URL Pharma, Inc.
URL Distribution
Mutual Pharmaceutical Company, Inc.
AR Scientific, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlpharma.com

Richard H. Roberts, M.D., Ph.D.
President
Chief Executive Officer

June 22, 2010

Mr. Said Darwazah
Chief Executive Officer
Hikma Pharmaceuticals PLC
13 Hanover Square
London, W1S 1HL
United Kingdom

Sent Via: Federal Express

RE: Recent Developments Regarding Unapproved Colchicine Tablets

Dear Mr. Darwazah:

As you know, West-Ward Pharmaceutical Corp. ("West-Ward"), a subsidiary of Hikma Pharmaceuticals PLC ("Hikma"), is manufacturing and distributing unapproved colchicine tablets in the United States. I am writing to inform you of recent developments that we believe you should take into consideration in order to avoid (i) potential liability to consumers injured by West-Ward's unapproved products and the negative publicity that would follow and (ii) potential action by U.S. government officials given the public health risks presented by the sale of dangerous, unapproved drugs. We trust that after reviewing this information, you will make a reasonable business decision and take immediate action to stop West-Ward from manufacturing and distributing unapproved and illegal colchicine products in the United States.

FDA Warning Letters

On January 14, 2010, the U.S. Food and Drug Administration ("FDA") issued a warning letter that cited Sunrise Pharmaceutical, Inc. ("Sunrise") for, among other deficiencies, manufacturing and distributing unapproved colchicine tablets. On April 29, 2010, a similar warning letter was sent to Vision Pharma LLC ("Vision"). In both letters, the agency concluded that colchicine requires an FDA approval to be legally marketed in the United States:

> Based on the information collected during the inspection, you manufacture the following prescription drugs, including but not limited to:
>
> - Colchicine Tablets, 0.6 mg
> - Hyoscyamine Sulfate Tablets, USP, 0.125 mg
> - Hyoscyamine Sulfate Orally Disintegrating Tablets, 0.125 mg
> - Hyoscyamine Sulfate Sublingual Tablets, 0.125 mg

> The above products are drugs within the meaning of Section 201(g) of the [Federal Food, Drug, and Cosmetic ("FDC")] Act, [21 U.S.C. 321(g)] because as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. **Further, they are "new drugs" within the meaning of Section 201(p) of the Act [21 U.S.C. 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Under Sections 301(d) and 505(a) of the Act [21 U.S.C. 331(a), (d) and 355(a)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA . . . is in effect.**

See Warning Letters from FDA to Sunrise Pharmaceutical, Inc. and Vision Pharma LLC (emphasis added) (attached as Exhibits 1 and 2).

Ineligibility for Medicaid Reimbursement

FDA's action renders unapproved colchicine tablets ineligible for inclusion in the Medicaid Drug Rebate ("MDR") Program. This action – brought by FDA under Sections 301(d) and 505(a) of the Food, Drug, and Cosmetic Act – requires Centers for Medicare and Medicaid Services ("CMS") to determine that unapproved colchicine tablets fail to satisfy the definition of a "covered outpatient drug" and must be excluded from coverage. The definition of "covered outpatient drug" permits the inclusion of an unapproved drug product only if it has not been the subject of a final determination by the Secretary that it is a "new drug" (within the meaning of section 201(p) of the FDC Act) or the drug has not been the subject of "an action brought by the Secretary under section 301, 302(a), or 304(a) of such Act to enforce section 502(f) or 505(a) of such Act." 42 U.S.C. § 1396r-8(k)(2)(A)(ii). The FDA's warning letters to Sunrise and Vision constitute an action under section 301 to enforce section 505(a), as contemplated by the Medicaid statute and renders unapproved colchicine tablets ineligible for CMS reimbursement.[1]

By continuing to sell unapproved colchicine you may be exposing your company, yourself, and your senior executive colleagues to potential government-initiated civil and criminal action. *See United States v. Actavis Totowa, Inc.*, No. 08-cv-5656 (D. N.J. filed Nov. 14, 2008); *see also* 18 U.S.C. § 287 and 42 U.S.C. § 1320a-7b(a).

Safety Issues Highlighted by Center for Drug Evaluation and Research

In conjunction with FDA's warning letters to Sunrise and Vision, we bring to your attention a March 3, 2010 letter from Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, highlighting several significant safety issues recently identified by FDA (attached as Exhibit 3). This information was brought to light through clinical research undertaken by Mutual Pharmaceutical/URL Pharma during the FDA approval process for Colcrys® (colchicine tablets 0.6 mg). FDA stated:

[1] CMS previously concluded that the product colchicine injection USP is an unapproved drug not meeting the definition of a "covered outpatient drug," and excluded it from Medicaid coverage. See *Medicaid Drug Rebate Program Release No. 151 for State Medicaid Directors* (April 13, 2009).

