Imprimis Pharmaceuticals 12/21/17

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food & Drug Administration
19701 Fairchild
Irvine, California 92612

December 21, 2017

WARNING LETTER

Mark Baum
Imprimis Pharmaceuticals Inc.
12264 El Camino Real, Suite 350
San Diego, CA 92130

Dear Mr. Baum:

This is to advise your firm that the U.S. Food and Drug Administration (FDA) has reviewed promotional materials disseminated by your firm, including the website at www.imprimisrx.com **1** where you take orders for the following compounded drug products:

• “Dropless” products

  o Tri-Moxi (triamcinolone acetonide, moxifloxacin hydrochloride), 15/1mg/ml
  o Tri-Moxi-Vanc (triamcinolone acetonide, moxifloxacin, vancomycin), 15/1mg/10mg/mL
  o Moxi (moxifloxacin hydrochloride), 5mg/mL

• “LessDrops” products

  o Pred-Gati-Nepaf (prednisolone acetate, gatifloxacin, nepafenac), 1/0.5/0.1%/mL
  o Pred-Gati (prednisolone acetate, gatifloxacin), 1/0.5%/mL
  o Pred-Nepaf (prednisolone acetate, nepafenac), 1/0.1%/mL

• “Simple Drops” products

  o Tim-Brim-Dor PF **2** (timolol/brimonidine/dorzolamide), 0.5/0.15/2%
  o Tim-Brim-Dor-Lat PF (timolol/brimonidine/dorzolamide/latanoprost), 0.5/0.15/2/0.005%
  o Tim-Dor-Lat PF (timolol/dorzolamide/latanoprost), 0.5/2/0.005%
  o Tim-Lat PF (timolol/latanoprost), 0.5%/0.005%

• “Klarity C-Drops” product (cyclosporine 0.1%/chrondroitin sulfate)

The claims on your website and other promotional materials establish that these products are drugs under section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 321(g)(1), because they are intended for use in the cure, mitigation, treatment or prevention of disease. As explained further below, your firm’s website and twitter account make false or misleading claims regarding “Simple Drops” and “Klarity C-Drops” – specifically, they represent that these products are made with FDA approved components or are FDA-approved, when that is not the case. In addition, your firm’s website makes false or misleading claims about your “Dropless,” “LessDrops,” and “Simple Drops” products by omitting important risk information, including side effects, contraindications, or consequences that may result from their use, and by presenting efficacy claims about your “Simple Drops” products while omitting material information.

Thus, the webpage and other promotional materials misbrand your “Dropless,” “LessDrops,” “Simple Drops,” and “Klarity C-Drops” products within the meaning of the FD&C Act and make their distribution violative. 21 U.S.C. 352(a), (bb); 321(n); 331(a).

These violations are concerning from a public health perspective because they create a false or misleading impression about the safety and effectiveness of these products. This is especially concerning in light of the many known risks associated with several of the active ingredients in these products, as reflected in the prescribing information for FDA-approved products containing the same active ingredients **3**, and the technique by which your website indicates your “Dropless” products should be administered. These risks include, but are not limited to, hemorrhagic occlusive retinal vasculitis (HORV) and ciliary body hemorrhage. Appendix I to this Warning Letter includes descriptions of these and other known risks associated with the active ingredients in your products and the technique by which your website indicates your “Dropless” products should be administered.

In addition, your website and other promotional materials contain claims regarding the effectiveness of your “Simple Drops” products that are not supported by the effectiveness data for the active ingredients in certain “Simple Drops” products. The claims on your website and in other promotional materials suggest that patients can treat elevated intraocular pressure with “One Simple Drop” according to “One Simple Regimen,” but fail to disclose that a patient would need to take more than one eye drop product pursuant to multiple, different dosing regimens in order for the active ingredients in those “Simple Drops” to be effective throughout the day. This is concerning because patients

can lose vision in the form of visual field loss (also known as glaucoma) if elevated intraocular pressure is not controlled thoughout a 24 hour period each day. Appendix II to the Warning Letter includes information about the effectiveness of the active ingredients in your "Simple Drops" products that does not support and is inconsistent with your effectiveness claims.

