PATTON BOGGS LLP
ATTORNEYS AT LAW

2550 M Street, NW
Washington, DC 20037-1350
202-457-6000

Facsimile 202-457-6315
www.pattonboggs.com

December 26, 2006

Paul D. Rubin
202-475-5646
prubin@pattonboggs.com

VIA ELECTRONIC FILING

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville MD 20852

Re: Docket 1978N-0065: Skin Bleaching Drug Products for OTC Human Use (RIN 0910-AF53)

Dear Sir or Madam:

Patton Boggs LLP ("Patton Boggs") respectfully submits these comments to the Food and Drug Administration ("FDA" or "Agency") to address safety and efficacy-related issues associated with over-the-counter ("OTC") and prescription skin bleaching drug products.

For the reasons set forth below, Patton Boggs strongly supports the Agency's proposed rule and further believes immediate steps should be taken to remove from the market unapproved prescription skin bleaching drug products that have never been reviewed for safety or efficacy by the FDA.

Currently, we are aware of only one FDA-approved skin bleaching prescription drug product containing hydroquinone, Tri-Luma® Cream, which was approved by the FDA on January 18, 2002 (NDA 21-112)[1]. All other prescription hydroquinone-containing drug products on the market have never been approved by the FDA for safety or efficacy. Moreover, due to the absence of enforcement, the companies marketing these products have the unfettered ability to make claims that far exceed those permitted for Tri-Luma® or OTC drugs currently marketed pursuant to the OTC Drug Review. Without FDA-enforcement, these companies not only have a competitive advantage over companies that participate in the NDA process, but they also jeopardize the health and safety of consumers.

[1] Tri-Luma® Cream, a combination product containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide, has been approved for the treatment of melasma. To our knowledge, Tri-Luma® Cream was the first, and remains the only, prescription hydroquinone product (either as a single entity or as a combination product) to be approved by the FDA.

78N-0062 C62

Therefore, in the context of the OTC skin bleaching monograph, it is imperative that the FDA not only state that an NDA is required for skin bleaching drugs, but also that the Agency actively enforce against companies that do not comply with this requirement - and in particular against those prescription skin bleaching drugs that are already on the market in the absence of FDA approval. The FDA's failure to take action to remove these products from the market not only would undermine the purpose of the proposed rule, but it would also weaken the integrity of the Agency's drug approval process and potentially subject consumers to the very health concerns this rule is intended to help them avoid.

I. The FDA's Proposed Rule Appropriately Restricts OTC Skin Bleaching Drugs to Prescription-Only Status

The Agency has proposed a rule that would classify OTC skin bleaching drug products as not generally recognized as safe and effective ("GRASE"), misbranded, and new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 321(p)).[2] Under the rule, skin bleaching drug products would be restricted to prescription use only and would no longer be available OTC. Specifically, manufacturers of OTC skin bleaching products would no longer be permitted to sell their products OTC once they deplete inventories in existence when the rule goes into effect, and would be required to obtain an approved NDA if they wish to continue to market their product(s) by prescription. We strongly support this proposal.

A. Potential Safety Concerns Associated with Skin Bleaching Drugs Containing Hydroquinone Make Prescription-Only Status Necessary

Under the FFDCA, a drug must be prescription-only where there are significant safety concerns making over-the-counter status inappropriate. Specifically, section 503(b)(1) of the FFDCA provides:

> (b)(1) A drug intended for use by man which—
>
> (A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or
>
> (B) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug;

[2] 71 Fed. Reg. 51146 (Aug. 29, 2006).

> shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.[3]

In light of this statutory framework, skin bleaching drugs containing hydroquinone should clearly be available by prescription only. The FDA has already recognized that these drug products are associated with potential safety concerns. Specifically, in issuing its proposal, FDA reviewed significant data on the safety of hydroquinone and identified the following potential safety issues:

- Toxicology and carcinogenicity studies on orally administered hydroquinone have indicated "some evidence" of carcinogenicity in male and female rats and female mice. Based on this evidence, FDA cannot rule out the potential carcinogenic risk from topically applied hydroquinone in humans;

- Hydroquinone has been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1-2 percent;

- Fertility studies evaluated by the Environmental Protection Agency and reviewed by FDA showed varied results regarding hydroquinone's impact on fertility. Thus, FDA cannot make a final determination on hydroquinone's potential to impair fertility in animals or humans and has concluded that additional studies are needed to make a better assessment; and

- Hydroquinone is absorbed into human skin at a high rate (57%).[4]

In light of these potential safety concerns, we strongly believe that skin bleaching drug products meet the statutory standard for prescription-only status, and thus we strongly agree with the FDA's conclusion that all skin bleaching drug products should only be available via prescription and should not be used without physician supervision. Moreover, we strongly support the FDA's proposed requirement that all prescription skin bleaching drug products seek and obtain

---

[3] 21 U.S.C. § 353(b)(1).

