dietary supplements prior to approval. By contrast, section 201(ff)(3)(B)(i) should only be read to *retroactively* apply to products containing articles that were approved as new drugs *before*

¹⁹ 221 F.3d 1151 (10th Cir. 2000).

²⁰ See *Landgraf v. USI Film Products*, 511 U.S. 244, 270 (1994) ("Since the early days of this Court, we have declined to give retroactive effect to statutes burdening private rights unless Congress had made clear its intent."); see also *United States v. Heth*, 7 U.S. (3 Cranch) 399, 413 (1806) (opinion of Paterson, J.) ("Words in a statute ought not to have a retrospective operation, *unless they are so clear, strong, and imperative, that no other meaning can be annexed to them*, or unless the intention of the legislature cannot be otherwise satisfied.") (emphasis added).

²¹ *Landgraf*, 511 U.S. at 271.

²² *Id.* at 272–73.

²³ Pub L. No. 103-417, 108 Stat. 4325 (1994).

October 25, 1994 if Congress expressed a clear, unambiguous intent for this provision to have a retroactive effect. A thorough review of both the text of DSHEA and the legislative history of this provision indicates that Congress expressed no clear intent for this provision to have a retroactive effect. Thus, this provision should not be applied in a retroactive manner.

Further, Congress created section 201(ff)(3)(B)(i) to protect commercial interests necessary to incentivize new drug development in the wake of DSHEA's enactment.²⁴ A retroactive application of this section does nothing to incentivize new drug development because drugs and supplements that were both on the market prior to DSHEA's passage already co-existed and drug companies developed these products with no expectation of DSHEA's protections. Congress's objective to preserve incentives for drug research would not be advanced by FDA's award of a monopoly to the drug industry for an ingredient that has co-existed in both drug and supplement forms for decades. Finally, as described above, CRN's review of the NAC drug approval records demonstrates another danger of statutory retroactivity – that decades-old records are often unreliable.

Here, even if NAC was approved as a new drug *before* October 25, 1994 in a form that can be considered the same "article" as NAC found in dietary supplements, dietary supplements containing NAC were also marketed during the intervening years between NAC's approval as a drug and the enactment of DSHEA.²⁵ So, FDA's application of section 201(ff)(3)(B)(i) to products containing NAC qualifies as a retroactive application of the statute. FDA may argue that dietary supplement companies could easily have reviewed drug approvals at DSHEA's passage and determined whether to continue to market an ingredient in a supplement, but the industry had no reason to do so given that Congress expressed no clear retroactive intent for section 201(ff)(3)(B). Further, as discussed in Section I of this letter, a search of FDA's drug approvals published in the Orange Book would have returned unreliable and incomplete information. Because there is no evidence that Congress intended for this provision to have a retroactive effect, FDA's actions in 2020 directly violate the presumption against statutory retroactivity, and will likely be struck down by any reasonable court.

4. FDA's policy change is an arbitrary and capricious agency action that is invalid under the Administrative Procedure Act.

It is a well-established principle of administrative law that an agency must provide a reasoned explanation when changing its policies.²⁶ It is particularly important that agencies provide such

²⁴ See, e.g., S. Rep. 103-410, Part V, § 3 (1994); 140 Cong. Rec. S11,709 (daily ed. Aug. 13, 1994).

²⁵ The dietary supplement industry considers NAC to be a "grandfathered" ingredient (i.e., marketed prior to DSHEA's passage on October 25, 1994). FDA has never questioned this status. For example, nowhere in FDA's record has FDA challenged the numerous companies who sell NAC as marketing this product without submitting a new dietary ingredient notification (NDIN) – a requirement of ingredients that were not marketed as dietary supplements prior to DSHEA's passage.

²⁶ See *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2125 (2016) ("One of the basic procedural requirements of administrative rulemaking is that an agency must give adequate reasons for its decisions."); *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (stating that, when adopting policy changes,

an explanation when the agency's prior position has "engendered serious reliance interests" among those whom it affects.²⁷ Policy changes that are not accompanied by an adequate explanation are deemed "arbitrary and capricious," and are invalid under section 706(2)(A) of the Administrative Procedure Act (APA).²⁸

Here, FDA has implemented a sudden policy change without providing a well-reasoned explanation, and has done so in a manner that will affect thousands of industry and consumer stakeholders in whom the Agency has "engendered serious reliance interests." As noted above, prior to July 2020, it was FDA's longstanding policy to permit the marketing of dietary supplements containing NAC. FDA had reviewed over 100 30-day notifications of structure/function claims for NAC and never raised any issues with the drug preclusion clause. FDA also had reviewed a qualified health claim for NAC and failed to raise the drug preclusion clause. As part of the qualified health claim review process, FDA specifically assesses whether the substance that is the subject of the qualified health claim qualifies as a food or dietary ingredient in dietary supplements. In response to the qualified health claim petition involving NAC, received by the agency in 2016, , FDA states that NAC is a dietary supplement.²⁹ This record demonstrates that FDA continued to treat NAC as a dietary supplement, even after the FDA 2011 letter in which FDA purportedly determined that NAC was subject to drug preclusion due to a 1985 drug approval.³⁰

In response to the extensive history of NAC being treated by FDA as a dietary supplement, manufacturers have invested substantial resources to develop hundreds of such products, and thousands of consumers have come to rely on such products to meet their daily nutritional needs. Now, FDA has decided to not only change its decades-long policy, but to do so through the issuance of warning letters that fail to provide any reasonable explanation for this consequential policy shift. Given the widespread implications of FDA's policy change—and the immense reliance interests of those whom it will effect—FDA's failure to provide an adequate explanation for this change renders it an invalid, arbitrary and capricious agency action.

agencies "must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" (citations omitted).

