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January 15, 2004

**VIA HAND DELIVERY**

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 161  
Rockville, MD 20852

Re: Docket No. 2003D-0478: Comments on Draft Guidance on Marketed Unapproved Drugs

Dear Sir/Madam:

Pursuant to the Food and Drug Administration's ("FDA's") October 23, 2003 notice in the Federal Register,<sup>1/</sup> Morgan Lewis submits these comments on the FDA's Draft Compliance Policy Guide on Marketed Unapproved Drugs ("Draft CPG"). Morgan Lewis is an international law firm that represents a broad range of manufacturers and marketers of pharmaceuticals sold in the U.S., including manufacturers and marketers of pre-1962 grandfathered<sup>2/</sup> and/or generally recognized as safe and effective ("GRASE") drugs<sup>3/</sup> without new drug approvals.

<sup>1/</sup> 68 Fed. Reg. 6072 (Oct. 23, 2003).

<sup>2/</sup> Grandfathered products are those products that entered the U.S. market prior to 1938 or 1962, and have remained essentially unchanged since that time. Pub. L. No. 75-717, § 201(p)(1), 52 Stat. 1040, 1042; Pub. L. No. 87-781, § 107(c)(4), 76 Stat. 788. These drugs are excepted from "new drug" provisions of the Federal Food, Drug, and Cosmetic Act.

<sup>3/</sup> Section 201(p)(1) and (2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(p)(1) and (2).

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The Draft CPG, which is intended to supersede the existing Compliance Policy Guide on the same topic,<sup>4/</sup> was issued to achieve two goals: (1) to clarify how the Agency intends to exercise its enforcement discretion; and (2) to emphasize that illegally marketed drugs must obtain FDA approval. We appreciate and understand these Agency goals, and support the Agency's plan to achieve its objectives "without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market."

We have several concerns, however, with the potential impact of the Draft CPG on those entities that are legally marketing, or reasonably believe that they are legally marketing, pre-1962 drugs that are grandfathered or GRASE. Our primary concern relates to three significant, substantive changes between the current CPG and the new draft document. Specifically, the new draft CPG: (1) incorporates significant changes involving the process for determining grandfathered and/or GRASE drugs; (2) adds a condition to further limit application of the 1938 and 1962 grandfather clauses; and (3) includes a new discussion concerning "de facto exclusivity," which will have important marketing consequences. As described further below, we believe that these changes could substantially affect both manufacturers and users of pre-1962 grandfathered and/or GRASE drugs, and, as such, trigger the need for notice-and-comment processes to ensure fair and deliberative review of all affected rights and interests. Part of this notice-and-comment review should involve an evaluation of whether FDA has overreached its statutory authority for certain of the changes proposed.

In addition to our comments on these significant new changes, we provide a discussion below regarding certain references in the draft document that raises concern under good guidance principles and should be deleted. We also request more meaningful discussion, and notice-and-comment debate, concerning the proposed prescription drug monograph process that Congress very recently has requested the Agency to further consider.

Our specific comments follow.

## **I. Certain Draft CPG Changes, If Not Removed, Require Notice and Comment**

### **A. Background**

The existing Compliance Policy Guide ("CPG") 7132c.02 for marketed new drugs without approved New Drug Applications ("NDAs") or abbreviated NDAs ("ANDAs") has a long history of application and interpretation.<sup>5/</sup> In order to understand and put into context administrative law

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<sup>4/</sup> FDA, Compliance Policy Guides, Marketed Unapproved Drugs Without Approved NDAs or ANDAs, Section 440.100 (CPG 7132c.02).

<sup>5/</sup> Id.

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concerns presented by the more significant changes to the new draft CPG, it is important to first follow the sequence of modifications made to the CPG over the years.