[4] *See generally*, 71 Fed. Reg. 51146, *supra* n.1.

NDA approval. This process is the only way to ensure that drug formulations are both safe and effective.

B. The Risk/Benefit Ratio of Hydroquinone-Containing Skin Bleaching Drug Products Also Demands That They be Limited to Prescription-Only Status

Not only does the FFDCA mandate prescription drug status where there are safety concerns that can only be mitigated by the supervision of a physician, but FDA regulations also indicate that prescription-only status is required if a drug poses risks that outweigh its potential benefits. In the case of skin bleaching drug products, an examination of the risk/benefit ratio leads to the clear conclusion that these products must not be available over-the-counter.

FDA regulations explicitly state that "[t]he benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness."[5] Specifically:

> Safety for OTC use means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use, as well as low potential for harm which may result from abuse under conditions of widespread availability. Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. The benefit-to-risk ratio of a drug must be considered in determining both safety and effectiveness.[6]

In the preamble to its recent proposed rule, the FDA elaborated on the risk/benefit analysis, explaining, "Because the choice to use a drug is not considered an inadvertent exposure, risks may be outweighed by benefits, where they exist. Where the benefit appears low and use of the drug is proposed for an otherwise healthy target population, the risks should be minimal."[7] For OTC skin bleaching drug products, the Agency concluded that "there is no benefit to physical health that would justify the continued marketing of these products. . . . For these OTC drug products, the sole intended benefit would be to improve the user's appearance by bleaching the skin. The actual risk to humans from the use of hydroquinone has yet to be fully determined. There is, however, evidence of carcinogenicity related to hydroquinone in animals and disfiguring

---

[5] 21 C.F.R. § 330.10(a)(4)(iii).

[6] FDA Notice of Public Hearing: Over the Counter Drug Products, 65 Fed. Reg. 24704, 24704 (Apr. 27, 2000).

[7] 71 Fed. Reg. at 51152.

effects (ochronosis) in humans. Under these circumstances, the use of hydroquinone as an active ingredient in OTC skin bleaching drug products cannot be justified." [8]

We agree with the FDA's conclusion that in the case of skin bleaching drug products, the cosmetic benefit does not outweigh the potential, and as yet unknown, negative health effects posed by hydroquinone formulations. Thus, we strongly support the FDA's conclusion that the safety concerns posed by these products demand prescription-only status.

C. NDA Approval Should be Required for All Skin Bleaching Drug Products to Ensure that Such Products are Safe for Human Use

We strongly agree with the FDA's proposal that NDA's be required for skin bleaching drug products containing hydroquinone. FDA review and approval of specific drug products is the only way to ensure that these products are safe and effective. The FDA's NDA regulations require substantial evidence consisting of adequate and well-controlled investigations that a drug product subject to NDA approval will have the effect it purports or is represented to have.[9] In the absence of such investigations, assertions about the safety or efficacy of skin bleaching drug products containing hydroquinone are purely anecdotal. The regulations clearly delineate the characteristics of an adequate and well-controlled study, without making any reference to inclusion of anecdotal data as an acceptable methodology. In fact, the regulations provide that "[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered" in the decision to approve an NDA.[10] In the absence of well-controlled investigations, it is not possible to know whether these drugs are, in fact, safe and effective, or whether they are ineffective or even dangerous.

In the case of skin bleaching drug products containing hydroquinone, the FDA itself noted in the proposed rule that there is currently an absence of sufficient science to determine the actual risk to humans for the use of hydroquinone formulations in general. Research to date has identified a potential carcinogenic risk from topically applied hydroquinone in humans, but the FDA has not been able to make a "final determination on hydroquinone's potential to impair fertility, toxicology and carcinogenesis."[11]

---

[8] *Id.*

[9] 21 C.F.R. §§ 314.125(a)(4), (a)(5).

[10] 21 C.F.R. § 314.126(e).

[11] 71 Fed. Reg. at 51151.

