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CITIZEN PETITION

The law firms of Kirkpatrick & Lockhart, LLP, Kleinfeld, Kaplan and Becker, LLP, McDermott, Will & Emery, and Olsson, Frank and Weeda, P.C. (hereinafter, the "Petitioners") submit this Citizen Petition ("Petition") on behalf of a number of pharmaceutical clients, pursuant to 21 C.F.R. §§ 10.25, 10.30 (2002). The pharmaceutical clients are representative of a broad range of specialty companies within the pharmaceutical industry, including manufacturers, wholesale distributors, and private-label distributors of pharmaceutical products. This Petition requests that the Commissioner of the Food and Drug Administration ("FDA") employ a reasoned, deliberate and graduated approach when FDA seeks to change the regulatory status of drugs, such as single ingredient extended release guaifenesin products, that have long been marketed safely without modern-day approved drug applications.

A. Action Requested

As FDA has explained in its Compliance Policy Guide ("CPG") 7132c.02 (1987) (originally published at 49 Fed. Reg. 38191 (Sept. 27, 1984)), there are presently many drug products on the market for which FDA has not made final determinations regarding their regulatory or legal status. FDA has stated its intention to make final determinations, at some time in the future, regarding these drug products' effectiveness, new drug status, or grandfather status. When FDA does so, the drug marketers will have notice of the regulatory procedures that must be undertaken in order to support the lawful marketing of the products. Until FDA makes these determinations, the drugs' marketers continue to rely on a variety of statutory exceptions for authority to market

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their products (hereinafter referred to as "exceptive drug products", denoting the statutory exceptions under which they are marketed). This Petition addresses the appropriate mechanism and timing for FDA to make these final determinations and to provide firms marketing the drugs with sufficient notice of the regulatory procedures for continued drug marketing.

The impetus for the Petition involves FDA's recent Warning Letters to approximately 70 parties involved in the manufacture and marketing of single ingredient extended release guaifenesin drug products, apparently intending to seek the immediate removal of those products from the market. The Petitioners object to FDA's action and file this Petition to detail the serious legal, procedural, policy and practical concerns associated with the FDA approach being pursued presently with respect to those drug products and the potential ramifications should FDA intend to apply this approach more broadly in the future.

Based on the concerns addressed herein, the Petitioners request that the Agency reconsider its approach and adopt an alternate approach that is consistent with its prior practice and that is fairly applied to all marketers of similarly-situated products. In particular, the Petitioners request that FDA establish an orderly process, with appropriate notice to drug marketers and timetables for responsive action, that allows firms marketing affected drug products to continue to market their products while taking appropriate steps to comply with the regulatory procedures called for by the Agency (e.g., to obtain FDA approval via the new drug application ("NDA") or abbreviated new drug application ("ANDA") process).

In so doing, the Petitioners call for the Agency to take the following actions with respect to exceptive drug products, including single ingredient extended release guaifenesin drug products:

- (1) Publish a *Federal Register* notice stating its conclusions about the regulatory status of particular exceptive drug products, as FDA identifies them;
- (2) Specify the regulatory procedures necessary to obtain (or continue) lawful marketing status;
- (3) Provide guidance concerning the scientific data necessary to meet the specified regulatory procedures; and
- (4) Establish a schedule for submitting the scientific data and obtaining any necessary review and approval – failing which, the agency would be

prepared to invoke its statutory authority to remove products from the market.

For the reasons outlined below, these procedures should be followed whenever the Agency changes its expectations about the regulatory status (e.g., the need to seek NDA or ANDA approval) of products that have been marketed historically and safely without modern-day approved applications.

B. Statement of Grounds

1. Background

On or about October 11, 2002, FDA issued Warning Letters to approximately 70 marketers of single ingredient extended release guaifenesin products (marketed in strengths of 575 mg to 1200 mg). The stated impetus for these Warning Letters was that the Agency had approved Adams Laboratories, Inc.'s ("Adams") NDA for Mucinex® (guaifenesin) extended release 600 mg tablets in July 2002. The Warning Letters acknowledged that, prior to Adams' NDA approval, FDA chose not to expend scarce enforcement resources to address prescription guaifenesin products but that, now, the single ingredient extended release guaifenesin products are considered new drugs subject to NDA/ANDA approval requirements.