1. 1976: In response to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (“Act”), requiring that new drugs be proven effective as well as safe to obtain FDA approval, the FDA initiated the DESI program -- an evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The first CPG addressing marketed new drugs without approved NDAs or ANDAs issued on October 6, 1976 and initially covered only those products subject to the DESI program.
2. Mid-1980s: In response to adverse reactions in infants to a Vitamin E intravenous injection (E-Ferol) in the mid-1980s, and related congressional concerns, the FDA revised and extended the CPG to address for the first time marketed drugs without NDAs or ANDAs, not covered by the DESI review. This 1980s version of the CPG remains in effect today. As with the original document, this CPG continues to establish in Part A, the priorities for enforcement action against those drugs “for which final determinations [of new drug status] have been made” under the DESI review. In Part B, however, the CPG also acknowledges that final determinations have not been made for other pre-1962 drugs not included in the DESI program. For this Part B category of drugs, the CPG states that “procedures are being implemented so that these drugs will be evaluated to determine whether the new drug provisions are applicable to them” or whether they are exempt from new drug provisions because they are grandfathered or GRASE.

In describing the conditions that define and limit application of the 1938 and 1962 grandfather clauses of the Act, the CPG states that drugs should not differ from earlier products in formulation, dosage or strength, dosage form, route of administration, indications for use, or intended patient population.

The CPG includes no discussion of de facto exclusivity.

3. The New Draft CPG: The latest draft revision of the CPG includes three significant differences from the current CPG.

The first set of changes relates to the process for determining the grandfathered or GRASE status of a drug. Specifically, the Draft CPG does not refer to, or provide for, the implementation of procedures to evaluate

pre-1962 drugs believed to have grandfathered or GRASE status. Also, for the first time, the CPG presumes the illegality of marketed grandfathered and GRASE drugs.

The second difference is that the Draft CPG includes more specific language regarding changes that will cause a drug to lose its grandfathered status. In addition to formulation, dosage or strength, dosage form, route of administration, indications, and intended patient population, the Draft CPG includes “method of manufacture,” not listed in the existing CPG or in the statute.

Finally, the Draft CPG provides a form of de facto market exclusivity to the first marketer of a pre-1962 drug that obtains new drug approval. In order to provide an incentive to marketers of pre-1962 drugs to file new drug approval applications, the Draft CPG indicates that FDA will apply enforcement priority against similar products to a newly approved pre-1962 drug (following a grace period to be determined by the Agency), thus providing a form of exclusivity to the marketer of the newly approved drug.

Each of these changes warrant notice-and-comment review for the reasons stated below.

**B. Process Changes**

As noted above, two longstanding Agency policies may be interpreted as having been revoked by the new Draft CPG: (1) the Draft CPG removes references to the implementation of procedures that would specifically review the status of pre-1962 grandfathered and GRASE drugs; and (2) the draft guide presumes the illegality of all those products. Both policy changes are of serious concern for marketers of legitimate pre-1962 grandfathered and/or GRASE drugs, who have come to rely on the historical CPG to guide their marketing over the decades.

Since the mid-1980s, the existing CPG has provided that “[p]rocedures will be implemented” to evaluate pre-1962 drugs not covered by an NDA “to determine whether the new drug provisions are applicable to them [or not].” No such reference is included in the new draft document. The removal of this reference, and the suggestion that status of pre-1962 drugs will be determined in the enforcement context, leads to the clear assumption that determinations will not permit the implementation of a systematic, objective GRASE/grandfather review process, as contemplated by the terms of the existing CPG. Moreover, under the new draft, enforcement could be triggered automatically for a legitimate marketer of a grandfathered or GRASE drug, if a marketer of a similar grandfathered or GRASE product decides to file an NDA. Because many adverse

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consequences attach to enforcement proceedings, companies may simply forgo their legitimate grandfather or GRASE rights and interests, to avoid the risks of such enforcement exposure.

In the Draft CPG, the FDA further states that, “there are few, if any, drugs on the market that are actually entitled to grandfather status . . .” and “the Agency believes it is very unlikely that any currently marketed drug is grandfathered or is otherwise not a new drug.”<sup>6/</sup> This presumption of illegality also carries with it profound implications for companies’ rights and interests. With these new references, companies that historically have relied on the 1938 and 1962 grandfather clauses and the statutory definition of “new drug” to except them from the new drug provisions of the Act, are fearful of several significant adverse consequences. The first is the most obvious -- that FDA’s draft nullifies a legitimate market option afforded companies under Section 201(p)(1) and (2) of the Act. These new statements also effectively deprive marketers of an objective, non-biased review of the GRASE or grandfathered status of their drugs. Additionally, as a matter of process, it is clear the evidentiary burden would shift with this new standard. Rather than FDA bearing the burden of proving the adulteration of such drugs, the manufacturer would need to overcome the presumption that its pre-1962 grandfathered or GRASE drug is illegal -- and do so in the enforcement context. Finally, there are significant product liability implications presented by this new Draft CPG language. Specifically, the language could be used inappropriately in tort litigation as an FDA stipulation of illegality and, thus, as evidence of negligence or even negligence *per se*.<sup>7/</sup>