In the absence of sufficient data and information documenting the safety of these specific products, there are a number of significant potential safety concerns, identified and discussed below, that warrant FDA's consideration. While the FDA has already identified potential safety issues posed by hydroquinone, there are also additional potential safety concerns regarding the inactive ingredients in these OTC products. Specifically, unapproved skin bleaching drugs containing hydroquinone may be formulated with other ingredients that could be toxic themselves or could produce toxic effects in combination with hydroquinone. For example, we understand that inactive ingredients may pose risks such as the following:

- Ingredients that appear on product labels as "inactive" may pose potential risks, including skin irritation, photosensitivity, contact dermatitis, allergenic effects, and/or toxicity concerns;

- Ingredients labeled as "inactive" may in fact have potential carcinogenic, estrogenic and other toxic effects;

- Ingredients in these products may enhance the skin's absorption of hydroquinone, thereby potentially increasing the risk that the hydroquinone may have unintended systemic effects; and

- The combinations of the ingredients in these products may have toxicological effects that differ from, and pose greater risk than, the effects of each ingredient alone.

In light of the above concerns, there is simply no way to know whether individual skin bleaching drug product formulations containing hydroquinone are safe and effective unless they are individually tested and reviewed through the NDA process.

II. FDA Should Actively Enforce Against Currently Marketed Prescription Skin Bleaching Drug Products Containing Hydroquinone That Are Marketed in the Absence of FDA Approval

We are encouraged that the FDA has recently begun to take enforcement action against a handful of unapproved prescription drugs, as it did earlier this month when it ordered firms to stop marketing unapproved drug products containing quinine.[12] We believe there is even a stronger

[12] *See* FDA Press Release, "FDA Advances Effort Against Marketed Unapproved Drugs: FDA Orders Unapproved Quinine Drugs from the Market and Cautions Consumers About "Off-Label" Use of Quinine to Treat Leg Cramps"

rationale for removing unapproved hydroquinone-containing prescription drugs from the market. As in the quinine situation, permitting hydroquinone-containing prescription drugs to remain on the market absent FDA approval creates the risk that these products will be marketed with claims far exceeding those permitted under the OTC drug review or even the prescription drug approval process. Unlike the quinine situation, however, a decision not to take enforcement action against unapproved prescription hydroquinone products would directly conflict with the FDA's policy under the OTC drug review. To our knowledge, there has never been an analogous situation where companies could subvert the OTC drug review process and threaten the integrity of the drug approval regime by ignoring an NDA mandate issued by the FDA pursuant to the OTC Drug Review.

If the FDA's proposed requirement that skin bleaching drug products receive FDA approval to enter or remain on the market is to have any meaning at all, the Agency must engage in active enforcement against companies that have failed to submit an NDA. In its proposed rule, the FDA specifically stated that it "intends to consider all skin bleaching drug products . . . to be new drugs requiring an approved new drug application (NDA) for continued marketing."[13] There is no greater threat to the integrity of this regulation or the drug approval process than an express demand by the Agency for approval that is not backed by strong enforcement.

Thus, the FDA must actively enforce against skin bleaching products that enter the market without going through the NDA process. Moreover, and perhaps more importantly, the FDA must take immediate steps to enforce against the numerous companies that are already marketing hydroquinone-containing skin bleaching prescription drug products without FDA approval. These unapproved "new drugs" have never been evaluated by the FDA for safety and effectiveness. In fact, to our knowledge, the only prescription hydroquinone drug product ever reviewed, and approved, by the Agency is the Tri-Luma® Cream combination product.

The FDA's failure to enforce immediately against these products will send the wrong message to companies subject to the new regulation. Companies that want to market skin bleaching products in the future will assume that an NDA is not really necessary; such companies may have the incentive to remain on the market in violation of the regulation to avoid the costs associated with the NDA process and to reap the profits associated with continued sales.

Failure to enforce immediately against companies that choose not to obtain an NDA creates a health and safety hazard for the public, raises serious questions regarding the presumed safety

---

(Dec. 11, 2006), *available at* http://www.fda.gov/bbs/topics/NEWS/2006/NEW01521.html (last visited Dec. 18, 2006).

[13] 71 Fed. Reg. at 51146 (emphasis added).

and efficacy of such products, and creates a disincentive for companies to seek FDA approval for new products.

A. Allowing Unapproved Prescription Drugs Containing Hydroquinone to Remain on the Market Undermines the FDA's Rationale for its Proposed Rule and Subjects Consumers to Potential Risk

The FDA is clear in its proposed rule that skin bleaching drug products are not GRASE and pose an as-yet-unmeasured risk to human health in light of preliminary research on the effects of hydroquinone. It is for these reasons that the Agency proposes to mandate prescription-only status and NDA approval for these drugs.