False or Misleading Claims

Your "Simple Drops" brochure states that your products are "Compounded with FDA-approved drug components." In addition, a press release, "Imprimis Pharmaceuticals to Launch its Simple Drops Combination Glaucoma Drops at Leading Cataract & Refractive Surgery Medical Meeting," May 4, 2017, states, "Simple Drops consist of high-quality sterile FDA-approved components that are made and dispensed from Imprimis' PCAB-accredited and FDA-inspected facilities." Furthermore, on October 25, 2017, you tweeted the following on your Twitter account, @markbaum4: "EyewireTV – Compounded Cyclosporine Introduced eyewiretoday.com/?v=mwloh #bauch lomb #dryeye #fdaapproval/clearance #imprmispharmaceuticals," suggesting your compounded cyclosporine product – "Klarity-C drops" -- is FDA approved. Because your "Simple Drops" products are compounded using bulk drug substances, which are not FDA-approved, and your "Klarity-C drops" product is not FDA-approved, these statements are false or misleading.

False or Misleading Risk Presentation

A drug is misbranded if its labeling, including promotional labeling, is false or misleading in any particular. 21 U.S.C. 352(a). In addition, a compounded drug is misbranded if its advertising or promotion is false or misleading in any particular. 21 U.S.C. 352(bb). In determining whether labeling or advertising is misleading, section 201(n) of the FD&C Act requires that it be taken into account whether the labeling or advertising fails to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the labeling or advertising or under such conditions of use as are customary or usual.

Your firm's website includes claims about the efficacy and use of "Dropless," "LessDrops," and "Simple Drops" products, each of which consists of multiple active ingredients. According to your website, "Dropless" products are intended for intravitreal injection during ocular surgery to prevent infection and inflammation; "Less Drops" products are intended for topical use post ocular surgery to prevent infection and inflammation; and "Simple Drops" products are intended for topical use to treat elevated intraocular pressure. Appendix III includes additional examples of claims made by your firm about the efficacy of your firm's ophthalmic products. However, your firm's website fails to communicate any risk information associated with these products.

This is particularly concerning in light of the many known risks associated with the active ingredients in these products and the technique by which your website indicates that your "Dropless" products should be administered. For example, one of your "Dropless" products includes triamcinolone, moxifloxacin, and vancomycin, and this product recently was associated with an incident of HORV, a rare, potentially blinding postoperative complication. **4** There are also many known risks associated with transzonular injection via cannula of "Dropless" products, such as floaters and ciliary body hemorrhage.

By failing to present any information regarding the risks associated with these products, the website is false or misleading. The omission of risk information suggests that the drugs do not bear the risks that are known to be associated with the active ingredients in these products and the technique by which your website indicates that your "Dropless" products should be administered. The absence of risk information on your website is especially problematic from a public health perspective. Because these risks are not described, the website does not enable healthcare providers to make informed decisions about whether the benefits of your products outweigh the risks for their patients or to inform patients of appropriate monitoring that could minimize consequences of these potential adverse events.

False or Misleading Efficacy Presentation

Patients often take multiple eye drop products with different active ingredients and different dosing regimens (e.g., one drop or multiple drops at different times of day) to treat elevated intraocular pressure. Your firm combines the active ingredients in those different eye drop products into single products, the "Simple Drops" products, and offers those products as treatments for elevated intraocular pressure. However, the effectiveness data for certain active ingredients in the "Simple Drops" products suggest that a patient would need to follow different dosing regimens for the various active ingredients in the "Simple Drops" products in order for each ingredient to be effective throughout the day.

