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December 28, 2006

VIA ELECTRONIC SUBMISSION
HARD COPY VIA OVERNIGHT COURIER

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

Docket No. 1978N-0065
RIN number 0910-AF53
Skin Bleaching Drug Products For Over-the-Counter Human Use
Proposed Rule

Dear Sirs or Madam:

This office represents Gapardis Health and Beauty, Inc., d/b/a Mitchell Group USA, a well-known and reputable distributor throughout North America of OTC products containing hydroquinone in concentrations of 2% or less. On August 29, 2006 the FDA published in the *Federal Register* a proposed rule withdrawing the tentative final monograph for skin-bleaching

OTC products that has governed the industry for more than 20 years. The proposed rule would be potentially fatal to our client and of no benefit whatsoever to the perhaps thousands of consumers each year whose physical and psychological health has enormously and measurably benefited from the products distributed by Gapardis and other small businesses like it.

This comment respectfully urges the FDA to reconsider its position and put a temporary stay on any action regarding withdrawing hydroquinone's status as a GRASE ingredient, pending a public hearing and a call for further studies and information.

Background on Gapardis Health and Beauty Services, Inc.

This comment to the FDA's docket is submitted on behalf of Gapardis Health and Beauty Services, Inc. who, by virtue of a license and assignment from the French manufacturer, Continental Labo Medica, has the exclusive right in the United States and Canada to distribute beauty aids containing hydroquinone and other effective ingredients.

Since 1982, Gapardis has relied on the FDA's tentative final monograph which determined that hydroquinone is safe and effective for use in concentrations of 2% or less as the basis for its ongoing business activities in a very limited and unique marketplace. Gapardis and/or the manufacturer is registered with the FDA and all hydroquinone-containing products are duly listed with the Agency. All labeling is carefully reviewed to ensure compliance with the FDA's rulemaking and Gapardis closely monitors related studies and information to ensure that its customers receive the highest quality and safest OTC products. The FDA now, without prior warning or stay, indicates that the hydroquinone products distributed by Gapardis are no longer safe and that the over 65 small businesses that distribute these products in the United States will have 30 days after publication of the final rule to essentially close their doors. This will cause such a dramatic, fatal and unnecessary affect on Gapardis and other small businesses like it that

the Agency, respectfully, is urged to reconsider such draconian measures, particularly when it has received hundreds of comments from this nation's leading dermatologists confirming the safety and effectiveness of hydroquinone as it is currently relied upon in the domestic OTC marketplace.

Summary of Skin Bleaching Monograph History

In May 1972, the FDA began a retrospective review of OTC drugs. The review was structured so that primarily the active ingredients of a myriad of then-available OTC drugs would be examined by panels of experts. Seventeen panels of experts were formed for the purpose of arranging the drugs into three distinct categories: Category I included ingredients which were safe and effective; Category II included ingredients which were unsafe and/or ineffective; and Category III included ingredients which were probably safe and effective but needed further testing to establish significant proof. After such classification, the second phase of the Agency's OTC review consisted of the FDA review of each classification of products relying upon the panels' findings, public comment, as well as consideration of any new data that may have since become available. After such a review, the FDA was to publish its findings in the *Federal Register* in the form of a tentative final monograph. After publication of the tentative final monograph, a period of time would be allotted for objections to the agency's proposal, after which time, the FDA was to consider all such comments and publish its final monograph setting forth the 'recipe' for labeling and formulation of that particular OTC product category.

In the case of skin-bleaching products, the FDA published its tentative final monograph on September 3, 1982 at which time the Agency definitively stated that it considered hydroquinone safe and effective for use in OTC skin-bleaching products. Comments were to be

accepted until November 2, 1982, after which date, the final monograph would be published[1]. However, the FDA published no other official documentation regarding this monograph until August 29, 2006 – nearly 24 years later! There are 65 businesses in the United States that have relied upon a 20-year old determination by the FDA that a particular is safe and effective to create consumer loyalty, recognition, reputation and good will. There are thousands of American consumers who have benefited and continue to benefit as a result of the products manufactured and/or distributed by these businesses It is, respectfully, unfair and incomprehensible that after nearly two and a half decades, the FDA looks to, with such ease and without scientific proof, reject its prior determinations of safety and effectiveness, considering its ignorance of any concomitant economic effect to be of such little consequence that it adds insult to injury by requiring full implementation within 30 days after publication of a final rule.