As discussed above, unapproved hydroquinone-containing skin bleaching prescription drug products, and their ingredients, pose potential safety concerns that warrant careful FDA review. These products have not gone through FDA's approval process, and it is unclear whether any safety evaluations have been conducted on them. It is our understanding that many of the ingredients contained in these unapproved prescription drugs may pose risks ranging from skin irritation to carcinogenicity. There is simply no way to know whether individual skin bleaching prescription drug products are safe unless their formulations are adequately tested through the FDA's drug approval process. This is precisely the goal behind FDA's proposed rule – to ensure that these skin bleaching drug products are given careful scrutiny by the FDA. Based on the risks these products pose – including the risks FDA has already identified – it is imprudent for the FDA to allow these drug products to stay on the market in the absence of FDA approval.

Moreover, failure to remove unapproved skin bleaching prescription drug products from the market undermines the very intent of the rule. The Agency is explicit and clear in mandating FDA-approval for skin bleaching drug products. The rule unambiguously states that skin bleaching drugs – whether currently marketed on a prescription or OTC basis – will be required to obtain an approved NDA in order to continue marketing:

> "Further, upon issuance of a final rule, FDA intends to consider all skin bleaching drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing."[14]

Given the Agency's clarity in requiring an approved NDA for a company to market a skin bleaching drug product, enforcement against skin bleaching prescription drug products on the market without FDA approval will be essential if the rule is to have any meaning at all. It simply

[14] 71 Fed. Reg. at 51146.

makes no sense to issue such a clear dictate and then allow companies to ignore it. Nowhere in the Federal Register notice does the FDA indicate that it will use its enforcement discretion and restrain from enforcing against these products. The FDA should thus cease exercising its enforcement discretion and should actively and strongly enforce against existing prescription products that are already on the market in the absence of FDA approval. Failure to do so not only subjects consumers' health and safety to excessive risk, but also completely undermines the FDA's stated goal of subjecting skin bleaching drug products to a full safety review and, as discussed below, threatens the integrity of the entire drug approval regime.

B. FDA's Compliance Policy Guide Requires Immediate Enforcement Action Against Unapproved New Drugs Containing Hydroquinone

The FDA has stated that enforcement against unapproved new drugs is necessary to maintain the integrity of the drug approval system. In June 2006, the FDA issued a guidance document, "Marketed Unapproved Drugs - Compliance Policy Guide" ("CPG").[15] In it, the Agency makes clear that firms marketing drugs requiring FDA approval must submit NDA's showing their drug products are safe and effective before marketing those products. The CPG outlines FDA's program for bringing unapproved drugs that require approval into the approval process. FDA has broad enforcement discretion, and gives highest priority to unapproved drugs that pose a risk to the public health, with enforcement priority also going to drugs that lack evidence of efficacy, constitute health fraud or threaten the integrity of the drug approval process.

In the CPG, the FDA states that drugs with potential safety risks, drugs that lack evidence of effectiveness, and fraudulent drugs "present direct challenges to the [drug approval and OTC monograph] systems" and that "[t]argeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health."[16]

As noted above, skin bleaching prescription drug products fall squarely within these categories and thus should be targeted by the FDA for strong and immediate enforcement. Failure to enforce against these drugs – when FDA has been explicit that approval will be required – will create a disincentive for companies to seek NDA approval, will send a message to companies that

---

[15] "Guidance for FDA Staff and Industry, Marketed Unapproved Drugs - Compliance Policy Guide: Sec. 440.100: Marketed New Drugs Without Approved NDAs or ANDAs" ("CPG 440.100") (June 2006), *available at* http://www.fda.gov/cder/guidance/6911fnl.htm (last visited, Nov. 12, 2006).

[16] *Id.*

they can blatantly ignore the Agency's dictates with no consequence, and will threaten the integrity of the entire drug approval process and OTC Drug Review.

1. **Enforcement is Essential if the Agency is To Further Its Stated Goal of Creating an Incentive for Companies to Seek NDA Approval**

In its CPG, as noted above, the FDA has indicated its desire to encourage companies to voluntarily comply with NDA requirements in order to benefit the public health. Yet, to the extent the Agency exercises broad discretion in enforcing against marketed unapproved drugs and permits such products to remain on the market, the FDA undermines this goal and in fact creates a disincentive for companies to seek approval.

First, the FDA's failure to require all companies to obtain NDA approval prior to marketing new drugs creates an enormous financial disincentive for companies to seek such approval. Obtaining NDA approval requires the expenditure of significant time and financial resources. Companies have no incentive to expend these considerable resources to seek and obtain NDA approval if they know they can simply place their products on the market and avoid FDA enforcement. It is entirely unfair and inappropriate to require companies that are willing to comply with the law to spend millions of dollars on clinical research and user fees, while companies that ignore the law are permitted to avoid these costs and to market their products without approval.