To the best of Petitioners' information and belief, single ingredient guaifenesin products have been marketed in the U.S. for over 65 years. The drugs' initial entry into the marketplace occurred before 1938, when Congress passed the Federal Food, Drug, and Cosmetic Act of 1938. As a result, the drugs were not reviewed explicitly by FDA pursuant to the modern-day NDA process, but may have been "grandfathered" or otherwise excepted from "new drug" status under the law so that their continued marketing remained lawful while FDA implemented the NDA procedures of the 1938 law and the later Kefauver-Harris Amendments of 1962 and Hatch-Waxman Amendments of 1984.

FDA's stated intention, following the E-Ferol tragedy in 1983, was to review grandfathered drugs, and those similarly-situated to them, in an orderly manner in the future. In so doing, FDA stated that it intended to make final determinations regarding these drug products' effectiveness, new drug status, or grandfather status. One way in which FDA intended to accomplish this task was via a program deemed the "Prescription Drug Wrap-Up" or "DESI-II". A listing of DESI-II drugs, incorporated in the

"Weiss List", was prepared in approximately 1984 and includes guaifenesin 600 mg extended release tablets. (The Weiss List includes a single ingredient extended release guaifenesin product as a "B04" drug, denoting its status as a DESI-II drug.)

Until the DESI-II review could be accomplished, FDA published CPG 7132c.02 in 1984 (revised in 1987) to describe the priorities that FDA intended to follow when taking action to remove drugs from the marketplace when warranted by subsequent determinations. The CPG represented FDA's attempt to prioritize its compliance activities and provide industry with an idea of the order in which the agency will take action against such products. Under the CPG, FDA has said that it will defer regulatory action against DESI-II drug products on a class-wide basis until the Agency is able to undertake an orderly review and make a decision as to the drugs' regulatory status. According to FDA, the orderly review would be governed *primarily by public health concerns*. Specifically, FDA stated "the priorities for enforcement action relate to a particular drug's effect on public health and safety, and are designed to have a maximum impact on violative products and to provide equitable treatment among competing firms." CPG 7132c.02 at 2.

Partially as a consequence of the procedures and priorities identified in the CPG, there are likely thousands of drug products in the U.S. market today, like single ingredient extended release guaifenesin products, which are marketed without modern-day NDA or ANDA approval, based on their marketers' view that they are not subject to approval requirements or that those requirements have been indefinitely deferred under the CPG. Although the guaifenesin drug products are provided as a useful example for this Petition, it is not just FDA's action against the guaifenesin products that is at issue. Rather, this Petition addresses a broader concern about FDA's enforcement policy generally and whether the policy is appropriately applied on an *ad hoc* basis, without prospective notice and a meaningful opportunity for products long and safely marketed under the CPG to be brought into compliance with new regulatory determinations.

2. The Agency's Action With Respect to Guaifenesin Raises a Host of Serious Legal, Procedural, Policy and Practical Concerns

As detailed in the following sections, the Agency's decision to announce a change in its policy toward the marketing of single ingredient extended release guaifenesin prescription products through the abrupt issuance of a mass mailing of separate Warning Letters raises several serious legal, procedural, policy, and practical concerns. Although the arguments set forth below describe the situation as it has been applied to

guaifenesin products, the Petitioners' concerns extend beyond the regulation of guaifenesin products since FDA's action could impact all prescription drug products that are marketed pursuant to regulatory avenues or FDA policies that are outside of the modern-day drug approval process. Given the extensive scope of FDA's action, a reasoned, orderly approach that incorporates prospective notice of new agency determinations and allows marketers to continue to distribute their products while seeking FDA approval or otherwise meeting new regulatory requirements would properly address these multiple concerns. To the extent that FDA's action signals a shift in policy to treat similarly-situated exceptive drug products in this manner, the Petitioners maintain that the shift in policy represents Agency action that is arbitrary and capricious and an abuse of discretion, in contravention of the Administrative Procedures Act ("APA"). See 5 U.S.C. §§ 551 *et seq.*, 701 *et. seq.*

- a. The Agency's Proposed Approach is Patently Unfair and Inconsistent with Reasonable Expectations Based Upon Past Agency Practice
 - i. FDA Did Not Provide Proper Notice to the Marketers of Guaifenesin Products

Dozens of drug marketers have distributed single ingredient extended release guaifenesin products under the Agency's CPG 7132c.02 for years without objection from FDA. No concerns about safety or efficacy have been directed at these products, and the Agency has never publicly solicited applications for the products. Accordingly, manufacturers had no notice that the Agency might be considering changing the status of these products, or that, if it did, the Agency would provide no opportunity to comply with the new requirements before seeking the products' removal from the market. Indeed, FDA's failure to publicize the conclusion it had apparently reached some time ago (either at the time it received the Adams NDA in June 2000 or at any time since then, until now) – that single ingredient extended release guaifenesin products should be transitioned to NDA or ANDA status – deprived manufacturers of years during which they could have been preparing their own NDAs.