As noted above, we are requesting that the FDA revise the Draft CPG in these two areas, so that the process for determining pre-1962 drug status tracks more consistently with the existing CPG. Entities marketing pre-1962 drugs with a reasonable basis for grandfathered or GRASE exceptions, should continue to have the opportunity to support the status of these products through “implemented procedures” other than new drug review and enforcement proceedings.

If, however, the Draft CPG is not revised to continue to permit the implementation of procedures to determine status, and if the presumption of illegality is not removed, these changes should proceed through notice-and-comment processes. Notice-and-comment processes, we believe, are needed for three reasons: (1) the policies substantially affect the rights and interests of manufacturers of covered products; (2) both the existing and Draft CPG are binding on

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6/ FDA, Compliance Policy Guide, Marketed Unapproved Drugs Without Approved NDAs or ANDAs, Section 440.100 (CPG 7132c.02) (emphasis added).

7/ See MacDonald v. Ortho Pharmaceutical Corp. 394 Mass. 131, 475 N.E.2d 65, cert. denied, 474 U.S. 92(1985) (noncompliance with FDA requirements held to be evidence of negligence); Orthopedic Equipment v. Eusstler, 276 F.2d 455, 461 (4th Cir. 1960) (violations of FDA requirements held to be negligence *per se*).

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manufacturers of covered products, and, thus, have the force and effect of substantive rules;<sup>8/</sup> and (3) regardless of the document's substantive rule status, the existing CPG has long been relied upon by the regulated industry in the conduct of its business, and for that reason alone, should trigger notice-and-comment procedures under administrative law principles. Each of these administrative law reasons supporting the need for notice-and-comment protections, is described below.

1. The Substantial Impact of the Existing and Draft CPG on the Rights and Interests of Affected Parties

The existing CPG "substantially affect[s]" the rights and interests of manufacturers of pre-1962 drugs who legitimately believe their products to have grandfathered or GRASE status, and also believe that "procedures [will be] implemented" before "final determinations" on status are made.<sup>9/</sup> For two decades, marketers of legitimate pre-1962 grandfathered and GRASE drugs have relied on FDA's promise of an implemented GRASE/grandfather evaluative process in continuing to market their drugs and, in many cases, have built businesses around these products. The Agency further has strengthened this reliance over the years, by accepting registration and listing forms for these products, conducting inspections of facilities manufacturing these products, and undertaking the other usual regulatory oversight activities associated with lawfully marketed products. Consistent with administrative law principles, therefore, notice-and-comment procedures are required to address the substantial impact of the Draft CPG changes on the rights and interests of manufacturers and marketers of these affected products.<sup>10/</sup>

2. The Binding Effect of the Draft CPG on Manufacturers of Covered Drugs

The Administrative Procedure Act ("APA") defines a "rule" as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy."<sup>11/</sup> Rules can be substantive, interpretative (or legislative), statements of policy, or rules of organization, procedure, or practice.<sup>12/</sup> Courts have stated that "the primary difference between a substantive rule [which is subject to notice-and-comment rulemaking requirements,] and a general

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<sup>8/</sup> 5 U.S.C. § 553(a).

<sup>9/</sup> See Cal-Almond, Inc. v. United States Department of Agriculture, 14 F.3d 429 (9th Cir. 1993); Batterton v. Marshall, 648 F.2d 694, 702-03 (D.C. Cir. 1979) (exemption from notice-and-comment requirements "cannot apply, . . . where the agency action trenches on substantial private rights and interests"); Vigil v. Rhoades, 746 F. Supp. 1471 (D.N.M. 1990).

<sup>10/</sup> See Batterton v. Marshall, 648 F.2d 694, 702-03 (D.C. Cir. 1979).

<sup>11/</sup> 5 U.S.C. § 551(4).