Particularly where the FDA has mandated that companies obtain FDA approval for their OTC skin bleaching drug products, the Agency should not permit these companies to market such products in the absence of FDA approval. Once the rule is finalized, no OTC drug product that is subject to the rule is supposed to be introduced to the market unless it is the subject of an approved NDA.[17] The purpose behind this rule is clear – to prevent drugs that have not demonstrated safety or efficacy from entering the stream of commerce. Yet this very purpose will be undermined – and the rule will make no sense at all - if companies already marketing skin bleaching drug products OTC can simply market their products as prescription products without submitting NDA's (as is currently the case with prescription hydroquinone-containing drugs).

If approval is required but the Agency exercises enforcement discretion, companies that comply with FDA requirements are penalized in that they become subject to considerable FDA scrutiny of labeling, claims, promotional materials, etc., while companies that choose to ignore the law are allowed to market their products in the absence of such constraints. To the extent the Agency allows these companies to market unapproved "new drugs" freely and without regulatory scrutiny, companies would have no incentive to comply with any regulatory requirements, and

[17] 71 Fed. Reg. at 51147.

the purpose behind this proposed rule, FDA's CPG, and the drug approval system would be undermined.

Therefore, we strongly encourage the FDA to finalize its proposed rule and to take prompt enforcement action against companies that introduce – or maintain – prescription skin bleaching drug products on the market without obtaining FDA approval.

2. Companies Readily Acknowledge the Risks Associated with the Marketing of Prescription Hydroquinone Drugs in the Absence of FDA Approval

The FDA has admitted that a lack of resources has prevented the Agency from addressing unapproved drugs in the past. Yet in the absence of enforcement, new entrants are emerging on a consistent basis. Companies are aware that the FDA is not taking enforcement against unapproved prescription skin bleaching drugs; these companies either incorrectly assume that they are not required to obtain an NDA, or they simply choose to ignore the FDA's drug approval requirements. Moreover, these companies are not afraid to acknowledge that they are marketing such drugs without approval.

For example, SkinMedica, Inc., which markets a prescription 4% hydroquinone skin bleaching drug product, readily admits in its public filings with the Securities and Exchange Commission that it is on the market in the absence of FDA-approval, and that FDA may disagree with its position that marketing without approval is permissible:

> Our EpiQuin Micro branded product has not been approved by the FDA. It contains the active ingredient hydroquinone at a 4% concentration and is sold on a prescription basis. We believe that EpiQuin Micro, as it is promoted and intended by us for use, does not require FDA approval, because it is generally recognized as safe and effective and thus exempt from being considered a "new drug." The FDA may take a contrary position. If the FDA were to do so, we may be required to seek FDA approval for EpiQuin Micro, market it as an OTC product or withdraw it from the market. In 1992, with the concurrence of the FDA, the industry initiated dermatologic metabolism and toxicity studies to fully support hydroquinone's OTC Category I status at a concentration of 1.5% to 2.0%. Notwithstanding the pendency or results of these tests, the FDA may elect to classify hydroquinone as a Category II ingredient. If hydroquinone is not maintained as a Category I or Category III ingredient, we might be required to cease marketing the prescription EpiQuin Micro branded product and could be subject to product liability claims. An adverse decision by the FDA on the safety of hydroquinone could harm our business, financial condition and results of

> operations. Even if the FDA determines that hydroquinone at 1.5% to 2% is generally recognized as safe and effective, this finding would not necessarily apply to our 4% hydroquinone product. Therefore, the FDA could require that we reformulate our product to 1.5% to 2% and sell it OTC or submit a new drug application for a 4% product. It is possible that we might not be allowed to continue to market our 4% product while we sought FDA approval.[18]

Other companies are also knowingly marketing prescription drug products at risk, in the absence of FDA approval. For example, one drug industry attorney recently a described the drug companies' perspective as follows: "I'll put a drug on market at no cost, make a quick buck and when they come after me, I'll shut down."[19] The attorney continued, "If the FDA does not get tough this will never end."[20]

In light of the above, failure to enforce against unapproved marketed skin bleaching products sends entirely the wrong message to companies. Instead, the FDA needs to send a clear message to industry that where premarket drug approval is required, compliance with the law is not optional. Without a clear pattern of enforcement against unapproved new drugs, the Agency will continue to send a signal to drug companies that they can ignore federal requirements and generate significant profits in the process.

3. Physicians Incorrectly Assume that All Prescription Drug Products - Including Skin Bleaching Drugs Containing Hydroquinone - Have Been FDA-Approved

In the absence of enforcement, physicians have been prescribing unapproved hydroquinone-containing skin bleaching drug products under the mistaken assumption that these products have undergone Agency review. In fact, a company-sponsored survey confirms that dermatologists mistakenly assume that all prescription drug products are FDA-approved. In this survey, 85% of the 165 dermatologists polled believed that the FDA has approved all marketed prescription drug products.[21] Clearly, based upon this survey, most dermatologists incorrectly assume that the drug

---

[18] SkinMedica, Inc., Securities and Exchange Commission Form S-1, Registration No. 333-124374 (April 27, 2005), at 72 (emphasis added).