²⁷ See *F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 515–16 (2009); see also *Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 742 (1996) ("Sudden and unexplained change . . . or change that does not take account of legitimate reliance on prior interpretation . . . may be 'arbitrary, capricious [or] an abuse of discretion' [under 5 U.S.C. § 706(2)(A)].") (citations omitted).

²⁸ See 5 U.S.C. § 706(2)(A).

²⁹ Letter to T. Shea, Sevo Nutraceuticals, Inc., Re: Petition for a Qualified Health Claim for a Nutraceutical Formulation and Management of Behavior and Cognitive Difficulties that Can Accompany Dementia (Docket No. FDA-2016-Q-1523), p. 7 ("the agency concludes that the six individual substances in the petitioner's dietary supplement are either components of food . . . or a dietary supplement that includes vitamins or other nutritional substances (i.e., N-Acetyl cysteine . . .)") (available at <https://www.fda.gov/media/119441/download>).

³⁰ See *supra*, n. 13.

5. The equitable defense of laches prevents FDA from enforcing its new policy.

The equitable defense of laches prohibits defendants from bringing unreasonably delayed legal claims.³¹ To prevail in asserting this defense, defendants must establish (1) that the delay resulted from the plaintiff's own lack of diligence, and (2) that the defendant has suffered undue prejudice as a result of the plaintiff's delay.³² Here, manufacturers of dietary supplements containing NAC can demonstrate both.

First, FDA's decades-long delay in bringing enforcement action against manufacturers of dietary supplements containing NAC indisputably resulted from a lack of diligence by FDA, rather than an unawareness that these products were on the market. In fact, there is ample evidence that FDA has long been aware that these products are on the market, and that FDA has *actively* considered—and failed to object to—structure/function and qualified health claim petitions regarding products containing NAC. Thus, FDA's long-delayed enforcement against these products resulted from the Agency's own lack of diligence.

Second, FDA's long-delayed enforcement actions severely prejudice manufacturers. Defendants can demonstrate prejudice by showing that a plaintiff's delayed action has caused economic losses that "could have otherwise [been] avoided had the suit been filed earlier."³³ Here, manufacturers are already suffering extreme economic consequences as a result of FDA's delayed enforcement. For decades, manufacturers have invested in developing and producing dietary supplements containing NAC, largely based on FDA's longstanding policy of allowing manufacturers to market these products. These expectation-backed investments have led to the development of hundreds of products that are now being affected by FDA's new policy—products that manufacturers would not have developed had FDA taken prompt enforcement action. That manufacturers will experience economic harm is not ideal speculation. As noted above, the largest U.S. ecommerce retailer, Amazon, has already taken action to remove NAC dietary supplements from its platform, specifically citing FDA's 2020 warning letters as the basis of its action. Amazon's actions severely limit manufacturers' distribution channels and source of revenue for these products. This large-scale economic prejudice, coupled with FDA's lack of diligence, will allow manufacturers to successfully invoke a laches defense in response to any attempt by FDA to take legal action against the marketing of dietary supplements containing NAC.

³¹ See *Gardner v. Pan. R.R. Co.*, 342 U.S. 29, 30 (1951). While the defense of laches is more commonly raised against private party plaintiffs, multiple courts have affirmed that this defense is available in response to suits brought by the government. See, e.g., *NLRB v. P*IE Nationwide*, 894 F.2d 887, 894 (7th Cir. 1990) ("[L]aches is generally and we think correctly assumed to be applicable to suits by government agencies as well as by private parties."); *Hickey v. Ill. Cent. R.R. Co.*, 220 N.E.2d 415, 426 (Ill. 1966) ("[T]he reluctance to apply equitable principles against the State does not amount to absolute immunity of the State from laches and estoppel under all circumstances.").

³² See *Costello v. United States*, 365 U.S. 265, 282 (1961).

³³ See, e.g., *A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1033 (Fed. Cir. 1992) ("Economic prejudice may arise where a defendant and possibly others will suffer the loss of monetary investments or incur damages which likely would have been prevented by earlier suit."); *Dennis Joslin Co., LLC v. Johnson*, 138 S.W.3d 197, 201 (Tenn. Ct. App. 2003).

C. Environmental Impact Statement

CRN maintains that the actions requested in this Petition are exempt from the requirement to provide an environmental impact statement pursuant to 21 C.F.R. § 25.30(h).

D. Economic Impact

Information on the economic impact of this proposal can be provided if requested.

E. Certification

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

Sincerely,



Steve Mister
President & CEO



Megan Olsen
Vice President & Associate General Counsel