- "The [yet-unapproved] colchicine products have not been evaluated and approved by FDA. They are unapproved drugs, not generic medications, and neither their safety nor their efficacy can be assured."

- "Although FDA is aware of 21 firms that manufacture and distribute unapproved oral colchicine, so far, only one, Mutual Pharmaceuticals/URL ('Mutual'), has chosen to take the clinically responsible step of seeking approval for unapproved oral colchicine."

- FDA credits Mutual and the Colcrys® approval process with helping the agency identify and communicate two significant, previously uncharacterized safety concerns associated with the use of colchicine:

  - Unapproved oral colchicine products have been associated with at least 169 deaths, the majority of which were within the therapeutic range of 2 mg or less per day. According to FDA: "These reports suggest [that] alterations in the pharmacokinetics of colchicine played a central role in the development of toxicity."

  - "FDA concluded there is a risk for severe drug interactions in certain patients.… The FDA-approved prescribing information for Colcrys contains recommended dosage adjustments."

  - Clinical data developed by Mutual suggest that prior use of colchicine may have exposed patients to increased toxicity with no greater efficacy than the low-dose regime now recommended in approved Mutual product labeling. FDA observed: "These adverse events, in addition to being tragic and in many cases preventable, place a serious burden on the healthcare system. [FDA] is particularly concerned because the labeling of many unapproved drugs does not adequately convey the risks … and how best to use drugs safely…."

See March 3, 2010 letter from Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research (attached as Exhibit 3).

FDA Video on Dangers of Unapproved Single-Ingredient Oral Colchicine

On May 14, 2010, FDA published a new video on single-ingredient oral colchicine. The video focuses on the dangers of unapproved single-ingredient oral colchicine tablets and the benefits of seeking FDA approval. The video points out that "without this review by FDA, outdated assumptions of what is safe and effective for treatment with oral colchicine would have remained unchecked, and patients would have continued to suffer from adverse reactions such as severe gastro-intestinal complications -- and even death -- needlessly."

The video is available on the FDA website at:

http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm211975.htm

A transcript of the video is available on the FDA website at:

http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm212566.htm

In light of these recent developments, the dangers of unapproved colchicine tablets have been made abundantly clear. Accordingly, the risk of potential uninsured product liability and false Medicaid claims, among others, will undoubtedly increase if you do not take immediate steps to prevent the manufacture and distribution of a product that the FDA has repeatedly and publicly stated to be illegal and dangerous.

After careful consideration of these facts, we trust you will agree that the risks and negative consequences stemming from the continued manufacture and distribution of colchicine tablets by West-Ward, including time-consuming and costly litigation, negative publicity, and public and government condemnation, far outweigh the short-lived financial benefits that you will gain from the sale of an illegal, dangerous, and unapproved drug.

If you have questions or comments please contact me at 215-807-1007**.**

Sincerely,

Richard H. Roberts, M.D., Ph.D.
President & CEO, and Chairman
RHR/ph
Enclosures
cc: Michael Raya, CEO
West-Ward Pharmaceutical Corp.
401 Industrial Way West
Eatontown, NJ 07724

Exhibit 1

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Sunrise Pharmaceutical, Inc. 1/14/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054
Telephone (973) 331-4910

January 14, 2010

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Utpal Patel
Chief Executive Officer
Sunrise Pharmaceutical, Inc.
665 E. Lincoln Avenue
Rahway, New Jersey 07065

10-NWJ-03

Dear Mr. Patel:

This is regarding our June 19 through July 17, 2009 inspection of your pharmaceutical manufacturing facility, Sunrise Pharmaceutical, Inc., located at 665 E. Lincoln Avenue, Rahway, New Jersey. The inspection identified significant violations of the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with CGMP regulations.

In addition, you manufacture a number of prescription drugs without approved applications. As described below, these drugs are unapproved new drugs, and by introducing them into interstate commerce you are in violation of 21 U.S.C. 355(a) (section 505(a) of the Act). These drugs are also misbranded under 21 U.S.C. 352(f)(1) (section 502(f)(1) of the Act).

We have reviewed your firm's responses of July 27, September 17, and November 18, 2009, and note that they lack sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

CGMP Violations

1. Your firm has not established laboratory control mechanisms, including any change, and has failed to document quality control unit review and approval at the time of performance [21 CFR 211.160(a)]. For example,

   a. Out-of-specification (OOS) humidity levels for the controlled room temperature stability chamber were noted on January 27, March 17, and April 5 and 6, 2009. Investigations and corrective actions were not conducted at the time to address these out-of-specification results. During the inspection, however, the Quality Unit presented back-dated service requests to investigators as evidence of proper OOS result handling when in fact, no actual service requests were initiated.

b. Investigation report #05072009 dated May 7, 2009, was initiated following a power failure during the coating of Senna & Docusate Sodium Film Coated Tablets, 8.6mg/50mg, lot 0904004. According to the report, the lot was inspected for peeled film tablets during May 8-26, 2009; however, the corrective actions and disposition of drug product were approved by the Quality Unit on May 7, 2009.