<sup>12/</sup> See, e.g., Thomas v. State of New York, 802 F.2d 1443, 1446-47 (D.C. Cir. 1986).

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statement of policy ... turns on whether an agency intends to bind itself to a particular legal position.”<sup>13/</sup>

The newly issued Draft CPG is unequivocally binding for two reasons: (1) it announces emphatically FDA’s binding authority to take enforcement action against marketed pre-1962 new drugs without approved NDAs or ANDAs; and (2) it presumes the illegality of these drugs, notwithstanding any asserted grandfathered or GRASE status. Concerning enforcement, the Agency states its intent to enforce against drugs “that present a challenge to the drug approval or OTC monograph system, directly or indirectly.” The Draft CPG further states in bold type that usual procedures followed for noncompliant pre-1962 drug products may not be followed (e.g., requesting voluntary compliance, issuing an untitled or Warning Letter, issuing a notice of action in the Federal Register), and that FDA will proceed to determine the status of a particular drug on a case-by-case basis in the enforcement context. Thus, the Draft CPG clearly announces the binding nature of FDA’s decisions and conclusions regarding pre-1962 drugs without approved NDAs or ANDAs.

As to the Draft CPG’s presumption of illegality, as described at I.B. above, the Appendix to this document clearly states FDA’s position that “it is very unlikely that any currently marketed product is grandfathered or is otherwise not a new drug.” Such statement, if published in a final Agency document, will be viewed by outside interests as the Agency’s binding position. Relatedly, the mere publication of FDA’s presumption will adversely affect the ability of marketers of legitimate grandfathered or GRASE products to support their legal status. Notice-and-comment procedures must be followed, therefore, to address the binding nature of these significant changes to the CPG.

### 3. Industry’s Longstanding Reliance on the Existing CPG

Even if the Agency does not consider the existing and/or Draft CPG to require notice-and-comment based on their status as substantive rules, industry’s long reliance on the existing CPG in the conduct of business, is reason alone to require notice-and-comment protection. Under administrative law principles, when an agency has imparted advice or issued guidance concerning its interpretation of statutory and/or regulatory requirements,<sup>14/</sup> and that interpretation has long been relied upon by regulated companies in the advancement of their business, the agency’s

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<sup>13/</sup> Syncor International Corp. v. Shalala, 127 F.3d 90, 94 (D.C. Cir. 1997); United States Telephone Association v. FCC, 28 F.3d 1232 (D.C. Cir. 1994).

<sup>14/</sup> See Clarry v. United States, 85 F.3d 1041, 1048 (2d Cir. 1996) (stating that interpretative rules clarify an existing statute or regulation), citing White v. Shalala, 7 F.3d 296, 303 (2d Cir. 1993).

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advice or guidance cannot be changed without proceeding through notice-and-comment procedures.<sup>15/</sup>

It is well established that regulated entities are entitled to “know the rules by which the game will be played.”<sup>16/</sup> As the court stated in Alaska Professional Hunters Association, an agency may have “doubts about the wisdom of the [current] regulatory system,” but that “does not justify disregarding the requisite procedures for changing that system.”<sup>17/</sup> The removal of FDA’s commitment to implement procedures for the orderly evaluation of the legal status of pre-1962 unapproved drugs, is more than a clarification. This loss of a process, combined with threatened enforcement action, and presumption of illegality, puts marketers of drugs believed to be grandfathered or GRASE in a far more precarious position than the position they have relied on for the past twenty years. We are aware, for example, that there are marketers of such drugs that, although they believe their products to have “grandfather” status, are now considering pulling those drugs from the market, because of the costs and resources associated with either defending their legal status in an enforcement proceeding, or preparing an NDA. Notice-and-comment procedures are necessary, therefore, to ensure that manufacturers who have long relied on the existing CPG, are permitted the opportunity to address and debate these significant changes.

Thus, for each of these reasons -- individually and collectively -- affected parties deserve full and formal notice-and-comment procedures, before the significant new CPG changes are made. Informal comments to a draft guidance are not sufficient under administrative law principles. Only with on-the-record review, will companies long vested in FDA’s initially stated system, be assured adequate protection of their rights and interests.