In determining whether labeling or advertising is misleading, section 201(n) of the FD&C Act requires that it be taken into account whether the labeling or advertising fails to reveal facts that are material in light of representations made. While your firm's website and other promotional materials suggest that "Simple Drops" products are effective in treating elevated intraocular pressure, they do not disclose that an effective treatment regimen using the active ingredients in the "Simple Drops" products would require additional doses of certain products. Instead, your firm's website and other promotional materials contain claims regarding the effectiveness of your "Simple Drops" products which are neither supported nor consistent with the effectiveness data associated with their active ingredients.

Examples of these claims include:

• "One Simple Drop. One Simple Regimen."
• "Imprimis Pharmaceuticals to Launch its Simple Drops Combination Glaucoma Drops at Leading Cataract & Refractive Surgery Medical Meeting," May 4, 2017

    o "Simple Drops preservative-free drops conveniently provide multiple glaucoma medications into a single bottle providing patients with a simple treatment option. By providing multiple medications into one combination drop, Simple Drops may increase patient compliance and reduce costs."

• "Simple Drops may simplify your patient's treatment regimen by combining multiple glaucoma medications into a single bottle"
• "May increase patient compliance by reducing the number of drops taken per day"
• "Reduce compliance issues with multiple drop bottles. Simplify your patient's treatment with one Preservative-Free Simple Drop"
• "Simple Drops include multiple medications into one drop bottle for your patient's convenience"
• "Provides convenience of multiple medications into one combination drop"
• "May increase patient compliance by reducing the number of drops needed per day"

In addition, a video, "Eye Drop Instructions For Use," states that "LessDrops" and "Simple Drops" products "may require fewer drops" and "may reduce post treatment confusion."

The claims described above suggest that to effectively treat elevated intraocular pressure, a patient would only need to take one product ("One Simple Drop") pursuant to one dosing regimen ("One Simple Regimen"), rather than multiple products pursuant to multiple, different dosing regimens. They also suggest that the purported benefits of doing so include increasing the simplicity of the dosing regimen, reducing the number of drops taken per day, increasing patient compliance, and reducing post treatment confusion. These claims are not accompanied by any additional information about the dosage regimen that would be necessary for each drug product in order to ensure effective treatment.

The false or misleading efficacy presentations for these products is particularly concerning because they may lead healthcare providers to prescribe only "Simple Drops" products to treat elevated intraocular pressure, when patients may not be receiving effective medications with certain "Simple Drops" products alone. Patients can lose vision in the form of visual field loss (also known as glaucoma) if elevated intraocular pressure is not controlled thoughout a 24 hour period each day.

Conclusion

For the reasons discussed above, your webpage and other promotional materials misbrand the "Dropless," "LessDrops," "Simple Drops," and "Klarity-C drops" products within the meaning of the FD&C Act, which makes their distribution violative. 21 U.S.C. 352(a), (bb); 321(n); and 331(a).

The violations cited in this letter are not intended to be an all-inclusive statement of violations associated with your drug products. It is your responsibility to ensure that your firm complies with all requirements of federal law, including 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.

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. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FD&C Act, include your reasoning and any supporting information for our consideration. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction.

In addition, we request that you include in your response copies of all labeling, including package inserts associated with the "Dropless," "LessDrops," "Simple Drops," and "Klarity-C drops" products, and indicate which one of your facilities distribute each of these products. **5**

Your firm's response should be sent to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild
Irvine, California 92612

If you have any questions regarding any issues in this letter, please contact Jessica Mu, Compliance Officer, at **Jessica.Mu@fda.hhs.gov (mailto:Jessica.Mu@fda.hhs.gov)**, and reference unique identifier CMS 540678.