Based upon the Agency's past practices, manufacturers reasonably expected that any change in FDA's policy about the need to seek NDA or ANDA approval to market products of this type would be announced as part of a program for systematic review of the status of unapproved drug products (e.g., the DESI-II program). The regulated industry also expected that, at a minimum, the Agency would *prospectively* announce any necessary filing, review, and approval criteria, along with implementation

timetables, that would permit fair and orderly transition of widely prescribed products such as extended-release guaifenesin tablets to NDA or ANDA status. For example, the Agency's recent handling of levothyroxine sodium and oral digoxin products confirmed regulated industry's expectations concerning the orderly manner in which the Agency would implement new requirements for products long marketed outside of the modern-day NDA approval process. Both situations also confirm that the orderly approach suggested herein by the Petitioners would effectively transition unapproved products to NDA or ANDA status while minimizing marketplace disruption.

In the case of levothyroxine, FDA published a *Federal Register* notice announcing its conclusion that levothyroxine products were new drugs, establishing a deadline, three years in the future, for submission of applications, describing the content of the required applications, and specifically addressing bioavailability requirements. See 62 Fed. Reg. 43535 (Aug. 14, 1997). Recognizing that manufacturers needed additional time to prepare applications, FDA later extended the deadline by one year, thus allowing manufacturers a total of four years from the date of the original notice to secure approval for their products. See 65 Fed. Reg. 24488 (April 26, 2000). Even then, FDA established an orderly, gradual phase-out of products that had not yet received approval upon expiration of the four year period. See 66 Fed. Reg. 36794 (July 13, 2001).

The Agency's experience with levothyroxine underscores the need for it to carefully consider the types of information to be included in an application and provide specific guidance to manufacturers at the time it first requests applications for a category of unapproved products. Two years after its initial *Federal Register* notice concerning levothyroxine, FDA issued a draft guidance document intended to answer the numerous questions that had arisen concerning the required applications. See 64 Fed. Reg. 44925 (Aug. 18, 1999). Subsequently, FDA revised its draft guidance document and issued another concerning the conduct of *in vivo* pharmacokinetic and bioavailability studies and *in vitro* dissolution tests. See 66 Fed. Reg. 13935 (March 8, 2001). Had FDA published these guidance documents with its initial *Federal Register* notice, the need for Agency consultations with individual manufacturers would have been reduced, and it may have been possible for manufacturers to secure the necessary approvals in fewer than four years.

The Agency's recent handling of digoxin products for oral use also confirmed manufacturers' expectations. Historically, oral digoxin products were marketed pursuant to a regulation establishing labeling requirements and other conditions for marketing those drugs. Although FDA had announced in 1974 that oral digoxin

products are new drugs and had required the submission of ANDAs, the requirement for submission of ANDAs was stayed indefinitely. FDA approved an NDA for digoxin tablets in September 1997 and subsequently, in 1999, FDA approved an ANDA. In 2000, FDA published a proposal to revoke its regulation establishing the conditions for marketing oral digoxin and a notice reaffirming FDA's previous conclusion that digoxin products for oral use are new drugs and requiring submission of an NDA or ANDA. See 65 Fed. Reg. 70538 (Nov. 24, 2000) and 65 Fed. Reg. 70573 (Nov. 24, 2000). FDA withdrew its digoxin regulation effective July 26, 2002, and announced that unapproved digoxin tablets marketed after that date would be subject to regulatory action. See 67 Fed. Reg. 42992 (June 26, 2002). In contrast, digoxin elixir manufacturers were provided an additional two years, until June 2004, to obtain approval of an NDA for their products. *Id.* Thus, manufacturers of digoxin tablets had almost two years after FDA's proposed rule and almost five years following approval of the first NDA for digoxin tablets to prepare and obtain approval of an ANDA. Manufacturers of digoxin elixir were also provided sufficient time to prepare an NDA or ANDA – almost four years following FDA's proposed rule.