Discussion

1. There is tremendous anecdotal evidence before the Agency of the safety of hydroquinone in OTC concentrations

In response to the August 29, 2006 Federal Register notice, the FDA has received hundreds of comments from this country's leading dermatologists confirming that hydroquinone, in its OTC concentration, is successfully relied upon by many patients to treat skin blotches, scarring and other benign skin conditions that individuals of all ethnicities seek to self-treat safely and cost-effectively. These doctors state unequivocally that there is no reason for the FDA to believe that hydroquinone in concentrations of 2% or less poses any great threat to the health or safety of American consumers. These doctors' anecdotes and information is based on decades and decades of successful medical practices and hundreds, perhaps thousands, of patient histories. For the benefits provided by OTC hydroquinone products, both physically and

[1] In fact, the industry for many years constantly monitored the *Federal Register* for notice of this final monograph confident that the FDA would not permit a tentative final monograph to linger for more than a year or two, at best.

psychologically, these doctors, together with the American Academy of Dermatological Association, is urging the FDA to reconsider its position.

The American Academy of Dermatological Association (AADA) is a highly prestigious organization which was formed in 1876 and continues to represent the best of its membership and the industry, now even promoting the needs of American consumers to sound healthcare through a lobbying PAC and regional associations throughout the United States. The AADA and others have clearly stated that any skin irritation caused by hydroquinone is the result of misuse of the product for prolonged periods of time and/or use in combination with other therapies or treatments – both of which behaviors are specifically warned against both by dermatologists and current manufacturers of OTC hydroquinone products.

Moreover, although the FDA contends that any benefits are clearly outweighed by potential risk of use of hydroquinone, it is clear from the comments already received by the FDA that this is not the case. Ochronosis, which appears to be the FDA's main focus and concern, is reported never or incredibly rarely to have been seen in American consumers using the hydroquinone OTC products and, even in those cases in which it has occurred, the condition is treatable, reversible and clearly worth it to those patients looking to overcome the severe psychological harm caused by the distressing appearance of conspicuous skin discolorations and hyper pigmentation.

Unless the FDA determines to ignore the recommendations of the American Academy of Dermatological Association, the members of which include the most learned and respected doctors within the United States, it must withdraw this proposed rule. It is simply counterintuitive for the Agency to declare it has no choice but to declare hydroquinone unsafe and ineffective because it lacks studies and information to state otherwise, when, in fact, it has

now received dozens of statements and pieces of evidence establishing both the safety and efficacy of this ingredient – when used according to label warnings and directions.

2. The OTC Monograph for Skin Bleaching Treatment Has Received Inequitable Review by the FDA: A Case Study on OTC Laxatives

In 1975, the FDA published advanced notice of proposed rulemaking for OTC laxatives and comments were accepted on the proposed rule until June 19, 1975. The following briefly summarizes the history on this rulemaking since that date in 1975 until today's date, when no final monograph has yet been issued:

1. **March 21, 1980:** The FDA published a notice indicating that new data had been submitted after the administrative record had closed on June 19, 1975 and that the FDA was reopening the administrative record while it considered this additional information.
2. **January 15, 1985:** The FDA published its proposed rule, or tentative final monograph, and that monograph set forth several upcoming dates: May 15, 1985 for comments on the tentative final monograph; January 15, 1986 for new data; and March 17, 1986 for comments on any such new data submitted.
3. **May 15, 1985:** The FDA extended the comment period on the tentative final monograph to June 14, 1985
4. **April 30, 1986:** Another tentative final monograph was published based upon the Agency's review of the comments and data submitted in response to its prior published notices requesting same. This tentative final monograph indicated that any final monograph issued would be effective 12 months after its publication and again indicated the acceptance of new data through its use of successive dates for comments after

publication of this tentative final monograph, so that comments on the tentative final monograph were due to be filed by June 30, 1986; new data had to be submitted by April 30, 1987 and comments on the new data needed to be submitted by June 30, 1987.

5. **October 1, 1986:** The FDA again amended its tentative final monograph and established yet additional, subsequent due dates for comments, new data and comments on that new data.
6. **June 2, 1992:** **T**he FDA again reopened the administrative record for the OTC monograph on laxative products, in order to consider additional data on certain active ingredients and that record was held open for comments until August 3, 1992.
7. **September 2, 1993:** The FDA published another amendment to its tentative final monograph with a 120-comment period.
8. **March 31, 1994:** Still another amendment to the tentative final monograph was published on March 31 1994 because yet additional data and comments had been received and were being considered by the Agency.
9. **September 1, 1997:** The administrative record was again reopened on September 2, 1997 as the Agency then considered reclassifying certain active ingredients as no longer safe and effective and the record was formally reopened for amendment to the tentative final monograph on June 19, 1998, when the Agency looked to reclassify other initially declared GRASE active ingredients into Category III. In that final amendment to the tentative final monograph for OTC laxatives, the FDA specifically invited studies and testing protocols addressing the reclassification of aloe and other ingredients from Category I to Category III products. Data was accepted until June 21, 1999 and comments on the new data accepted until August 19, 1999.
10. **May 9, 2002:** When no comments or data was submitted, the FDA issued a final rule on May 9, 2002 on those particular active ingredients, still inviting additional testing and further data by manufacturers before issuing a final monograph.