[19] "As unapproved drugs come into spotlight... Drug Industry Lawyers Say 'DESI' System Broken, In Need Of Reform," Insidehealthpolicy.com (Oct. 30, 2006) (last visited Oct. 31, 2006).

[20] *Id.*

[21] *See* Attachment, Question 1. This survey of 165 dermatologists was conducted online between November 6, 2003 and November 11, 2003.

products they are prescribing to their patients are FDA-approved, and therefore safe and effective, simply because the products are being marketed in the United States.

As the FDA acknowledged when it proposed its current Compliance Policy Guide on Unapproved Marketed New Drugs, the belief by health care professionals and consumers that unapproved new drugs are safe and effective is not based on scientific evidence, but rather on anecdotal data. The Agency has indicated on numerous occasions, however, that anecdotal data are insufficient to establish drug product safety and/or efficacy. Rather, the only way to determine that these products are safe and effective is to subject them to the FDA's rigorous drug approval process.

Yet the unapproved prescription skin bleaching products currently on the market have not been subjected to this process. Specifically, the safety of their formulations has not been evaluated, and the safety of the actives and inactives in these products – as well as the combined effects of these ingredients – have not been thoroughly reviewed and deemed safe by the FDA. In fact, there is a lack of information regarding whether any safety evaluations have been conducted on these products.

Consumers and health care professionals have a significant interest in access to useful, thorough and truthful information about medical products. Therefore, doctors and consumers should not be left under the mistaken assumption that the drugs they prescribe have been subject to FDA's rigorous review and approval process, if in fact they have not. If the FDA designates skin bleaching products as prescription drugs and mandates that companies seek and obtain FDA approval for these products, it simply cannot, through lack of enforcement, allow skin bleaching drug products to remain on the market without obtaining an NDA. If the Agency fails to enforce, physicians will continue to prescribe, and consumers will continue to use, drugs they mistakenly believe to have been FDA-approved, when in fact there is no evidence to demonstrate that these drugs are safe and effective for their patients' use.

4. Marketed Unapproved Skin Bleaching Prescription Drug Products May Violate a Variety of Other Regulatory Requirements

In its Compliance Policy Guide 440.100, "Marketed Unapproved Drugs – Compliance Policy Guide,"[22] the FDA indicated that drugs that have not received FDA approval or that are not being marketed in accordance with the OTC drug review are unlawful. To address the problem of unlawful marketed unapproved "new drugs," FDA has indicated in the CPG that its highest

[22] "Guidance for FDA Staff and Industry, Marketed Unapproved Drugs - Compliance Policy Guide:, Sec. 440.100: Marketed New Drugs Without Approved NDAs or ANDAs" ("CPG 440.100") (June 2006), *available* at http://www.fda.gov/cder/guidance/6911fnl.htm (last visited, Nov. 12, 2006).

enforcement priorities include drugs with potential safety risks; drugs that lack evidence of effectiveness; drugs that present direct challenges to the new drug approval and OTC drug monograph systems; and unapproved new drugs that are also violative of the Federal Food, Drug, and Cosmetic Act in other ways.

In the case of prescription skin bleaching drug products that are already on the market, all of these conditions appear to be present. These drugs may pose significant potential safety concerns, as the FDA has already recognized, and to our knowledge they have never been reviewed for safety or efficacy. Moreover, companies are currently marketing unapproved skin bleaching prescription drug products in a manner that may also violate numerous other regulatory requirements.

To the best of our knowledge, the following companies, among others, have been marketing, and continue to market, prescription drug products containing 4% hydroquinone in the United States in the absence of FDA approval:[23]

- Obagi Medical Products, Inc. (Obagi Nu-Derm® System and Obagi-C™ Rx System)
- Medicis Pharmaceutical Corporation/Taro Pharmaceuticals U.S.A., Inc. (Lustra®, Lustra-AF® and Lustra Ultra™)
- SkinMedica, Inc. (EpiQuin™ Micro)
- Stiefel Laboratories, Inc. (Claripel™)
- Stratus Pharmaceuticals Inc. (Alphaquin HP® and Nuquin HP®)
- Valeant Pharmaceuticals International (Glyquin®)
- JSJ Pharmaceuticals (Aclaro®)
- Axia Medical Solutions (Dermesse™)
- Consolidated Midland Corp. (generic 4% hydroquinone cream)
- Ethex Corporation (generic 4% hydroquinone creams)
- Fougera E. & Co. (generic 4% hydroquinone cream)
- Glades Pharmaceuticals, LLC (generic 4% hydroquinone creams and gel)
- Pharma Pac, a service of H.J. Harkins Co, Inc. (generic 4% hydroquinone cream (repack))
- Qualitest Pharmaceuticals, Inc. (generic 4% hydroquinone creams)

---

[23] We understand that companies continually modify their products and formulations, and this list is therefore subject to change. Additional companies may be marketing unapproved 4% hydroquinone prescription drug companies, and the companies included in this list may have abandoned or reformulated their hydroquinone-containing prescription drug products.