These recent examples of orderly FDA action underscore the Petitioners' contention that a *Federal Register* notice, and an orderly schedule for market withdrawal, should be provided for single ingredient extended release guaifenesin products, and as a broader policy matter, for all exceptive drug products.

ii. FDA Did Not Identify Any Safety Concerns When It Sought the Market Removal of the Guaifenesin Products

Significantly, the FDA permitted unapproved levothyroxine products to remain on the market while manufacturers prepared applications despite its conclusion that the products exhibited stability and potency problems that had the potential to cause serious health consequences. See 62 Fed. Reg. 43535 (Aug. 14, 1997). Similarly, manufacturers were permitted a reasonable amount of time to secure approvals for their oral digoxin products, despite the Agency's documented concerns about the bioavailability of those narrow therapeutic range drugs. See 65 Fed. Reg. 70538 and 70573 (Nov. 24, 2000). With guaifenesin products, however, the Agency has expressed no safety concerns, and such concerns would be unwarranted based on the long history of safe use of extended release guaifenesin products and the Agency's conclusions regarding the generally recognized safety of guaifenesin in large doses. See 60 Fed. Reg. 38643, 38645 (July 27, 1995). Accordingly, adoption of an orderly approach

allowing continued marketing while manufacturers prepare applications is even more appropriate in the case of guaifenesin than in the cases of levothyroxine and digoxin.

Moreover, the Agency adopted and widely publicized generally applicable implementation timetables in the levothyroxine and digoxin situations, despite the fact that relatively few companies marketed these products. In this case, dozens of manufacturers and distributors and individual products are involved. This too suggests that a public approach permitting a fair and orderly transition of products to NDA or ANDA status is even more warranted in the case of guaifenesin than in the cases of levothyroxine and digoxin.

In sum, allowing a reasonable amount of time to obtain approval of single ingredient extended release guaifenesin products following publication of the Agency's conclusions and specific guidance on applications would accomplish the Agency's goal of ensuring that these products are promptly transitioned to NDA or ANDA status. Equally important, such a procedure would be fully consistent with FDA's past practices and reasonable industry expectations and would ensure equitable treatment of all affected parties. Consequently, the procedure would comply with the APA and serve as an appropriate template for future action under similar circumstances.

b. The Agency's Action Is Inconsistent with CPG 7132c.02 and Unprecedented

Given that extended-release guaifenesin products have been marketed for decades, and the continued marketing of the products poses absolutely no safety concerns, FDA's departure from its prior policies and practices is particularly puzzling and unjustified, calling into question its legality.¹

CPG 7132c.02 outlines the FDA's strategy to address exceptive drug products that are marketed without a modern-day NDA or ANDA. It formalized the Agency's enforcement efforts by establishing and publicizing priorities for enforcement action. Priorities were

¹ See, e.g., *Atchison, Topeka & Santa Fe Railway Co. v. Wichita Bd. of Trade*, 412 U.S. 800, 808 (1973) (agency has a duty to explain its departure from prior norms); *Leach Corp. v. N.L.R.B.*, 54 F.3d 802, 806 (D.C. Cir. 1995) (agency must "provide a reasoned justification for any departure from its prior policies or practices"); *National Black Media Coalition v. F.C.C.*, 775 F.2d 342, 355 (D.C. Cir. 1985) (reasoned analysis required when agency departs from prior policies and standards).

established based primarily on a drug's potential impact on public health and safety. Application of the CPG was intended to have a maximum impact on violative products while providing equitable treatment among competing firms.

The CPG states that enforcement actions may be initiated outside of established priorities in certain circumstances. One so-called "policy guideline exception" involves: "initiating regulatory action against any drug on the market without an approved new drug application if it is identical or related to a post-1962 NDA approved for safety and effectiveness or it contains a new chemical entity not previously marketed." It appears that FDA may believe that its approval of Adams' NDA suddenly results in single ingredient extended release guaifenesin products being within this exception, but in fact, this exception provides no basis for the Agency's recent slew of Warning Letters.

By its terms, the exception was intended to allow the Agency to take immediate action against a new product that is either identical or related to a product approved *before* adoption of the CPG or that contains a new chemical entity not marketed before adoption of the CPG. The exception was not intended to address, and to our knowledge has never been applied to, a situation such as this, in which one manufacturer obtains approval of an unsolicited application years *after* adoption of the CPG for a drug that has long been marketed under the CPG.