Sincerely,
/S/
Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

APPENDIX I

Technique-related risks

*Risks associated with transzonular injection via cannula of "Dropless" products include **6***:

Ciliary body hemorrhage
Vitreous floaters
Blurred vision

Active ingredient-related risks 7

Risks associated with "Dropless" products include:

Tri-Moxi (triamcinolone acetonide, moxifloxacin hydrochloride), 15/1mg/mL

Elevated intraocular pressure
Glaucoma
If a lens is still present, cataract formation
Allergic reactions
Vitreous floaters
Blurred vision

Tri-Moxi-Vanc (triamcinolone acetonide, moxifloxacin hydrochloride, vancomycin), 15/1mg/10mg/mL

Elevated intraocular pressure
Glaucoma
If a lens is still present, cataract formation
Allergic reactions

Hemorrhagic occlusive retinal vasculitis (HORV)
Vitreous floaters
Blurred vision

Moxi (moxifloxacin hydrochloride), 5mg/mL

Allergic reactions
Prolonged use may result in overgrowth of non-susceptible organisms, including fungi.

Risks associated with "LessDrops" products include:

Pred-Gati-Nepaf (prednisolone acetate, gatifloxacin, nepafenac), 1/0.5/0.1%/mL

Elevated intraocular pressure
Glaucoma
Allergic reactions
Hyphema Keratitis
Increased potential for corneal healing problems
Corneal thinning
Corneal erosion
Corneal ulceration
Corneal perforation
If a lens is still present, cataract formation

Pred-Gati (prednisolone acetate, gatifloxacin), 1/0.5%/mL

Elevated intraocular pressure
Glaucoma
Allergic reactions
Increased potential for corneal healing problems
Corneal thinning
Corneal erosion
Corneal ulceration
Corneal perforation
If a lens is still present, cataract formation

Pred-Nepaf (prednisolone acetate, nepafenac), 1/0.1%/mL

Elevated intraocular pressure
Glaucoma
Allergic reactions
Hyphema
Keratitis
Increased potential for corneal healing problems
Corneal thinning
Corneal erosion
Corneal ulceration
Corneal perforation
If a lens is still present, cataract formation

Risks associated with "Simple Drops" products include:

TIM-LAT (timolol/latanoprost)

Use of timolol, including topical ophthalmic timolol is contraindicated in patients with bronchial asthma or a history of bronchial asthma
Use of timolol is contraindicated in patients with second or third degree atrioventricular block
Use of timolol is contraindicated in patients with overt cardiac failure
Use of timolol is contraindicated in patients with severe chronic obstructive pulmonary disease
There are respiratory and cardiac contraindications because severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma have been reported following ophthalmic administration of timolol
Masking of certain clinical signs (e.g., tachycardia) of hyperthyroidism
Masking of the signs and symptoms of acute hypoglycemia
Increased pigmentation of the iris
Increased pigmentation of the periorbital tissue (eyelid)
Increased pigmentation and growth of the eyelashes
Latanoprost should not be used in patients with active intraocular inflammation
Macular edema may occur particularly in patients with pseudophakia with a torn posterior capsule

BRIM-DOR (brimonidine/dorzolamide)

Hypersensitivity reactions
Potentiation of syndromes associated with vascular insufficiency
Fatigue/drowsiness
Corneal edema in patients with low endothelial cell counts
Lethargy/Coma in patients under two years of age

TIM-BRIM-DOR (timolol/brimonidine/dorzolamide)

Use of timolol, including topical ophthalmic timolol is contraindicated in patients with bronchial asthma or a history of bronchial asthma
Use of timolol is contraindicated in patients with second or third degree atrioventricular block
Use of timolol is contraindicated in patients with overt cardiac failure
Use of timolol is contraindicated in patients with severe chronic obstructive pulmonary disease
There are respiratory and cardiac contraindications because severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma have been reported following ophthalmic administration of timolol
Masking of certain clinical signs (e.g., tachycardia) of hyperthyroidism
Masking of the signs and symptoms of acute hypoglycemia
Hypersensitivity reactions
Potentiation of syndromes associated with vascular insufficiency
Corneal edema in patients with low endothelial cell counts

