A PATIENT-CENTERED APPROACH TO LABELING FOR OVER-THE-COUNTER MEDICATIONS: USING DATA TO DRIVE DESIGN DECISIONS FOR THE BENEFIT OF OLDER ADULT

By

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ABSTRACT

A PATIENT-CENTERED APPROACH TO LABELING FOR OVER-THE-COUNTER MEDICATIONS: USING DATA TO DRIVE DESIGN DECISIONS FOR THE BENEFIT OF OLDER ADULTS

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One of the largest challenges for drug manufactures is ensuring safe and effective medication use. Older adults are four times more likely to experience an adverse drug reaction (ADR) than younger people. Labeling is a crucial strategy in the prevention of adverse effects related to OTC medication use. We proposed a novel label design for OTC medications, utilizing a small box which includes drug drug and drug diagnosis indications on the front of the package (an FOP label). To test the efficacy of the strategy, we employed a change detection methodology. Two main objectives framed our work: (1) to determine if older adults would be more accurate and faster in finding changes to an FOP than comparable changes to existing commercial standards for labeling, and (2) whether they would be more accurate and faster in finding changes to highlighted information than comparable changes that were not highlighted. Sixty older adults (65+) were recruited to participate. Results suggest that the presence of an FOP did not impact either the accuracy of the ability to find the information or the time to find it. By contrast, there was a significant difference in detecting critical information when treatments that were highlighted were compared to those that were not ($p<0.0001$) although there was no significant effect of highlighting on the time participants took to find the changes.

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CHAPTER 1 – INTRODUCTION & LITERATURE REVIEW

1.1 Introduction

In 1951, US medications were legislated into two broad categories, termed prescriptions and over-the-counter (OTC) products with the passage of the Durham-Humphrey Amendment to the Federal Food Drug and Cosmetic Act (FFDCA)(Amendment, Durham-Humphrey, 1951)(A Food Labeling Guide (FDA), 2018). Prescribed medications were defined as requiring doctor's supervision and must be labeled with the statement, "Caution: Federal law prohibits dispensing without a prescription" due to the potential to be habit-forming or potential for harm associated with inappropriate use (Amendment, Durham-Humphrey, 1951).

By contrast, OTC medications, also called non-prescription medications or proprietary medications, are considered to be safe and effective for use by people without a physician's orders or oversight (Albert et al., 2014). In order for a drug to be categorized as an OTC, it generally undergoes a rigorous, data-driven process referred to as an "Rx to OTC switch". In the US, this process is regulated by the US Food and Drug Administration (FDA).

It has been estimated that the healthcare system saves $6 to $7 for every dollar expended on OTC drugs (as opposed to utilizing the healthcare system and obtaining prescribed medications). This leads to an estimated total of $102 billion savings in the US annually (Consumer healthcare products Association, 2012).

Other advantages of OTC utilization include convenience, privacy, quick access, and flexibility. Consequently, OTC use is growing, largely fueled by these benefits.

As a result, over 100 medications have been switched from prescription to OTC in recent decades (McGee & Wilkin, 2019). In order to successfully "switch status," manufacturers must demonstrate, through a data-driven process, that the drug is effective, has a wide margin for safe use and that it bears understandable labeling which ensures its proper use (Consumer Health Products Association, 2020).

Although OTC drugs provide many benefits, as with any medication, there are risks associated with their use as well. Ghaswalla showed some of these risks are particularly pronounced for older adults. Age adversely affects functionality of human organs such as the eyes, brain, kidney and liver. These, in turn, can create reading difficulties, lead to the incorrect interpretation of printed matter, difficulty remembering medication instructions, and also have the potential to affect drug absorption and elimination (Andrus & Roth, 2002)(Matthews, Shine, Currie, Chan, & Kaufman, 2012)(Lee et al., 2009)(Wolf et al., 2012). Furthermore, the increased complexity of medical regimens required by older consumers combined with these factors can heighten the probability of an adverse drug reaction (ADR) in this vulnerable population (Ghaswalla, 2011).

Edwards and Aronson defined the adverse drug reaction (ADR) as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." (Edwards & Aronson, 2000). A meta-analysis of prospective studies suggests that 106,000 US deaths happen every year as a result of ADRs (Lazarou, Pomeranz, & Corey, 2019).

A single study of an emergency department in Canada reported that about 0.75 percent of older adult patients who visit the emergency department have an ADR, costing

approximately $333 per visit. Moreover, 21.6 % of these patients have to hospitalized at an average cost of $7,528 per person. Consequently, the overall costs for Canadian healthcare resulting from ADRs is estimated at $13.6 million annually (Wu, Bell, & Wodchis, 2012).

Although it is important to remember that OTCs are not the singular cause of ADRs, they do play a role. Studies conducted in Europe implicate OTCs (Eaves, 2015)(Schmiedl, Rottenkolber, & Hasford, 2014)(Bourgeois, Shannon, Valim, & Mandl, 2011). Though the prevalence of ADRs associated with OTCs is generally regarded as low, studies have found that among ADR patients engaged in self-care, between a third and (Bourgeois et al., 2011) half (Schmiedl et al., 2014) of incidents are attributable to OTCs.

While multiple strategies are required to mitigate the likelihood of an ADR, when the focus is on OTCs, one strategy for ADR prevention that is employed is labeling. Although multiple sources of information *can* be utilized when selecting and using an OTC, studies have suggested that frequently labeling is the sole source of information accessed by the consumer (Brass & Weintraub, 2003). Germane to the work presented here, drug manufacturers should demonstrate to FDA that consumers can use the product as directed using its label (Nguyen, Cook, & Bero, 2006).