FDA's sudden interpretation of the CPG in this new and unexpected way is unprecedented. This interpretation does not serve the CPG's stated objectives to direct scarce resources toward unapproved products that may negatively impact public health or safety or to direct those resources in a manner that is fair to all competing firms.

c. The Agency's Action Improperly Cedes FDA's Enforcement Discretion to Private Parties

Perhaps the single most surprising aspect of the approach suggested by the October 11th Warning Letters is its effect of ceding the Agency's enforcement discretion to a private party. FDA has indicated that the reason it is addressing single ingredient extended release guaifenesin products now is the recent approval of Adams' NDA. Adams did not submit its NDA in response to a generally applicable request for applications for these products; rather, the submission was unsolicited. In essence, FDA has allowed the conduct of one manufacturer – one who stands to gain considerably, should all of its competitors be forced off the market – to drive its actions

in this matter. While the Agency has considerable enforcement discretion, no legal authority permits the Agency to cede that discretion to a private party.²

Additionally, as a matter of policy, an agency should exercise its enforcement discretion in a manner designed to fulfill its mission – here, the protection of public health. To accomplish this mission, FDA has historically determined which practices or specific products raise the type of safety and efficacy concerns that warrant expenditure of the Agency's limited resources. Allowing a private party with obvious commercial motives to drive enforcement decisions undermines both the Agency's ability to accomplish its mission as well as its credibility.

d. The Agency's Action Creates a Monopoly Unnecessarily, to the Detriment of the Public

The current market for prescription single ingredient extended release guaifenesin drug products marketed under FDA's Compliance Policy Guide is highly efficient and competitive. However, we understand that, in informal discussions with representatives of marketers of single ingredient extended release guaifenesin products, FDA's Office of Compliance has indicated that it does not believe further enforcement action should be deferred while manufacturers take the actions necessary to obtain the NDA/ANDA approvals that FDA has now decided to require.³ Should FDA maintain this position, the result will be a swift and decisive end to the efficient, competitive market in favor of a

² See, e.g., *Perot v. F.E.C.*, 97 F.3d 553, 559 (D.C. Cir. 1996) ("when Congress has specifically vested an agency with the authority to administer a statute, it may not shift that responsibility to a private actor"), *cert. denied*, 520 U.S. 1210 (1997); *National Ass'n of Reg. Util. Com'rs v. F.C.C.*, 737 F.2d 1095, 1143 and n.41 (D.C. Cir. 1984) (cautioning the FCC not to cede its duties to private parties and noting such agency actions are unquestionably subject to challenge), *cert. denied*, 469 U.S. 1227 (1985); *Sierra Club v. Sigler*, 695 F.2d 957, 962-63 n.3 (5th Cir. 1983) (agency subdelegation to private party is particularly troubling given party's financial stake in the project under review); *Michigan Pork Producers Ass'n v. Campaign for Family Farms*, 174 F. Supp. 2d 637, 645 (W.D. Mich. 2001) ("Federal precedent restricts the ability of agencies to delegate executive and/or legislative responsibilities to persons outside the executive branch in the absence of a grant of authority by Congress to delegate those responsibilities in manners previously allowed by the Supreme Court").

³ A similar statement attributed to FDA has appeared in the trade press. See *Adams Mucinex Spurs FDA Crackdown on Guaifenesin Products*, F-D-C Reports, Inc., The Tan Sheet, Vol. 10, No. 42 (Oct. 21, 2002).

monopoly and subsequent windfall for Adams. The sudden elimination of all competition will surely lead to higher prices for consumers. Indeed, Adams has already announced that forty count bottles of its 600 mg product will retail for about \$25.00,⁴ whereas existing prescription 600 mg tablets are widely available at \$15 or less for the same size bottle. Yet FDA has identified no safety or efficacy problems that might justify this anti-competitive result. Indeed, the long marketing history of single ingredient extended release guaifenesin products, and the general recognition of the safety and efficacy of guaifenesin itself (21 C.F.R. § 341.18) confirm that these products are safe and effective. Because these products present no public health concern, and instead provide safe and effective relief from respiratory congestion, the Agency's willingness to facilitate a monopoly for Adams is completely unjustified.

Moreover, Congress set forth specific requirements for a market exclusivity award in the Hatch-Waxman Amendments to the Act and FDA should not grant *de facto* exclusivity by another means. The administratively-devised exclusivity being afforded in this case is simply not an appropriate "reward" for Adams' unsolicited efforts, which are believed to have been substantively minor and were certainly no greater than other firms would have undertaken if FDA had prospectively announced an approval requirement.

Nor would the competitive impact necessarily be short-lived. If manufacturers cannot market their single ingredient extended release guaifenesin products during the time they are seeking FDA approval, Adams will have the opportunity to build its brand, unimpeded by competition for several years, and Mucinex® will become entrenched. Given the well-known difficulty of regaining market share once lost, many manufacturers may simply choose to abandon their competitive products and not pursue FDA approval. In short, the healthy competition that exists today in the guaifenesin market may be forever damaged by FDA's approach to regulate via Warning Letter.