TIM-DOR-LAT (timolol/dorzolamide/latanoprost)

Use of timolol, including topical ophthalmic timolol is contraindicated in patients with bronchial asthma or a history of bronchial asthma
Use of timolol is contraindicated in patients with second or third degree atrioventricular block
Use of timolol is contraindicated in patients with overt cardiac failure
Use of timolol is contraindicated in patients with severe chronic obstructive pulmonary disease
There are respiratory and cardiac contraindications because severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma have been reported following ophthalmic administration of timolol
Masking of certain clinical signs (e.g., tachycardia) of hyperthyroidism.
Masking of the signs and symptoms of acute hypoglycemia
Hypersensitivity reactions
Corneal edema in patients with low endothelial cell counts
Increased pigmentation of the iris
Increased pigmentation of the periorbital tissue (eyelid)
Increased pigmentation and growth of the eyelashes
Latanoprost should not be used in patients with active intraocular inflammation
Macular edema may occur particularly in patients with pseudophakia with a torn posterior capsule

TIM-BRIM-DOR-LAT (timolol/brimonidine/dorzolamide/latanoprost)

Use of timolol, including topical ophthalmic timolol is contraindicated in patients with bronchial asthma or a history of bronchial asthma
Use of timolol is contraindicated in patients with second or third degree atrioventricular block
Use of timolol is contraindicated in patients with overt cardiac failure
Use of timolol is contraindicated in patients with severe chronic obstructive pulmonary disease
There are respiratory and cardiac contraindications because severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma have been reported following ophthalmic administration of timolol
Masking of certain clinical signs (e.g., tachycardia) of hyperthyroidism
Masking of the signs and symptoms of acute hypoglycemia
Hypersensitivity reactions
Corneal edema in patients with low endothelial cell counts
Increased pigmentation of the iris
Increased pigmentation of the periorbital tissue (eyelid)
Increased pigmentation and growth of the eyelashes
Latanoprost should not be used in patients with active intraocular inflammation
Macular edema may occur particularly in patients with pseudophakia with a torn posterior capsule
Potentiation of syndromes associated with vascular insufficiency

APPENDIX II

Efficacy information associated with "Simple Drops" products:

Timolol/Latanoprost

This combination has been studied. It was determined that giving timolol in the morning and latanoprost at night, i.e., splitting the timing of the dosing, was more effective than giving the combination once or twice a day.

Timolol/Brimonidine/Dorzolamide

Timolol is most effective when administered in the morning, and should not be given more than twice a day. In order for Brimonidine and Dorzolamide to be effective throughout the entire day, they must be administered three times a day because they only work for 8 hours. As a result, any patient who uses this product would also have to use multiple other products that include Brimonidine and Dorzolamide in order for this product to be effective throughout the entire day.

Timolol/Dorzolamide/Latanoprost

Timolol is most effective when administered in the morning, and should not be given more than twice a day. Latanoprost is administered once per day, and is most effective when administered just before bedtime. If Latanoprost is administered more than once a day, it can be less effective in lowering intraocular pressure than being dosed once a day or it can cause paradoxical elevations in intraocular pressure. In order for Dorzolamide to be effective throughout the entire day, it must be administered three times a day because it only works for 8 hours. As a result, any patient who uses this product would also have to use another product that includes Dorzolamide in order for this product to be effective throughout the entire day.

Timolol/Brimonidine/Dorzolamide/Latanoprost

Timolol is most effective when administered in the morning, and should not be given more than twice a day. Latanoprost is administered once per day, and is most effective when administered just before bedtime. If Latanoprost is administered more than once a day, it can be less effective in lowering intraocular pressure than being dosed once a day or it can cause paradoxical elevations in intraocular pressure. In

order for Brimonidine and Dorzolamide to be effective throughout the entire day, they must be administered three times a day because they only work for 8 hours. As a result, any patient who uses this product would also have to use multiple other products that include Brimonidine and Dorzolamide in order for this product to be effective.