Regarding the above examples, the corrective action in your July 27, 2009 response states, ''The employees involved will be retrained and warned that a future recurrence will have zero tolerance resulting in severe action, including possible immediate termination." Your response fails to describe the specific type of training that will be provided and how the effectiveness of the training will be evaluated.

This is a repeat observation from the February and August 2007 inspections.

2. Your firm does not have adequate written procedures for production and process control designed to assure that your drug products have the identity, strength, quality, and purity that they purport or are represented to possess [21 CFR 211.100(a)].

For example, the validation studies for Guaifenesin and Dextromethorphan HBr 400mg/20mg Caplets are inadequate in that they do not demonstrate that the manufacturing process is reproducible. Specifically, one of your three validation lots, S0712012 (manufactured December 21, 2007), failed the blend uniformity test specifications. This same lot was blended for an additional 10 minutes without the review and approval of the Quality Unit. In addition, the validation protocol was not approved until April 2008, which is four months after the validation lot SO712012 was manufactured.

In your July 27, 2009 response, you promised to retrain your employees. However, we are concerned that this same commitment was made in the past for other deficiencies. Please specify the type of training that will be offered and how retraining will prevent recurrence of violations.

In your September 17, 2009 response, you provided an amendment to the validation report which referenced an additional validation lot (S0908003) of Guaifenesin and Dextromethorphan HBr 400mg/20mg Caplets. This additional lot was manufactured to fulfill your protocol requirements. However, your response does not specifically address: a) the blend uniformity failure for validation lot S0712012; b) whether the mixing time is a critical process parameter; and c) your rationale for concluding that your process is validated. You have not demonstrated that your manufacturing process is in a sufficient state of control and capable of reproducing acceptable product.

In addition, Section 5.4.2, Sampling Requirements, in your Process Validation Protocol, PVP-2000M-122T-04, states that **(b)(4)** tablets should be collected at **(b)(4)** for analytical testing. However, 10 tablets were collected from 14 sampling locations for a total of 140 tablets in lot S0908003. Your response does not address this apparent deviation from your protocol. Also, be advised that the degree of validation sampling (e.g.,number and frequency) and testing should be more extensive (than routine production) in order to provide sufficient statistical confidence of quality within a batch and between batches. Please address your confidence level when sampling a total of 140 tablets from a lot of **(b)(4)** tablets (protocol batch size).

Your response also fails to address the additional mixing of validation lot S0712012. We reviewed the amendment to your Process Validation Report, dated June 23, 2009, regarding the 10 additional minutes of mixing time (for a total **(b)(4)** of minutes). Your amendment states that "All Lots tested were complying with tolerance's set." However, your amendment further states that your total mixing time (i.e., established tolerance) was **(b)(4)** minutes as per your batch records and that the "Additional 10 minutes time has no impact on product Quality." Please provide the total mixing time established in the validation protocol and specifically, address any deviation from this established specification during the manufacture of the validation lot S0712012. Also, provide your rationale for concluding that your validation data supports an additional 10 minutes of mixing time.

In addition, periodic process verification is essential for ensuring that a manufacturing process continues to be reproducible.

3. Your firm does not have master production and control records that justify variation in the amount of components necessary for the preparation of the dosage form [21 CFR 211.186(b)(4)].

For example, some of your products were formulated with excess amounts of active pharmaceutical ingredient (API). Specific instances include an excess of Dextromethophorphan HBr API in Guaifenesin and Dextromethorphan HBr Tablets, a excess of Colchicine API in Colchicine Tablets, and an excess of Hyoscyamine Sulfate API in Hyoscyamine Sulfate Subligual Tablets. You failed to provide documented scientific justification to explain why the excess API is necessary. In addition, you deemed the excess amounts as necessary due to "process loss;" however, none of these losses were documented.

Your July 27,2009 response states 'The master formulas justify whenever overages are used, i.e., moisture or solvent compensation." This response is inadequate because it does not address why excess amounts of API are needed for moisture or solvent compensation, or manufacturing process losses when charging the APIs used in drug product manufacturing. Your process is not considered to be in an adequate state of control when excess API (than as required in your batch records) is routinely used by your firm. To ensure proper formulation, you must document and justify the need for any excess amount of a component in each batch record.

4. Your firm has not established an adequate written testing program designed to assess the stability characteristics of your drug products in determining appropriate storage conditions and expiration dates since your program does not include reliable, meaningful, and specific test methods [21 CFR 211.166(a)(3)].