Moreover, should the Agency insist that manufacturers immediately cease marketing their extended-release guaifenesin products, this precedent may trigger a rush by manufacturers to secretly manipulate FDA's approach to apply to other categories of exceptive drug products. If Adams is successful in obtaining a monopoly, other manufacturers can be expected to submit their own NDAs for exceptive drug products – targeting not those products where NDA status would be most important from a public health perspective but, rather, those products where there is the most aggressive

⁴ See *Adams Labs Mucinex Marketing Strategy Targeting Healthcare Professionals*, F-D-C Reports, Inc., The Tan Sheet, Vol. 10, No. 29 (July 22, 2002).

competition. That is, manufacturers will pursue applications, not for those products that warrant approval due to public health concerns or other Agency priorities, but rather for those products that can be leveraged most effectively in a monopoly market. Thus, setting such an ill-conceived precedent with such wide ranging implications can only be described as a recipe for chaos in both this instance and in the future.

e. The Agency's Action Unnecessarily Disrupts the Marketplace

Forcing guaifenesin products off the market would not only unfairly penalize manufacturers other than Adams, but it would also disrupt physicians, patients and the overall marketplace. Single ingredient extended release guaifenesin products are sold by prescription in a variety of strengths (e.g., 600 mg, 1000 mg, 1200 mg). The products are comparatively inexpensive due to the vigorous competition among their manufacturers. Furthermore, because they are prescription products, insured consumers are reimbursed for all or part of the cost of the products.

Adams has obtained approval for a 600 mg over-the-counter ("OTC") product, which the company is selling "behind the counter" via pharmacists. Accordingly, if the FDA does preclude marketing of other guaifenesin products until approvals are obtained, physicians' and consumers' choices will be suddenly and severely limited. A 600 mg unreimbursed product may be an option for some consumers. Others, however, will require a reimbursed product, which may cause physicians to write prescriptions for other, more expensive cough/cold remedies. Still others may require a different strength product, yet the advantages offered by 1000 mg and 1200 mg products, including dosage convenience and lower cost (compared to multiple 600 mg tablets), will no longer be available to patients who require these higher doses. Any Agency approach to extended-release guaifenesin products should take these important patient and physician considerations into account.

In this regard, we also note that agency consideration of whether the Adams product should be approved for OTC distribution was accomplished entirely without input from the public or the marketers of the dozens of prescription versions of these products. To switch a widely-prescribed drug product from prescription marketing to OTC status in this way, via a non-public NDA review, is imprudent and contrary to FDA's past practice. For example, FDA's abrupt withdrawal of OTC marketing authority for metaproterenol sulfate metered-dose inhaler drugs in 1983 is illustrative of the need for public input into the switch of marketed products from prescription to OTC status, and the confusion and disruption that can be caused in the absence of such input. See 48 Fed. Reg. 24925

(June 3, 1983). FDA's action followed by less than a year the announcement by the Agency that it had decided, based on internal deliberations, to permit OTC marketing of those products. See 47 Fed. Reg. 47520 (Oct. 26, 1982). Prior to the 1982 announcement, there had been no consideration of the possible switch by an Advisory Panel and no prior notice that the matter was under consideration. Subsequent to the announcement, however, and once manufacturers began marketing their products OTC, a firestorm of criticism erupted. FDA concluded:

The controversy provoked by the unanticipated appearance of metaproterenol sulfate metered-dose inhaler as an OTC drug is undesirable irrespective of the merits of the decision on whether OTC status is appropriate for the drug. The controversy cannot but create doubts among practitioners and confusion and anxiety among asthma patients concerning this drug. In FDA's view, it is important that any decision to convert metaproterenol sulfate to an OTC drug be reached in a way that takes into account the views and concerns of practitioners and patients so that the decision has the confidence and support of those who will be most affected by it.

48 Fed. Reg. at 24927-28.

Since this debacle, FDA generally has reviewed Rx-to-OTC switch candidates in a manner that provides the opportunity for public comment, whether through Advisory Committee review, *Federal Register* publication, or other open process. Clearly, open debate on this issue is the sensible path, given the complexities of the U.S. health care system and probable impact on insurers, the Medicaid program, physicians, pharmacists and patients.

f. The Agency's Action Fails to Provide a Reasonable Opportunity for Firms to Challenge the Agency's Conclusion about the Status of Guaifenesin Products

FDA's Office of Compliance has suggested that marketing of all single ingredient extended-release guaifenesin prescription products should cease immediately. Apparently, the Agency does not intend to consider arguments that these products are not subject to the new drug requirements of the Act before initiating further enforcement action. Yet, it would be particularly inequitable for FDA to attempt to remove these products from the market before carefully considering any arguments on this issue. Indeed, apparently recognizing this, FDA solicited citizen petitions on precisely this

issue in the case of another exceptive drug product, levothyroxine sodium. See 62 Fed. Reg. 43535 (Aug. 14, 1997). There is no reasonable rationale for FDA to deny this consideration to firms that market guaifenesin products.