11. **October 22, 2003:** The FDA again opened the administrative record on the OTC monograph for laxatives in light of new data and inviting comments through January 20, 2004.

Following is a brief review of the rulemaking history for skin bleaching treatments:

1. **November 3, 1978:** The FDA published its notice of proposed rulemaking reviewing a variety of studies and data, including those from South Africa with reports of ochronosis, and concluding that hydroquinone in concentrations between 1.5% and 2% was the single active ingredient in Category I, GRASE. Comments were accepted on the proposed rule first by February 1, 1979 and then replies to those comments through March 5, 1979.
2. **March 12, 1980:** The FDA published a notice reopening the administrative record to consider information and data it received after the closing date of comments to the previous notice of March 5, 1979 and, although the Agency indicated that no public comments to this new information were then able to be submitted, the March 12, 1980 Federal Register did indicate that an additional comment period would open in the future.
3. **September 3, 1982:** The FDA published its tentative final monograph, having never provided the public with an opportunity to comment on data submitted to the Agency between March 5, 1979 and March 12, 1980 or thereafter. That tentative final monograph indicated that the Agency would consider all testing and data during the course of its OTC review and prior to issuance of a final monograph pursuant to *Cutler v. Kennedy*, 475 F. Supp 838 (D.D.C. 1979), in which case it was determined that products could not contain active ingredients categorized as Category III for which insufficient studies existed to determine safety. The tentative final monograph retained GRASE status for hydroquinone in concentrations between 1.5% - 2%.

4. **April 29, 2006:** FDA publishes a notice proposing to withdraw its tentative final monograph in total and requiring NDA's to be submitted on all products distributed in the United States containing hydroquinone.

There is no question that the review given to these OTC products by the FDA has been inequitable and that the FDA has determined hydroquinone OTC products deserving of less attention, less public notice and less study than other, similarly classified human drugs, such as laxatives. This is, respectfully, an indefensible, arbitrary policy that demands further scrutiny and review by all parties subjecting themselves to FDA jurisdiction.

3. **The FDA May Be Seeking More Regulation Over Cosmeceuticals**

For a period of 24 years, the FDA published no information or notification regarding hydroquinone OTC rulemaking. Contrarily, over a period of 22 years, the Agency has amended its tentative final monograph for laxative OTC products 4 or 5 times and has reopened its administrative record to review additional data even more often. There can be no rationale for such a distinction in treatment unless one were to suspect an urgent desire for Agency oversight over what are often referred to as cosmeceutical products.

Although the FDA does not recognize the term "cosmeceutical," these products nevertheless exist in today's marketplace. According to Chain Drug Review (September 1996) "Cosmeceuticals and nutraceuticals represent one of the hottest segments of the skin care category, positioned to deliver not just cosmetic benefits but therapeutic ones as well." And Legal Affairs reports[2] that: "According to an estimate from the market research company Packaged Facts, cosmeceutical skincare products took in more than $6.4 billion domestically in

2004. That's more than half of the $12.4 billion for all cosmeceuticals, an amount that is expected to increase to over $16 billion by 2010." As a result, the FDA is certainly under some pressure to take a stronger stance against unregulated distribution of these products, which routinely make drug-like claims while delivering merely cosmetic-like results[3]

Respectfully, to the extent the FDA's clearly abbreviated review and study of hydroquinone may reflect the Agency's renewed fervor for review of the emerging classification of products referred to as cosmeceuticals, Gapardis suggests that these products are inappropriate to use as proof of FDA's commitment to such oversight. Simply, it is already illegal to distribute any cosmetics in the United States that include hydroquinone. And, even though Gapardis itself may describe its hydroquinone skin care products as cosmeceuticals, the fact is that any skin care product that contains hydroquinone distributed in the United States in concentrations of 2% or less is subject to the same regulation and FDA oversight as any other OTC *drug* product. All manufacturers and re-labelers of OTC products, including Gapardis, are registered with the FDA, all products are listed with the FDA and all labeling must comply with the FDA tentative final monograph. While it may be true that the FDA needs to take a closer look at cosmeceuticals looking to avoid regulation as OTC drug products through manipulation of claims and misleading labeling, no such fear exists in connection with OTC hydroquinone products such as those distributed by Gapardis – because these are already clearly and strictly regulated as drug within the entire domestic marketplace