**C. New Substantive Limitations on the 1938 and 1962 Grandfather Clauses**

In support of its statement that there are few, if any, grandfather drugs on the market, the Appendix to the Draft CPG states that currently marketed drugs likely differ from previous

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<sup>15/</sup> See Alaska Professional Hunters Association v. FAA, 177 F.3d 1030, 1033-34 (D.C. Cir. 1999) (“[o]nce an agency has given its regulations a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment”); Paralyzed Veterans of America v. D.C. Arena, 117 F.3d 579, 586 (D.C. Cir. 1997) (“[o]nce an agency gives its regulation an interpretation, it can only change that interpretation as it would formally modify the regulation itself: through the process of notice and comment rulemaking”).

<sup>16/</sup> Alaska Professional Hunters Association, 177 F.3d at 1035 (stating that “[t]hose regulated by an administrative agency are entitled to ‘know the rules by which the game will be played,’” quoting Holmes, Holdsworth’s English Law, 25 Law Quarterly Rev. 414 (1909)).

<sup>17/</sup> 177 F.3d at 1035.

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versions in some respect, “such as formulation, dosage, or strength, method of manufacture, dosage form, route of administration, indications, or intended patient population.”<sup>18/</sup> The two statutory grandfather clauses, however, do not refer to changes in “method of manufacture” as altering a drug product’s grandfather status, nor does the existing CPG. Specifically, the 1938 grandfather clause states that a drug is not a “new drug” if:

at any time prior to [June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and at such time its labeling contained the same representations concerning the conditions for use.<sup>19/</sup>

The 1962 grandfather clause states that, for any drug:

which, on [October 9, 1962] (1) was commercially used or sold in the United States, (2) was not a new drug as defined by section 201(p) of the basic Act as then in force [the 1938 law], and (3) was not covered by an effective application under section 505 of that [1938] Act, the amendments to section 201(p) by this [1962] Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.<sup>20/</sup>

Reflecting this statutory authority, the current CPG provides that, to avoid enforcement, a pre-1962 drug without an approved NDA or ANDA, should not differ from a drug covered by Part B of the CPG (*i.e.*, a grandfathered or GRASE drug) in formulation, dosage or strength, dosage form, route of administration, indications for use, or intended patient population.

Thus, the 1938 and 1962 clauses and CPG all require that a grandfathered drug not have different representations in labeling concerning conditions of use. Although courts have further interpreted the “new drug” aspects of the grandfather clauses over the years, they have -- like the statute and

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<sup>18/</sup> Draft CPG (Appendix) at 9 (emphasis added).

<sup>19/</sup> Pub. L. No. 75-717, § 201(p)(1), 52 Stat. at 1042 (emphasis added).

<sup>20/</sup> Pub. L. No. 87-781, § 107(c)(4), 76 Stat. 788. (emphasis added).

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existing CPG -- focused on the drug's composition<sup>21/</sup> and drug labeling,<sup>22/</sup> and thus far have not ruled on issues involving manufacture.

Because these statutory provisions and related court interpretations have not extended grandfathered conditions to method of manufacture, and because method of manufacture represents a significant departure from conditions stated in the existing CPG, this type of proposed extension of the law should proceed through notice-and-comment protection, for the administrative law reasons cited at I.B. above.

#### **D. New "De Facto Market Exclusivity"**

In the Draft CPG, FDA seeks to motivate marketers to file NDAs by promising a form of "de facto market exclusivity."<sup>23/</sup> When a company obtains approval of an NDA for a product that other companies are marketing without approval, in an effort to provide incentives for companies to file applications, the Agency indicates that it will be more likely to take enforcement action against identical or similar drugs because "they present a direct challenge to the drug approval system."<sup>24/</sup> The Draft CPG states that FDA normally intends to allow a grace period of one year from the date of approval before it will initiate enforcement action, although the length of the grace period could vary depending on safety and other issues. The Agency suggests that "[t]he shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval."<sup>25/</sup>

Congress has set forth very specific requirements for awards of drug market exclusivity in the orphan drug legislation, the Hatch-Waxman amendments, and pediatric amendments to the Federal Food, Drug, and Cosmetic Act.<sup>26/</sup> Unlike these forms of exclusivity, the FDA's new concept of "de facto market exclusivity" has no statutory authority. A "de facto market

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<sup>21/</sup> See, e.g., USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655, 663 (1973); Rutherford v. United States, 616 F.2d 455, 457 (10th Cir.), cert. denied, 449 U.S. 937 (1980); United States v. Alcon Laboratories, Inc., 636 F.2d 876, 879 (1st Cir.), cert. denied, 451 U.S. 1017 (1981).