The Agency's Warning Letters apparently conclude that extended release guaifenesin products are new drugs based on FDA's regulation stating that timed release products are new drugs, citing 21 C.F.R. § 310.502(a)(14). The current version of section 310.502(a)(14) is the product of the Agency's attempt to consolidate a list of drugs, and provide for more concise and efficient drug regulations in response to then President Clinton's "Regulatory Reinvention Initiative," commonly known as the "Reinventing Government" or "REGO" initiative. See 61 Fed. Reg. 29502 (June 11, 1996). The preamble to the proposed rule for this regulation provided that:

FDA is proposing to revise § 310.502 to consolidate into one section a list of drugs *that have been determined by previous rulemaking procedures to be new drugs* within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) for which approved new drug applications under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 are required for marketing.

61 Fed. Reg. at 29503 (emphasis added). The agency received no comments to amend or remove this proposal, and the final rule was promulgated in March 1997. See 62 Fed. Reg. 12083 (March 14, 1997). By its terms, section 310.502 would therefore not apply to drugs that had not been determined by previous rulemaking procedures to be new drugs.

In fact, the underlying regulation that was recodified in 1997, in what is now section 310.502(a)(14), was only a "Statement of General Policy or Interpretation." See 24 Fed. Reg. 3756 (May 9, 1959).⁵ Such a regulation does not have the force of law and cannot form the basis for the Agency's refusal to consider arguments that extended release

⁵ In 1967, the Agency again confirmed that the existing regulation was a "statement of policy" and solicited comments on a revised version of the regulation. See 32 Fed. Reg. 12756 (Sept. 6, 1967). However, the Agency never acted on this proposed rule, and withdrew it in 1991. See 56 Fed. Reg. 67440, 67446 (Dec. 30, 1991).

products, such as the guaifenesin products referenced in the recent Warning Letters, are not new drugs.⁶

At the same time, the regulations dealing with agency definitions and interpretations of the newness of a drug provide that a new dosage, or method or duration of administration, or application for an existing drug *may be* considered in determining whether a drug is a new drug. See 21 C.F.R. § 310.3(h)(5). Therefore, the indefinite language of section 310.3(h)(5) applies to drugs that have not been determined by previous notice-and-comment rulemaking procedures to be new drugs, and this language does not require – or support – a conclusion by the agency that a new dosage, or method or duration of administration, or application for an existing drug *shall* render the product a new drug.

Indeed, given the long history of safe and effective use of extended release guaifenesin products, and the Agency's conclusion that guaifenesin is safe and effective in the dosages provided by the extended release products (21 C.F.R § 341.18), manufacturers would likely be able to establish that extended release guaifenesin, in the existing dosage range, is generally recognized as safe and effective. The OTC monograph for cold, cough, allergy, bronchodilator, and antiasthmatic drug products confirms that 200 to 400 mg of guaifenesin every four hours, up to 2400 mg in a 24 hour period, is safe and effective. See 21 C.F.R. § 341.78(d); 54 Fed. Reg. 8494, 8496-97 (Feb. 28, 1989). The extended release formulas that are the subject of the Warning Letters deliver these amounts of guaifenesin over a 24 hour period at approximately the same intervals recommended in the monograph. The only difference is the convenient, extended release dosage form, where the status as generally recognized as safe and effective may still be assured through compliance with general regulatory requirements. In this regard, applicable good manufacturing practice ("GMP") requirements, including dissolution specifications, are sufficient to ensure that there is no "dose dumping", and, thus, that the dosages provided are reliably within the wide range acknowledged by FDA to be generally recognized as safe and effective. In sum, FDA's apparent

⁶ See *Shalala v. Guernsey Mem. Hosp.*, 514 U.S. 87, 99 (1995) (interpretive rules "do not have the force and effect of law and are not accorded that weight in the adjudicatory process"); see also *American Mining Congress v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1111 (D.C. Cir. 1993) (noting that agency statements not subjected to notice and comment rulemaking are "vulnerable to attack" and cautioning agencies to "pay attention to facts and arguments submitted in derogation of any rule not supported by notice and comment, even as late as the enforcement stage").

conclusion that NDAs and ANDAs are the only regulatory avenue for single ingredient extended release guaifenesin products is far from settled.