Specifically, some of your firm's analytical methods have not been validated to demonstrate that they are stability indicating. In other instances, test methods that you claim to be stability indicating are inadequate or not followed by your firm. For example,

a. A stability indicating test method has not been developed and validated for Senna & Docusate Sodium tablets.

b. Stability indicating test methods are developed, but not validated, for Guaifenesin and Dextromethorphan HBr Tablets, and impurity specifications have not been established for the finished product release or stability samples. as required by 21 CFR 211.160(b).

c. Validated stability indicating test methods are established, but are not followed, to analyze impurity levels for Phenazopyradine HCl Tablets, Bisacodyl Tablets, and **(b)(4)**. Further, impurity specifications have not been established for any of the aforementioned finished product release testing or stability samples as required by 21 CFR 211.160(b).

Your September 17, 2009 response did not include the following: a) specifications; b) allowable levels of impurities; or c) test results regarding impurity testing for Bisacodyl tablets. We note your response states that your firm has discontinued manufacturing of **(b)(4)** and Phenazopyradine HCl Tablets.

Your November 18, 2009 response included method validation impurity testing results for Senna & Docusate Sodium Tablets and the Guaifenesin & Dextromethorphan drug products. However, your response did not state whether the impurity specification of Not More Than (NMT) **(b)(4)** noted in the method validation report, will be used during routine testing or stability testing in the future.

5. Your firm has not followed the written procedures for reprocessing batches that do not conform to standards or specifications for ensuring that the reprocessed batches conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)].

For example, your firm did not follow SOP SMP-07, "Performance, Documentation and Approval of Reprocessing Operation," after Guaifenesin and Dextromethorphan HBr Caplets, validation lot S0712012, failed blend uniformity testing. A reprocessing master batch record was not prepared to reprocess the batch as per your SOP. Instead, production personnel remixed and resampled the lot, after which passing results were obtained and the lot was released.

The corrective action in your July 27, 2009 response indicates that employees will be retrained on existing procedures. This response is inadequate because it fails to describe when and how the employees will be retrained.

6. Your firm has not exercised appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 CFR 211.68(b)].

For example, your firm lacks systems to ensure that all electronic data generated in your Quality Control laboratory is secure and remains unaltered. All analysts have system administrator privileges that allow them to modify, overwrite, and delete original raw data files on the **(b)(4)** used **(b)(4)** in the High Performance Liquid Chromatography (HPLC) units. There are no procedures that address the security measures in place for generation and modification of electronic data files for these instruments used for raw material, in-process, finished product and stability testing. In addition, your firm's review of laboratory data does not include a review of an audit trail or revision history to determine if unapproved changes have been made.

Your September 17, 2009 response states that you replaced the **(b)(4)** HPLC systems operating on **(b)(4)** software with **(b)(4)** new qualified HPLC units from **(b)(4)** software. This validation information will be reviewed at the next inspection. In addition, your response is inadequate because it lacks a retrospective evaluation of the data from the former HPLC units. This will prevent an alteration of data prior to implementation of your corrective actions. Further, your response does not address security procedures to ensure that the data generated using the new HPLC units is secure and remains unaltered.

This is a repeat observation from the February and August 2007 inspections.

Misbranded and Unapproved New Drugs

New drug and misbranding violations for prescription drug products

In addition to the CGMP violations, you manufacture and market unapproved new drugs in violation of the Act at your facility at your facility at 665 E. Lincoln Avenue in Rahway, New Jersey. Based on the information collected during the inspection, you manufacture the following prescription drugs, including but not limited to:

- Colchicine Tablets, 0.6 mg
- Hyoscyamine Sulfate Tablets, USP, 0.125 mg
- Hyoscyamine Sulfate Orally Disintegrating Tablets, 0.125 mg

- Hyoscyamine Sulfate Sublingual Tablets, 0.125 mg

The above products are drugs within the meaning of Section 201 (g) of the Act, [21 U.S.C. 321 (g)] because as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are "new drugs" within the meaning of Section 201 (p) of the Act [21 U.S.C. 321 (p)] because they are not generally recognized as safe and effective for their labeled uses. Under Sections 301 (d) and 505(a) of the Act [21 U.S.C. 331 (a), (d) and 355(a)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. 355(b) or (j)] is in effect for the drug. Based on our information, there are no FDA-approved applications on file for these drug products.

Additionally, the above products are misbranded because, as prescription drugs, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under Sections 502(f)(1) of the Act [21 U.S.C. 352(f)(1)] and because the products lack required approved applications, they are not exempt from this requirement under 21 CFR 201.115. The introduction or delivery for introduction into interstate commerce of these products without approved new drug applications violates Section 301 (a) and (d) of the Act [21 U.S.C. 331 (a) and (d)].