<sup>22/</sup> See, e.g., United States v. 1,048,000 Capsules, More or Less, 347 F.Supp. 768, 770 (S.D. Tex. 1972), aff'd on other grounds, 494 F.2d 1158 (5th Cir. 1974); Alcon Laboratories, Inc., 636 F.2d 876, 879 (1st Cir. 1981).

<sup>23/</sup> Draft CPG at 5.

<sup>24/</sup> Id.

<sup>25/</sup> Id.

<sup>26/</sup> Section 527 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 360cc; Sections 505(c)(3)(D), (j)(5)(D) of the FFDCA, 21 U.S.C. §§ 355(c)(3)(D), (j)(5)(D); Section 505A of the FFDCA, 21 U.S.C. § 355a.

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exclusivity” period, which would be determined by the length of time FDA determines to exercise its enforcement discretion, presents the potential for gamesmanship when there are multiple, competing pre-1962 drugs. For example, one company, even if it believes there is a legitimate basis for grandfathered status, may seek to be the first to file an NDA, in order to obtain “de facto market exclusivity” and the ability to charge a single-source price for its products. The Draft CPG thus could substantially impact the marketing of legitimate grandfathered or GRASE drugs and potentially raise public health and supply/cost concerns.

Given these potential marketing and public health consequences, we request that the Draft CPG be revised to eliminate any provision for de facto market exclusivity, until the statutory authority for such a proposal, and the public health and economic impact of exclusivity, can be considered under appropriate notice-and-comment procedures. As with the “method of manufacture” amendment, this exclusivity concept effectively extending the law, requires notice-and-comment protections for the administrative law reasons noted at Section I.B above.

**E. Reexamination of Statutory Authority for FDA’s Proposed Changes as Part of Notice-and-Comment Processes**

Part of the reason that notice-and-comment protections are needed, is that several of the changes proposed by FDA appear to exceed and/or contravene existing statutory authority. Although questions of authority are mentioned in passing above, we discuss these concerns again separately, because they deserve separate attention and response from the Agency. Specifically, the presumptive illegality of grandfathered and/or GRASE drugs, in contravention of Section 201(p)(1) and (2) of the Act; the additional “method of manufacture” limitation to the 1962 and 1938 grandfather clauses; and the new “de facto market exclusivity” proposal, should all be evaluated as to whether they have proper statutory authority under existing law. We request that, pursuant to notice-and-comment procedures, these concerns be specifically addressed.

**II. The Draft CPG Includes Commentary on the Existence of Pre-1962 Grandfathered and GRASE Drugs, Contrary to Good Guidance Principles**

Attached to the Draft CPG is an Appendix that provides a brief history of the FDA marketing approval requirements and the various categories of pre-1962 drugs. In the section captioned “Prescription Drug Wrap-Up,” the Agency briefly describes the 1938 and 1962 grandfather clauses. As noted above, the Appendix states that the courts have very narrowly construed the grandfather clauses and that “[t]he FDA believes that there are few, if any, drugs on the market that are actually entitled to grandfather status” (emphasis added), because drugs on the market have likely changed in certain respects from the pre-1938 or pre-1962 versions. Similarly, the Appendix describes the GRASE criteria, stating that these criteria have been construed very narrowly by the courts, and that “the Agency believes it is very unlikely that any currently marketed product is grandfathered or is otherwise not a *new drug*” (emphasis added).

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Other than its general reference to changes likely made to drugs over the years and to court rulings for specific drugs, the FDA provides no evidence or examples supporting these sweeping conclusions. To our knowledge, no systematic review of the facts and circumstances for the thousands of drugs affected by these statements, has occurred thus far.