APPENDIX III

The following are additional examples of claims made by your firm about the efficacy of your firm's ophthalmic products:

Web content:

- "Dropless" products
  - o "Dropless Cataract Surgery"
  - o "Reduce issues with patient compliance"
  - o "Single Intraocular administration"
  - o "Quality sterile injectable compounded medications for use in ocular surgery"
  - o "Ophthalmologists currently using Dropless Therapy formulations believe the optimal location for the injection would be the vitreous due to the depot effect. This is achieved by one of two approaches:

 Transzonular injection via cannula.
 Pars plana injection via needle"

- "LessDrops" products
  - o "Keep It Simple"
  - o "Provide fewer drops . . . with our proprietary topical ophthalmic compounded formulations for patients following LASIK, PRK, cataract, and other ocular surgeries (and non-surgical applications)"
  - o "Combination drop therapy may reduce the number of eye drops needed after ocular surgery"
  - o "Quality sterile compounded medications for pre and post ocular surgery"

- "Simple Drops" products
  - o "Simple Drops may simplify your patient's treatment regimen by combining multiple glaucoma medications into a single bottle"

"Simple Drops" Brochure on website:

- "Reduce compliance issues with multiple drop bottles. Simplify your patient's treatment with one Preservative-Free Simple Drop"
- "Simple Drops include multiple medications into one drop bottle for your patient's convenience"
- "Provides convenience of multiple medications into one combination drop"
- "May increase patient compliance by reducing the number of drops needed per day"

Press releases posted on your website:

- "Imprimis Pharmaceuticals Secures First Key Composition Patent for Dropless Therapy Formulations," October 2, 2017
  - o "Imprimis' Dropless Therapy compounded antibiotic and steroid formulations are available in single, injectable intraocular doses administered by physicians following ocular surgery. Dropless Therapy may substantially reduce or eliminate the need for patient-administered eye drops following surgery, thereby potentially eliminating patient non-compliance and dosing errors associated with post-operative care regimens."
  - o "Dropless Therapy can simplify the post-operative care process, provide safeguards against bacterial infection and inflammation, and may decrease overall cost."

- "Imprimis Pharmaceuticals Patent-Pending Dropless and LessDrops Formulations Exceed One Million Patient Eyes Milestone," July 27, 2017
  - o "By eliminating or reducing the need for post-surgery eye drop regimens, Dropless injectable formulations…"
  - o "…Imprimis' affordably priced LessDrops combination topical drops serve patients following cataract, refractive and other ocular procedures."
  - o Mark L. Baum, CEO of Imprimis, stated, "Our innovative solutions, which all have come from the clinical experience of our physician-customers, have eliminated or reduced post-surgery drop regimens, provided better medication adherence and recovery, in addition to saving customers money compared to the standard of care."
  - o "Two compounded antibiotic and steroid formulations currently available in single, injectable, intraocular doses administered during ocular surgery include preservative-free combinations of triamcinolone acetonide and moxifloxacin hydrochloride and triamcinolone acetonide, moxifloxacin hydrochloride and vancomycin….Intraoperative administration of drugs has been shown to reduce both non-compliance and patient error, significantly lessening the surgeon's concern and elevating the patient's experience with cataract surgery. Physicians have prescribed Imprimis' proprietary formulations for use in thousands of cataract surgeries, and have reported advantages including reduction of compliance concerns and reduction of staff and chair time spent on instructions and follow-up with post-operative surgical patients and pharmacists."
  - o "Imprimis' portfolio of combination drop therapy topical formulations may require up to 50% fewer drops to be administered by patients and may provide significant cost savings of up to 75% compared to current traditional post-surgery eye drop treatments."

- "Imprimis Pharmaceuticals to Launch its Simple Drops Combination Glaucoma Drops at Leading Cataract & Refractive Surgery Medical Meeting," May 4, 2017