New drug and misbranding violations for retail OTC drug products

Based on the information collected during the inspection, you manufacture and package for retail sale the following finished OTC drug products, including but not limited to:

- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 100 Tablets
- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, Enteric Sugar Coated, 100 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, 1000 Enteric Sugar Coated Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 100 Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 1000 Tablets
- **(b)(4)** (Bisacodyl USP), Comfort Coated Stimulant Laxative, 5 mg, 100 Tablets (distributed by **(b)(4)**)
- **(b)(4)** Enteric Coated Stimulant Laxative (Bisacodyl USP), 5 mg, 100 Tablets (distributed by **(b)(4)**)
- Sunrise Pharmaceutical, Guaifenesin, 400 mg, Expectorant, 100 Tablets
- **(b)(4)** Guiafenesin, 400 mg, Expectorant, 100 Tablets (distributed by **(b)(4)**)
- Sunrise Pharmaceutical, Guaifenesin, 400 mg, Dextromethorphan HBR 20mg, Expectorant/Antitussive, 30 Tablets
- **(b)(4)**, Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 100 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 1000 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 25 mg, Antihistamine, 1000 Capsules
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 120 Tablets
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Senna, 8.6 mg, Docusate Sodium, 50 mg, Natural Vegetable Laxative plus Stool Softener, 60 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 1000 Tablets

The above products are drugs within the meaning of section 201(g) of the Act, [21 U.S.C.321 (g)] because as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases.

Further, the three **(b)(4)** Diphenhydramine HCL Capsule products manufactured and packaged by Sunrise Pharmaceuticals as noted above for use as antihistamines are "new drugs" within the meaning of Section 201(p) of the Act [21 U.S.C. 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Specifically, OTC drug products intended for use as OTC antihistamines with an active ingredient of diphenhydramine HCL, are subject to the requirements of the final monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Human Use at 21 CFR Part 341. The labeling for all three diphenhydramine HCL products state the following indications for uses: "temporarily relieves· hay fever or other upper respiratory allergies like: • runny nose· sneezing ·watery eyes· itchy nose or throat". However, the final monograph does not allow for the use of antihistamines to relieve hay fever or other upper respiratory allergies, rather the permitted uses are for temporary relief of such symptoms listed on your products label (i.e. runny nose, sneezing, watery eyes, itchy nose or throat) "due to hay fever ... or other upper respiratory allergies ...."[emphasis added] (21 CFR 341.72(b)).

Therefore, the three **(b)(4)** Diphenhydramine HCL products described above are "new drugs" as defined by section 201 (p) of the Act, 21 U.S.C. 321 (p) and 21 CFR 310.3(h), because the labeled uses are not in accordance with the Antihistamine Final Monograph (21 CFR 341.72). Additionally, none of the three

diphenhydramine HCL products are the subject of an approved new drug application. Because the three **(b)(4)**Diphenhydramine HCL products above are new drugs and not the subject of an approved new drug application, the current marketing of these products in the United States violate sections 301(d) and 505(a) of the Act (21 U.S.C. 331(d), 355(a)).

Several of the products listed above are also misbranded. Specifically, both Sunrise Pharmaceutical Aspirin 325 mg Enteric Safety Coated drug products (100 and 1000 tablets) are misbranded under sections 201 (n) and 502(a) and (f) of the Act because both products' labeling have the Reye's Syndrome warning as the third warning under the 'Warnings" section, whereas, under 21 CFR 201.315(h)(2), the Reye's Syndrome warning is required to be "the first warning statement under the heading 'Warnings'" (see also 21 CFR 201.315(h)(4)).

In addition, the following products are misbranded under 502(c) and 502(e)(1)(A)(iii) because the inactive ingredients are not listed in alphabetical order, as required under 502(e)(1)(A)(iii) and 21 CFR 201.66(c)(8):

- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 100 Tablets
- Sunrise Pharmaceutical, Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxative, Enteric Sugar Coated, 100 Tablets
- Sunrise Pharmaceutical, Bisacodyl USP, 5 mg, Laxactive, 1000 Enteric Sugar Coated Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 100 Tablets
- **(b)(4)** Bisacodyl Tablets, USP, 5 mg, Delayed-Release Tablets Enteric Coated, 1000 Tablets
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 100 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 50 mg, Antihistamine, 1000 Capsules
- **(b)(4)** Diphenhydramine HCL Capsules, USP, 25 mg, Antihistamine, 1000 Capsules
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 120 Tablets
- Sunrise Pharmaceutical, Aspirin, 81 mg, Pain Reliever Adult Low Dose, Enteric Safety Coated, 1000 Tablets
- Sunrise Pharmaceutical, Senna, 8.6 mg, Docusate Sodium, 50 mg, Natural Vegetable Laxative plus Stool Softener, 60 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 100 Tablets
- **(b)(4)** Natural Vegetable Laxative Plus Stool Softener, 1000 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets
- **(b)(4)** Docusate Sodium, Stool Softener Plus Laxative, 100 Tablets

Furthermore, all of these products that do not list the inactive ingredients in alphabetical order--except the diphenhydramine HCL products--also have an inactive ingredients header under the "Drug Facts" that states "May contain the following inactive ingredients" (emphasis added). The use of "May contain" in the inactive ingredients header does not comport with the appropriate heading under 21 CFR 201.66(c)(8) and makes the product misbranded under 502(c) of the Act. Also, the use of "May contain" to list inactive ingredients indicates that there are inactive ingredients that may or may not be present in the product. Such labeling that lists all ingredients as potentially alternative ingredients is false and misleading and makes the product misbranded under 502(a) because it fails to identify which inactive ingredients are present in the product (See FDA's "Guidance for Industry Labeling OTC Human Drug Products", May 2009, for guidance on labeling inactive ingredients that may or may not be contained).