We request that, consistent with good guidance principles, the CPG and any Appendix to that document should be stated as concisely as possible, and avoid non-constructive commentary that is not based on careful review of case-by-case facts. Inclusion of speculative commentary on grandfathered or GRASE drugs in an Agency compliance/enforcement document, is unfair to marketers of these products for a number of reasons. As noted above, such statements effectively nullify an express legislative intent that grandfathered and/or GRASE drugs are permissible.<sup>27/</sup> These statements, combined with the loss of an orderly procedure to determine whether drugs are grandfathered and/or GRASE, also effectively deprive marketers of an objective, non-biased review of the status of their drugs. The commentary likewise unfairly shifts the evidentiary burdens that would otherwise exist in an enforcement proceeding against the products (i.e., manufacturers would need to overcome the burden of presumptive illegality). Finally, the references create unnecessary and significant tort litigation exposure concern -- a concern that is particularly inequitable since the comments made by the Agency appear not to rest on drug-specific facts and circumstances. For all of these reasons, we respectfully urge the removal of this non-helpful commentary from any final version of a document that issues.

### **III. FDA Should Provide Notice and Comment Mechanisms to Permit Public Debate on Least Burdensome Procedures to Evaluate Grandfathered or GRASE Drugs**

Finally, as FDA considers continuing its CPG commitment to implement evaluative procedures for determining the status of pre-1962 grandfathered or GRASE drugs, we ask the Agency to respond in notice-and-comment form to Congress' request that there be a prescription monograph process established for this purpose. As the Agency is aware, just last year, Senate Appropriators requested the following:

PRESCRIPTION DRUG MONOGRAPH SYSTEM -- The Committee is aware of interest in the establishment of a monograph system for prescription drug products that have been marketed to a material extent and for a material time without apparent safety or efficacy problems and do not have premarket approval. FDA currently regards these products as "DESI" (Drug Efficacy Study Implementation) or "DESI-II" products for compliance purposes. Such a monograph system would be modeled after the Agency's

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<sup>27/</sup> Section 201(p)(1)-(2) of the FFDCA, 21 U.S.C. § 321(p)(1)-(2).

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system for over-the-counter pharmaceuticals that was established 30 years ago for products that were similarly generally recognized as safe and effective due to their long history of safe and effective marketing. The Committee is sympathetic to those who advocate such a monograph system, but recognizes that review of a proposal to establish such a system falls under the jurisdiction of the Health, Education, Labor, and Pensions Committee. However, in an effort to start the dialogue, the Committee directs FDA to prepare a report for the Committee on Appropriations and the Committee on Health, Education, Labor, and Pensions regarding the feasibility and cost of such a new monograph system for prescription drug products as described above. In the meantime, the Committee believes that enforcement resources regarding pharmaceutical products should be dedicated to activities that are most likely to improve the public health.<sup>28/</sup>

The House Committee likewise made a similar form of request:

PRESCRIPTION DRUG MONOGRAPH SYSTEM -- The Committee requests a report from FDA regarding the feasibility and cost of a new monograph system for prescription drug products that have been marketed to a material extent or for a material time without a premarket approval, provided such products are without apparent safety or efficacy problems. Enforcement resources regarding pharmaceutical products should be dedicated to activities that are most likely to improve public health.<sup>29/</sup>

Consistent with these congressional statements of intent, we respectfully request that the Agency permit more specific public dialogue and debate of this proposal, through written notice-and-comment processes.

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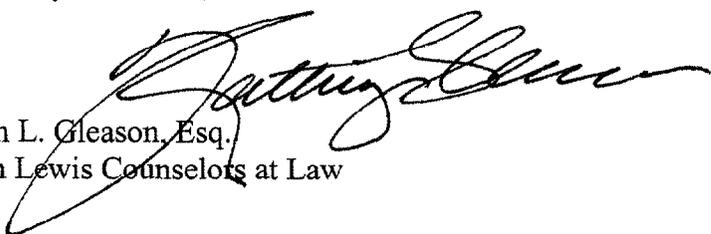
<sup>28/</sup> Senate Agriculture Appropriations Report 108-107 (July 17, 2003) at 157.

<sup>29/</sup> House Agriculture Appropriations Report 108-193 (July 9, 2003) at 86.

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We appreciate the opportunity to submit these comments on the Draft CPG and look forward to FDA's responses to these concerns.

Respectfully submitted,

  
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