- Breckenridge Pharmaceutical, Inc. (generic 4% hydroquinone cream)

Despite clear FDA requirements, many of these companies appear to be engaged in promotional and advertising practices for their hydroquinone prescription drug products that, in our view, should draw immediate enforcement under the Agency's current CPG.[24] As noted above, the FDA has already indicated, in CPG 440.100, that it intends to prioritize enforcement against companies marketing unapproved new drugs that also violate other Agency regulations:

> The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation and the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action.[25]

As noted above, and as discussed further, below, unapproved prescription drugs, including 4% hydroquinone prescription drug products, are already being marketed in ways that may violate numerous laws and regulations, and therefore enforcement should follow. Such marketing is a frontal challenge to the FDA's regulations, and in the case of skin bleaching drug products, it is a direct challenge to the Agency's proposed rule.

---

[24] In fact, the Agency has recently shown that it is willing to include "unapproved new drug" allegations when taking enforcement action against companies violating other FDA requirements. For example, on August 15, 2006, the Agency issued a Warning Letter to Actavis Totowa, LLC. While the focus of the Warning Letter was on the company's failure to comply with certain postmarketing Adverse Drug Experience (ADE) reporting requirements, FDA also noted the company's marketing of unapproved new drugs: "Based on our observations during the inspection and information submitted by your firm to comply with the drug listing requirements of Section 510(j) of the Act [21 U.S.C. § 360], your firm manufactures numerous prescription drug products without approved applications . . . These products appear to be unapproved new drugs introduced into interstate commerce in violation of section 505(a) of the Act [21 U.S.C. § 355(a)]. . . . You should take prompt action to correct all of the deficiencies discussed above."

[25] CPG 440.100, Section A.

a. **Marketers of Skin Bleaching Prescription Drug Products are Apparently Touting Ingredient Combinations that have Never Been Reviewed by the FDA and Should be Subject to Immediate Enforcement**

Although most prescription 4% hydroquinone products are labeled as single-ingredient products, we are aware that these drugs may have numerous ingredient combinations that have never been FDA-approved. For example, Obagi Medical Products, Inc. markets its Obagi Nu-Derm Sunfader™ product with the active ingredient combination of 4% hydroquinone, octinoate and oxybenzone. Similarly, Valeant Pharmaceuticals markets Glyquin® with a combination of hydroquinone, octocrylene, oxybenzone and avobenzone. In other products, it is often not clear which ingredients are active and which are not, as ingredients labeled as inactives are apparently being touted as actives.

Specifically, a number of the 4% hydroquinone prescription drug products currently being marketed in the United States appear to be formulated in conjunction with other ingredients - such as sunscreens, retinol, glycolic acid, and antioxidants - that are labeled as inactives but are being promoted as active ingredients.[26] Accordingly, such products are in essence combination 4% hydroquinone drug products which are not authorized under CPG 440.100. They are therefore subject to immediate FDA enforcement.

The FDA's concerns about hydroquinone do not necessarily preclude the introduction of either single-entity or combination 4% hydroquinone prescription products into the market. On the contrary, the FDA has approved such a prescription combination drug product, *after* the submission of an NDA and the opportunity to review the product and the supporting data to determine that all of the above concerns had been addressed.

It is our understanding that none of the unapproved 4% hydroquinone products on the market - whether single-ingredient or combination - has gone through this rigorous review process. Moreover, to the best of our knowledge, none of the manufacturers of these products has submitted any of the types of studies or data the FDA has required to ensure safety and efficacy, despite the fact that some of these products may combine 4% hydroquinone with numerous other active ingredients and appear to be touted for long-term use. Thus, we strongly urge the FDA to remove these products from the market immediately.

