Confusion in Product Packaging

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Recently, I went to the store to purchase shampoo. I was looking for a particular brand, Trader Joe's® Refresh Citrus Shampoo. I thought I found it on the shelf — but then was confused as I saw that the conditioner and body wash looked nearly exactly the same (Figure 1).

As an adult over the age of 50, I was scheduled for a colonoscopy. My gastroenterologist prescribed a pre-procedure preparation, which I obtained from the local pharmacy. When I opened the outer box of the preparation (Moviprep®, PEG-3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution), I found two clear cellophane packets. As I read the package insert and the instructions from the gastroenterologist, I expected to find two perfectly identical packets ("…Each carton contains a disposable container for reconstitution of Movi-Prep®") and 4 pouches (2 of pouch A and 2 of pouch B, Moviprep® package insert, August 2012). However, as I looked at the packets, they did not seem to be exactly the same. As I kept rotating them, they seemed to each have an "A" and a "B" packet, but the shading was different (Figure 2, left). When I finally opened the cellophane, I found each packet contained an "A" and a "B" pouch. It became clear that each pouch was shaded differently on the front and back, and that indeed I had two sets (Figure 2, right). However, from the manner in which they were packaged in the cellophane, this was not apparent.

Perhaps more relevant to readers of *The Ocular Surface*, I heard from a patient who had confused her unit-dose products for the treatment of her ocular surface disease. The patient had accidentally instilled Refresh®/Celluvisc® lubricant instead of the Restasis® (cyclosporine aqueous emulsion). From her perspective, this meant that she could not read for some period while the viscous product cleared from the precorneal space. I took a look at the two products side by side. The color of the liquid in the emulsion was white, in contrast to the lubricant which was clear. However, the type size was about 6 point, which is below my usual limit of resolution. This small type size probably results from the need to put a required amount of text in a small space (Figure 3).

There are contact lens cleaners, *not* intended for use in the eye, that contain 3% hydrogen peroxide (Clear Care, CibaVision). The Institute for Safe Medication Practices (**ISMP**) has multiple reports of patients inadvertently using this product in their eye. Such use causes profound discomfort and, in some cases, the potential of a chemical burn. Many multipurpose cleaning and disinfecting solutions used for rinsing and soaking lenses are packaged in look-alike containers and stored side-by-side on store shelves. The manufacturer states that they have improved the warnings regarding this inappropriate use (as recently as 2011), but patient advocacy groups complain that these changes are inadequate (www.ismp.org). Some products have colored caps to help indicate the need for caution in their use (eg, Boston Advance Enzymatic Cleaner® has a red cap.)

The American Academy of Ophthalmology (**AAO**) has had a long-standing policy regarding the uniform use of a color-coding system for the caps and labels of topical ocular medications. To date, voluntary cooperation between the pharmaceutical industry, the FDA, and the American Academy of Ophthalmology has been very effective in meeting the interests of patient safety. http://www.aao.org/about/policy/upload/color-codes-for-topical-ocular-medications-2010.pdf. However, with the advent of more generic products, as well as novel combination products, more and more products have "white caps." For example, at launch in 2013, Simbrinza™ (brinzolamide/brimonidine tartrate ophthalmic suspension) had a white cap.

The U.S. Food and Drug Administration (**FDA**) is very concerned with how products are labeled and adequately informing patients about the risks of medications. Previously in this column, I discussed perspectives on the package insert with respect to indications and adverse events.[1-3] I also discussed how drugs get their brand names, and FDA's concern about potentially confusing brand names (eg, Zantec® [ranitidine] for heartburn vs Zyrtec® [cetirizine] for allergy; Propine® [dipivefrin] and Pilopine® [pilocarpine HCl], both for glaucoma, and Durezol®

Accepted for publication October 2013.

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Figure 1. Trader Joe's® Refresh Citrus shampoo, conditioner, and body wash.

[difluprednate ophthalmic emulsion] for the treatment of postoperative inflammation vs Durasal® [salicylic acid 26%] for the topical treatment and removal of warts).[4]

Requirements for labeling of prescription and over-the-counter (**OTC**) drugs are given in 21CFR201. These regulations include the name of the product, list of active ingredients, excipients and amounts, directions and warnings, and the need for tamper-evident packaging. In particular, there are detailed instructions for more readable OTC drugs including the type size (Figure 4). http://www.fda.gov/Drugs/ResourcesForYou/ucm133411.htm

In the several examples of confusing product labeling I provided above, there is a range of the severity of safety issues. My hair would be only a little worse for wear if I used conditioner or body wash instead of shampoo. Taking the packages of colonoscopy prep in the incorrect order might result in only gastrointestinal upset or perhaps a less efficient bowel cleansing. However, improper use of treatments for ocular surface disease might have long-term consequences on efficacy or patient performance. Instillation of 3% sodium hydroxide into the eye could lead to somewhat more serious consequences, as could using the incorrect medication container due to patient confusion. FDA's efforts in this regard are admirable but challenging due to the limit of authority and the "real estate" space on product labels, especially on non-preserved unit dose containers.

REFERENCES

1. Novack GD. Pipeline: Clinical indications for ophthalmic corticosteroids. *Ocul Surf* 2008;6:199-202
2. Novack GD. Pipeline: Decoding the package insert: adverse events. *Ocul Surf* 2003;1:202-3
3. Novack GD. Pipeline: Decoding the package insert: indications. *Ocul Surf* 2003;1:150-1
4. Novack GD. Pipeline: How do drugs get their brand names? *Ocul Surf* 2012;10:117-20

NEWS FROM PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES

Ophthalmic Products Related to the Ocular Surface

- **Adamis Pharmaceuticals Corporation** is evaluating its antimicrobial and spermicidal agent, C31G, in a preclinical model of ocular keratitis (September 2013).
- **Mimetogen Pharmaceuticals** has enrolled patients in a Phase 3 study of MIM-D3 ophthalmic solution for the treatment of dry eye syndrome (October 2013).

Ophthalmic Products Not Related to the Ocular Surface

- **Akorn** will acquire **Hi-Tech Pharmacal Co** (August 2013).
- **Alcon** announced that the National Institute for Health and Care Excellence (**NICE**) Appraisal Committee has delivered a positive Final Appraisal Determination (**FAD**) for Jetrea®, recommending its use to treat adults with vitreomacular traction, including macular hole. This product was also approved in Canada (August 2013).
- **Alimera Sciences** announced that the Transparency Commission of the French National Health Authority issued a positive opinion regarding the reimbursement and hospital listing of Iluvien™ (fluocinolone acetonide intravitreal implant (July 2013)). The firm also announced that in its Final Appraisal Determination, the United Kingdom's National Institute for Health and Care Excellence (NICE) has recommended Iluvien™ (fluocinolone acetonide intravitreal implant) funding for the treatment of pseudophakic eyes in chronic diabetic macular edema (DME) patients that are insufficiently responsive to available therapies (September 2013). FDA provided a complete response to the firm regarding a U.S.resubmission of Iluvien for treatment of DME, requesting additional research prior to a reconsideration of approval (October 2013).
- **Allergan**'s patents on two glaucoma products (Ganfort®