3. A Prospective, Generally Available Announcement Is the Best Method for Communicating Changes in Agency Policy Impacting the Regulatory Status of Products Long Marketed Safely Without Modern-Day Approved Drug Applications

To avoid the serious concerns discussed above, the Agency should prospectively publish its decisions concerning the regulatory status of products marketed safely without modern-day approved drug applications, preferably in the *Federal Register*. In particular, whenever the Agency determines that a change in the status of unapproved products is warranted in light of the nature of the products, their marketing history, and the Agency's other priorities, the Agency should publish its conclusions in a generally applicable *Federal Register* notice, which also: (1) identifies the public health issues, if any, underlying the action, (2) identifies a process for manufacturers to secure approvals, (3) provides specific guidance concerning required applications and necessary studies, and (4) establishes a schedule for submission and approval of any required applications, the length of which should depend upon the nature of the Agency's specific requirements and the amount of time the Agency will require to review and approve the applications.⁷ Where a safety concern is not identified, products marketed at the time of FDA's notice should be permitted to remain on the market as long as their manufacturers conform to the requirements and timetables that have been set out in the notice.

Such a reasoned, orderly approach would address properly the multiple concerns discussed above. Specifically, this approach has the following advantages:

- is consistent with the Agency's past practices, CPG 7132c.02, and regulated industry's expectations;
- provides notice of the Agency's intentions to all affected manufacturers, resulting in fair and equitable treatment of similarly situated parties;

⁷ If the Agency changes its expectations about the need to seek NDA or ANDA approval for certain unapproved products while an unsolicited application is pending, in fairness to all manufacturers, the Agency should, as soon as possible and prior to approval of the pending application, publish its conclusions in a generally available notice, without reference to the pending application, if necessary to maintain the confidentiality of the application.

- avoids the appearance that the Agency had ceded its enforcement discretion to a private party;
- does not create an unwarranted monopoly or facilitate continuance of one;
- minimizes abrupt marketplace disruption;
- reduces the need for the Agency to interface with multiple manufacturers, thereby minimizing the burden on the Agency; and
- provides manufacturers a reasonable opportunity to challenge the Agency's conclusion about the status of the products concurrently with efforts to meet the Agency's new expectations, if possible.

Although FDA's failure to announce its new standards and expectations for approval of extended release guaifenesin products before now has already prejudiced other manufacturers, the resulting prejudice can be reduced by recognizing that the Adams approval does not remove FDA's authority and responsibility to craft an appropriate and efficient compliance program, such as the approach outlined above. FDA has wisely chosen to exercise its enforcement discretion in an orderly manner in the past and the same type of orderly, public approach is warranted here. By allowing all drug marketers a reasonable amount of time in which to secure FDA approval for their products or otherwise respond to a call for NDAs/ANDAs, fairness can be achieved without compromising the Agency's overall public health objectives. The Petitioners' proposed approach accomplishes FDA's goal of requiring approved applications for the marketing of these products without unfairly penalizing manufacturers who had no prior notice of this new requirement, creating a monopoly, or disrupting the marketplace.

C. Environmental Impact

The Petitioners claim a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31 (2002).

D. Economic Impact

Information under this section will be submitted upon request by the Commissioner.

E. Certification

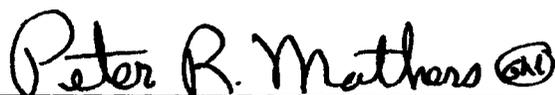
The Petitioners certify that, to their best knowledge and belief, this Petition includes all information and views upon which the Petition relies, and that it includes representative data and information known to the Petitioners which are unfavorable to the Petition.

 (SK)

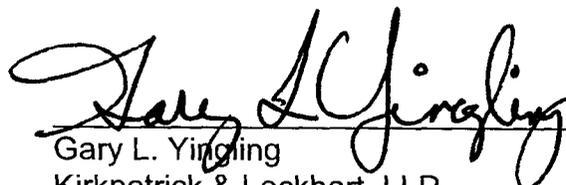
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U.S. Food and Drug Administration
5630 Fishers Lane, First Floor
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Rockville, Maryland 20852

Dear Sir or Madam:

We have attached four copies of a Citizen Petition and request that it be filed by your office.

One extra copy also is attached. Please date-stamp the copy as received and return it to my attention in the attached self-addressed Federal Express envelope.

Thank you for your attention to this matter. If you have any questions regarding this submission, please contact me at 202-778-9124.

Very truly yours,



Gary L. Yingling

02P-0483