---

[26] Moreover, many of these companies appear to be making claims that these inactive ingredients provide efficacy benefits, and are therefore violating FDA regulations in clearly featuring "inert inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation." *See* 21 C.F.R. § 201.10(c)(4).

b. **Unapproved 4% Hydroquinone Prescription Drug Products Appear to be Making a Wide Range of Promotional Claims That Should Subject Them to Immediate FDA Enforcement Under CPG 440.100**

An advertisement is false, lacking in fair balance or otherwise misleading if it contains a representation or suggestion not approved or permitted for use in labeling, that a drug is useful in a broader range of conditions than has been demonstrated by substantial evidence or clinical experience.[27] Despite these regulatory requirements, many of the unapproved 4% hydroquinone products on the market are marketed with a wide variety of unapproved claims – including claims touting unapproved ingredient combinations, claims promoting inactive ingredients as active ingredients, claims broadening indications for use, and claims promoting new dosages or drug delivery systems.[28] To our knowledge, none of these products has been approved to make such claims.[29] Thus, it is critical that the FDA, and specifically, the Division of Drug Marketing and Advertising Compliance ("DDMAC"), enforce against these products.

In particular, as noted above, one of the key factors the FDA used to determine that skin bleaching drug products should not be available over-the-counter is the products' risk/benefit ratio. The only way to assess the risk/benefit ratio is to examine the drug's potential risk against its intended benefit, as it is claimed by the manufacturer. OTC monograph drugs are limited to the specific claims – and thus the intended benefits - that are authorized under the relevant monograph. Prescription drugs, on the other hand, are restricted to intended uses as approved in the drug's NDA. The only way for the FDA to assess the intended benefit for these drugs,

---

[27] *See* 21 C.F.R. § 202.1(e)(6)(i).

[28] According to CPG 440.100, the use of new dosages or delivery systems requires NDA approval. Yet companies appear to be marketing skin bleaching prescription drug products with claims that promote new dosages and delivery systems – such as claims for SkinMedica's EpiQuin™ Micro's "Microsponge® technology" – that to our knowledge have never been FDA-approved. In the absence of FDA approval, we believe such changes to drug formulations - and claims regarding the benefits and/or superiority of these formulations - should result in immediate FDA enforcement.

[29] To our knowledge, the only topical 4% hydroquinone combination prescription drug product approved by the Agency (Tri-Luma® Cream) was approved in 2002 to treat melasma. Yet many of the unapproved drug products on the market are making claims in promotional material suggesting indications for use that go well beyond melasma. For example, promotional materials for currently marketed unapproved 4% hydroquinone prescription drug products suggest indications for use that include melasma, post-inflammatory hyperpigmentation and photodamage, as well as the treatment of discoloration caused by acne, burns, surgery, insect bites, ultraviolet- induced dyschromia and other skin trauma.

and thus to weigh the benefit against the available scientific evidence of risk, is through the NDA process. If the FDA mandates that skin bleaching drug products be available by prescription only, yet fails to enforce the requirement that these drugs go through the NDA process, there will be no review of product claims, and therefore no consideration of the actual risk/benefit ratio.

This would result in the perverse scenario where FDA would have determined that the limited benefits that could be claimed under the OTC monograph were not insufficient to outweigh the products' potential risks, yet the very same products would be permitted to remain on the market making potentially even broader claims. Moreover, in the absence of FDA review and approval, physicians would continue to prescribe these drugs, unaware that the drugs have never been reviewed or approved for their intended uses. Thus, without enforcement of the NDA requirement, FDA will have traded one risk – the risk of allowing these products to remain OTC – for another, far greater risk, of unfettered claims in support of unproven endpoints that increase health risks.

III. Conclusion

For the reasons stated above, we strongly support the FDA's proposal to make skin bleaching drug products containing hydroquinone available by prescription only, and to require that all such products receive FDA approval through the NDA process. These product formulations pose potential safety concerns that make OTC status inappropriate.

We also believe that all prescription skin bleaching products containing hydroquinone currently on the market in the absence of FDA approval should be subject to immediate Agency enforcement. These products pose potential safety risks because they have never been evaluated by the Agency, and allowing them to remain on the market not only places consumers at risk, but also threatens the integrity of FDA's proposed rule and the drug approval process. To our knowledge, there has never been an analogous situation where companies could subvert the OTC drug review process and threaten the integrity of the drug approval regime by ignoring an NDA mandate issued by the FDA pursuant to the OTC Drug Review.

Finally, enforcement against unapproved prescription hydroquinone drug products would also prevent the inequities created when companies that comply with FDA approval requirements become subject to considerable regulatory scrutiny (and are assessed significant user fees), while companies that choose to ignore the approval process are permitted to market their products in the virtual absence of regulatory constraints.

We therefore respectfully request that the Agency finalize its proposed rule and take immediate enforcement action against unapproved prescription skin bleaching drug products.

Sincerely,

Paul R

Paul D. Rubin