Also, for your information, the formatting of the "Drug Facts" section on several of your OTC products is inconsistent with the requirements under 21 CFR 201.66. For example, the "Aspirin, 325 mg, Pain Reliever Enteric Safety Coated, 1000 tablets" product does not have its "Drug Facts" header in larger font than the rest of the "Drug Facts" (see 21 CFR 201.66(d)(2).

Misbranding of bulk packaged finished OTC drug products intended for repackaging

In addition, based on the information collected during the inspection, you also manufacture the following OTC drugs that are finished OTC products shipped with bulk package labeling for repackaging, including but not limited to:

- Aspirin Film Coated White Tablets, 325 mg
- Aspirin Enteric Coated Orange Tablets, 325mg
- Phenylephrine Hydrochloride Film Coated Red Tablets, 5mg
- Phenylephrine HCL F/C Red Tablets, 10mg
- Bisacodyl E/C Orange Tablets, 5mg
- Chlorpheniramine Maleate Yellow Tablets 4mg
- Guaifenesin Caplets
- Guaifenesin & Dextromethorphan HBr. Caplets, 400mg & 20mg
- Chewable Aspirin Orange Flavor Tablets 81 Mg
- Diphenhydramine HCL Capsules, 50mg
- Diphenhydramine Hydrochloride Capsules, 25mg
- Aspirin Enteric Coated Yellow Tablets, 81 mg
- Senna & Docusate sodium F/C Orange Tablets, 8.6mg & 50mg

- Senna & Docusate sodium F/C Red Tablets, 8.6mg &50mg
- Aspirin Enteric Coated Peach Tablets, 81 mg

Based on documentation and bulk package labeling collected for the above products, the products are finished OTC drug products labeled for repackaging. As finished OTC drug products, the above OTC drug products once introduced into interstate commerce for repackaging, unless exempted under 21 CFR 201.150, must meet all drug labeling requirements described in section 502 of the Act (21 USC 352) and in 21 CFR 201, including the "Drug Facts" labeling requirements under 21 CFR 201.66. Based on documentation collected there is no evidence that the operators of the establishments where the drugs are to be repackaged are part of Sunrise Pharmaceuticals nor is there evidence that there are labeling agreements in place with such operators, and, in turn, neither exemption under 21 CFR 201.150(1) or (2), respectively, are met. Therefore, the above products, which only have bulk package labeling, are misbranded: (1) under section 502(c) of the Act because none of the outer container labeling contains "Drug Facts" required by 21 CFR 201.66; (2) under section 502(e)(1)(A)(iii) because the inactive ingredients are not listed; (3) under 502(f) of the Act because there are not adequate directions for use and warnings; and (4) under sections 502(a) and 201(n) of the Act because the bulk labeling is misleading by conveying the products are exempt from required FDCA labeling.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. We note that several deficiencies were cited in the August 2007 inspection and correction actions were promised. The current inspection found that promised corrective actions have not occurred and the same deficiencies exist at your firm. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

We also request that you outline the action you are taking to discontinue the marketing of the unapproved drug products at your facility, or any other applicable drug which you may market. Also please note that if you are no longer marketing these products, you must update the Drug Listing files in accordance with 21 CFR 207.30(a)(2).

Your response should be sent to the following address: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,

/s/

Diana Amador-Toro
Director, New Jersey District

Links on this page:

Exhibit 2

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Vision Pharm, LLC 4/29/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Southeast Region
555 Winderley Place
Suite 200
Maitland, Florida 32751

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

FLA-10-17

April 29, 2010

Sander S. Busman
President & Chief Executive Officer
Vision Pharma, LLC
9180 Estero Park Commons Boulevard
Unit 1
Estero, FL 33928

Dear Mr. Busman:

On **(b)(4)** FDA issued a warning letter to **(b)(4)**. Inc. **(b)(4)** (copy attached). As explained more fully in that **(b)(4)**, certain drug products that **(b)(4)** has manufactured are new drugs that lack approved applications as required under the Federal Food, Drug, and Cosmetic Act (the Act). **(b)(4)** **(b)(4)**. These drug products include, but are not necessarily limited to:

- Colchicine Tablets, 0.6 mg
- Hyoscyamine Sulfate Tablets, USP, 0.125 mg
- Hyoscyamine Sulfate Orally Disintegrating Tablets, 0.125 mg
- Hyoscyamine Sulfate Sublingual Tablets, 0.125 mg

The above products are drugs within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because, as demonstrated by their labeling, they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331 (d) and 355(a)], a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. Based on our information, there are no FDA - approved applications on file for these drug products **(b)(4)**

Additionally, because the above prescription drug products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses, as described in 21 C.F.R. § 201.5. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. Because the products lack required approved applications, they are not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these products without approved new drug applications violates section 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and (d)].