4. **The FDA Does Not Routinely Prohibit OTC Sales Without Proof of Substantial and Common Misuse and Risks**

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[2] http://www.legalaffairs.org/issues/November-December-2005/feature_kawalek_novdec05.msp

[3]. The general disdain with which the FDA considers these cosmeceutical products is clearly set forth in its article "Science Meets Beauty: Using Medicine to Improve Appearances" found in the March-April 2004 volume of the FDA Consumer Magazine,[3] in which the agency refers to such products, with clear suspicion, as "vanity drugs."

The FDA does not ban the sale of acetaminophen, even though consumers who misuse the product have needed liver transplants and have ended up in emergency rooms after overdosing on the product[4]. The FDA also does not ban OTC ibuprofen products even though it has data clearly linking popular products such as Motrin and Advil to severe stomach bleeding. The FDA itself has stated that "…non-steroidal anti-inflammatory drugs are blamed for sending more than 200,000 Americans to the hospital every year, and are linked to an estimated 16,000 deaths." Nevertheless, the FDA is not thinking of prohibiting such OTC sales; rather, it is considering stronger warnings and more consumer education. Interestingly, however, even though the FDA knows that American consumers are not dying because of misuse of OTC hydroquinone products and even though the FDA knows that there are not even a dozen incidents reported within this country of severe, irreversible or dramatic side effects caused by these products, when used as directed, the Agency is now seeking to prohibit all such sales.

During this present comment period, the FDA has learned that OTC hydroquinone products provide measurable benefits to many consumers who are urging --- even begging --- the Agency to permit continued OTC distribution because of known relief to symptoms both physically and emotionally. Respectfully, and certainly without intending to make light of the scientific research conducted to date, it is inappropriate for the FDA to ban OTC sale of hydroquinone products based primarily on certain rat studies suggesting that injections of hydroquinone may cause tumors in male rats, when the Agency believes it is unnecessary to prohibit the sale of the other OTC products which its own data confirms is linked to at least 16,000 deaths of actual human beings.

Closing Remarks and Conclusion

In its August 29, 2006 *Federal Register* notice proposing that no OTC skin-bleaching product would be GRASE and would require the submission of an NDA to be distributed within the United States, the FDA indicated that it based that decision solely on data that had come to its attention regarding this ingredient between publication of the tentative final monograph on September 3, 1982 and August 29, 2006. The FDA clearly states in its August 29, 2006 notice that its decision to withdraw the 1982 tentative final monograph was not based on any particular study confirming that hydroquinone posed great risks to human being, but, rather, was based only on the fact that it did not have sufficient information on hand to determine conclusively one way or another. This is insufficient justification for the United States government to destroy the businesses - like our client's - which have lawfully relied upon a 24 year old Agency determination to manufacture and market over the counter medications that have proven to be of such benefit to American consumers.

- The FDA should publish the studies it considered as a basis for this proposed rule and accept public comment on those studies before it decides to change its mind on 24 years of accepted practice and policy.
- The FDA should hold a public hearing on its proposed rule inviting each of the patients, businesses and dermatologists from whom it has received comments to submit testimony and oral evidence.
- The FDA should reopen the administrative record and specifically call for additional data about the safety and efficacy of hydroquinone before it proposes withdrawing the tentative final monograph which has governed the industry for over 20 years.
- The FDA must conduct a thorough economic analysis of its proposed rule and not be permitted to merely declare it has no such information available as the basis to

[4] Alonso-Zaldivar, R; "Warnings on common painkillers may get stronger"; 12/20/06; republished in the *Los Angeles Times* and found at www.yourlawyer.com/articles/read/12410

determine no substantial impact on the domestic economy. In point of fact, Gapardis itself estimates a loss of annual profits exceeding $2 million should the FDA's proposed rule become final.

- The FDA must, in all events, reconsider a 30 day effective date after any final rule is published respecting the good will and reputation earned by businesses lawfully operating pursuant to the regulations set forth in a tentative final monograph issued over 24 years ago.

If the Agency would like to discuss any of the comments made herein or otherwise, it is respectfully requested that the undersigned be contacted directly at any time.

Sincerely,
Sandler, Travis & Rosenberg, P.A.

By: Lauren Perez
Lauren V. Perez
Vice President for Regulatory Matters

cc: Gapardis Health & Beauty, Inc.