Further, as explained in the **(b)(4)**, the above drug products are adulterated, 21 U.S.C. 351(a)(2)(B), and thus your firm may not introduce or deliver them for introduction into interstate commerce, 21 U.S.C. § 331(a).

The violations cited in this letter are not intended to be an all-inclusive statement of violations that may exist in connection with your products. In particular, violations cited in this letter are not necessarily limited to drug products manufactured by Sunrise and may apply to all drug products that you market without FDA-approved applications. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure, and injunction. Other federal agencies may take this **(b)(4)** into account when considering the award of contracts.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. If you no longer market the above products, your response should so indicate, including the reasons that, and the date on which, you ceased production.

Your reply should be sent to U.S. Food & Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida, Attn: Winston R. Alejo, Compliance Officer.

Sincerely,

/s/

Emma R. Singleton
Director, Florida District

Enclosure

(b)(4)

Links on this page:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drug Evaluation
and Research
Food and Drug Administration
Silver Spring, MD 20993

Exhibit 3

March 3, 2010

Thank you for taking the time to write to the Food and Drug Administration (FDA) regarding your concerns over the current market prices of approved oral colchicine (Colcrys). I am writing to address your concern and to share FDA's perspective regarding the use of unapproved oral colchicine.

While the Agency does not regulate the pricing of prescription drugs, I appreciate your concern about increased prices of Colcrys. At FDA we are well aware that price affects access. Given that important reality, I would like to take this opportunity to discuss the drug approval process and the specific benefits offered by the required approval of oral colchicine.

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that safe and effective drugs are available to the American public. FDA's drug approval process ensures that drugs are safe, effective, of a suitable quality and purity, and are properly labeled. Drugs that have not been approved by FDA may not be safe and effective, may have been manufactured under sub-standard conditions, may contain too much or too little (if any) active ingredients, and may not have necessary labeling information and warnings.

Although FDA has not, to date, taken any regulatory action to remove unapproved oral colchicine products from the market, we have been in long-term communication with all manufacturers of unapproved drugs Since FDA announced its Unapproved Drugs Initiative in June 2006, marketers of unapproved drugs have been on notice that addressing risks from unapproved drugs is a high priority for FDA, and that the Agency plans to systematically and responsibly ensure that all products on the U.S. prescription drug market become compliant with current FDA approval requirements for safety and efficacy. Although FDA is aware of 21 firms that manufacture and distribute unapproved oral colchicine, so far, only one, Mutual Pharmaceuticals/URL ("Mutual"), has chosen to take the clinically responsible step of seeking approval for unapproved oral colchicine.

Of important note, the colchicine products you are referring to in your communication to FDA are not "generic" drugs. By definition, generic drugs are those evaluated and approved by FDA to demonstrate bioequivalence to a brand name reference product. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same quality, strength, purity and stability as brand-name drugs. Additionally, the generic manufacturing, packaging, and testing sites must meet the same quality standards as those of brand-name drugs. These colchicine products have not been evaluated and approved by FDA. They are unapproved drugs, not generic medications, and neither their safety nor their efficacy can be assured.

Mutual recently obtained approval of its oral colchicine product, Colcrys. During the drug approval process, FDA identified two previously uncharacterized safety concerns associated with the use of colchicine (marketed as Colcrys).

First, FDA analyzed safety data for colchicine-related deaths described in the published literature, adverse events reported to FDA's Adverse Event Reporting System (AERS), and company-sponsored pharmacokinetic and drug interaction studies. All of the reported safety data were related to unapproved oral colchicine. The analysis found 169 deaths associated with the use of unapproved oral colchicine.

Of the 169 deaths, 117 were not reported as overdoses; the majority of reported deaths had colchicine doses within the therapeutic range of less than or equal to 2 mg per day. The reported death cases did not contain information regarding patients' renal or hepatic function. Sixty of the 117 reported deaths (51%) involved patients who were concomitantly using clarithromycin. These reports suggest alterations in the pharmacokinetics of colchicine played a central role in the development of toxicity.

Based on review and analysis, FDA concluded there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors. FDA recommends that P-gp or strong CYP3A4 inhibitors not be used in patients with renal or hepatic impairment who are currently taking colchicine. Furthermore, FDA recommends that healthcare professionals consider a dose reduction or interruption of colchicine in patients with normal renal and hepatic function if treatment with a P-gp or a strong CYP3A4 inhibitor is required. The FDA-approved prescribing information for Colcrys contains recommended dosage adjustments.

Second, as part of the approval process, the sponsor of Colcrys submitted data from a clinical trial to evaluate the safety and efficacy of a low-dose regimen of oral colchicine for treatment of acute gout flares compared to the traditional high-dose regimen. The trial was a multicenter, randomized, double-blind, placebo-controlled trial of patients meeting American College of Rheumatology criteria for gout who were assigned to one of three treatment groups within 12 hours of a gout flare, as follows:

- Group 1: high-dose colchicine (1.2 mg, then 0.6 mg hourly for 6 hours [4.8 mg total])
- Group 2: low-dose colchicine (1.2 mg, then 0.6 mg in 1 hour [1.8 mg total] followed by 5 placebo doses hourly)
- Group 3: placebo (2 capsules, then 1 capsule hourly for 6 hours).

The trial found that a statistically significantly greater proportion of patients in the low-dose (38%) and high-dose (33%) colchicine groups achieved a 50% reduction in pain in the target joint compared to placebo (16%). Additionally, the rate of gastrointestinal adverse events (diarrhea, nausea, vomiting, abdominal pain) was considerably lower in low-dose patients (26%) compared to high-dose patients (77%). Further, there were no severe adverse events reported in low-dose patients compared to 10 reported in high-dose patients. These findings suggest that prior use of high-dose colchicine may have exposed patients to increased toxicity with no greater efficacy than the low-dose regimen.

FDA is highlighting these important safety considerations in the approved prescribing information to help ensure safe use of Colcrys. Without this review by FDA, outdated assumptions of what is safe and effective for treatment with oral colchicine would have remained unchecked, and patients would have continued to suffer from adverse reactions such as severe gastro-intestinal complications -- and even death -- needlessly.

The fatalities associated with unapproved oral colchicine products are among many other serious adverse events associated with unapproved drugs. These adverse events, in addition to being tragic and in many cases preventable, place a serious burden on the healthcare system. The Agency is particularly concerned because labeling of many unapproved drugs does not adequately convey the risks of the drugs and how to best use drugs safely, such as what kind of other medicines should be avoided at the same time to lower the chances of side effects. When a drug is not used properly because the labeling is inadequate, there is a cost to patients and the healthcare system because of the care required as a result of adverse events.

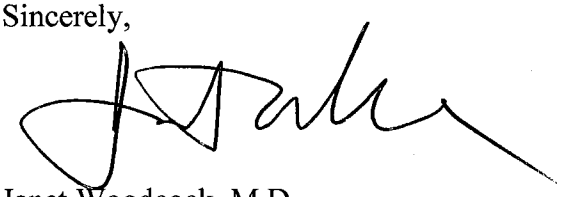
The approval of Colcrys demonstrates that while a patient or prescriber may believe that a drug is safe or effective because of individual experience, such subjective experiences can be misleading and insufficient to establish safety and effectiveness. Instead, FDA relies on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with the risks and benefits of taking a placebo or another accepted therapy. Carefully designed clinical trials have repeatedly demonstrated that the safety and effectiveness of drugs cannot be adequately established from anecdotal evidence or consumer or prescriber preferences.

Only Mutual has submitted an application to FDA for the approval of single-ingredient oral colchicine. We have discussed with the American College of Rheumatology (ACR) the importance of unapproved oral colchicine products obtaining FDA approval. ACR informed us that it would reach out to the unapproved manufacturers to encourage them to become engaged in the FDA approval process. FDA has an Unapproved Drugs Coordinator in the Office of New Drugs who is available to assist manufacturers in obtaining information regarding the application process.

I recognize that there is a real concern that prices of oral colchicine have increased substantially following the approval of Colcrys. Again, FDA has no statutory authority to control the prices charged for marketed drugs in the U.S. These prices are established by manufacturers, distributors, and retailers. I would, however, like to note that Mutual has started the Colcrys Patient Assistance Program, an initiative that will enable some patients with various limited financial means to save on Colcrys prescriptions. Unlike other patient assistance programs that may target primarily patients at or near the poverty level, Mutual's tiered program is designed to help patients in a variety of socio-economic situations. For instance, according to a December 22, 2009 letter written by Mutual president and chief executive officer Richard H. Roberts, M.D., Ph.D. to the American College of Rheumatology, a patient in a family of four whose yearly income is $132,000 would be eligible to receive a month's supply of Colcrys for $30. [see http://www.urlpharma.com/NewsView.aspx?code=140O5M23J30&archived=False.]

The Agency will continue to ensure that all prescription drugs are safe, effective, high quality, and properly labeled by encouraging companies to comply with FDA approval requirements. I ask your support in this important initiative.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research