Although labeling is recognized as a crucial strategy in the prevention of adverse effects related to OTC medication use (Roumie & Griffin, 2004), multiple researchers have suggested that empirical studies of label use are needed to enhance the labeling of OTCs (Brass & Weintraub, 2003)(Roumie & Griffin, 2004)(Catlin et al., 2012)(Bix, Kosugi, Bello, Sundar, & Becker, 2010).

It is a commonly recommended strategy because of the important role it plays in the safe and effective use of these medicines, partly because it is a present, available accessible

source of information for consumers who are self-diagnosing and "prescribing" these medications at both the point of selection and use (Brass & Weintraub, 2003). Unlike prescription medications which are chosen and taken under the care of doctors and pharmacists, OTC use is not guaranteed to have the oversight of learned intermediaries. Among the recommendations for improved label design is the use of highlighting for warning instructions, bigger and bolder fonts and placement of important information on the front of the package (Shiyanbola, Smith, & Mansukhani, 2016)(Shiyanbola, Meyer, Locke, & Wettergreen, 2014).

Thus, studying the effects of label design on the ability to notice information critical to the safe and effective use of these products is an important goal. The first step in such a study, is to understand the common terminology surrounding the issue.

1.2 Regulatory Authority for the Labeling of US Drug Products

The US Food and Drug Administration (FDA) is a federal agency within the United States Department of Health and Human Services (DHHS); they are granted the authority to regulate the labeling of OTC products by the US Congress through the Federal Food Drug and Cosmetic Act (FFDCA), and its subsequent amendments.

Regulations regarding the content and formatting of the information on the label of OTC drugs are promulgated through the Agency, which ultimately reviews label designs prior to approval for sale in interstate commerce (A Food Labeling Guid (FDA), 2018). Most OTC medications made available for sale in US commerce require labeling that is dictated in format and content by FDA requirements.

The term "labeling" is defined in within section 201(m) of the FFDCA as:

"all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article"

The term "label" falls within the broad definition of labeling; and is defined in section 201(k) of the FFDCA as a:

"display of written, printed, or graphic matter upon the immediate container of any article…" (A Food Labeling Guid (FDA), 2018).

FDA not only has the authority to develop and administer regulations applicable to drugs, but also regulates the labeling of food (A Food Labeling Guid (FDA), 2018), cosmetics (Food and Drug Administration Cosmetic Labeling Guide, n.d.), medical devices (Regulatory Requirements for Medical Devices, 1989), and radiation-emitting electronic products (Electronic Product Radiation Control (FDA), 2018).

Historically, policy makers have focused regulatory efforts regarding the information required for the safe and effective use of OTC products on optimizing the presentation of the detailed drug information on the back of the package (Catlin et al., 2012).

Although there are information and formatting requirements related to the principle display panel (PDP) (Fair Packaging and Labeling Act, 1966), the information presented on the PDP is generally heavily driven by the need to attract attention and sell the product.

Information required on the PDP (statement of identity and declaration of net quantity of contents) is mandated within 21 CFR 201.61 and 201.62 requiring "The general pharmacological category(-ies) of the drug (b) or principal intended action (s)" of the drug (b), measure, weight, size and numerical count (a), and statements related to the accuracy of the quantity of drug or device in package (f), respectively (A Food Labeling Guide (FDA), 2018).

Details regarding the Drug Facts Label (DFL) are found in Title 21, Chapter 1, Subchapter C (Drugs), Part 201 Sub Part C (Labeling requirements for Over the Counter Drugs). Specifically, Section 201. 66 dictates both the content and formatting requirements for the DFL. The following headings are currently required: (1)"Title (Drug Facts or Drug Facts (continued)), (2)Active ingredient(s), (3) Purpose(s), (4) Use(s), (5) Warning(s), (6) Directions, (7) Other information, (8) Inactive ingredients, and (9) Questions? Or Questions or comments?"(Otc & Drug, 2009)(see Table 1).

Accordingly, requirements for labeling that appears on the front of the package are more limited than the DFL mandates which appear on the back and sides of packaging (Catlin et al., 2012).

1.3 OTC Drugs' Label Importance

As comprehensive as the requirements for OTC labels in the US are, documented shortcomings exist. Researchers have postulated that current regulations for label requirements are not enough. Specifically, that the existing labels do not adequately capture consumer's attention to convey necessary information about the drug in a suitable manner (Shaver & Wogalter, 2003). In a study of prescription warning labels, yellow highlighting was found to draw attention (Shiyanbola et al., 2014). Because labeling has been indicated as the primary means of communicating with the consumers of these products (Catlin et al., 2012), and the label is commonly indicated to be the only source of information used when selecting and dosing these products, the effect of label design on attention is a serious issue worthy of study. It is crucial for the label to capture consumer's attention and engage them to read it. Important information for the safe and effective use of OTC not only includes

Table 1-Summary of labeling requirement and relevant contacts (Otc & Drug, 2009)

Paragraph	Description of Paragraph	Comments
(c)(1)	Drug Facts, Drug Facts (continued)	The title to be used is Drug Facts (on subsequent panels use Drug Facts (continued)).
(c)(2)	Active ingredient(s) (established name, quantity)	For drug-cosmetic products, the drug ingredients are considered the active ingredients, and the cosmetic ingredients are considered the inactive ingredients. See §§ 201.66(b)(2), (b)(8), and (c)(8); and § 701.3(a) and (f).
(c)(3)	Purpose(s)	If there is no statement of identity or no applicable OTC drug monograph, the ingredient purpose is stated based on its general pharmacological category(ies), or the principal intended action(s) of the drug product.
(c)(4)	Use(s)	The use(s) are the specific indication(s) or approved use(s) for the drug product. For drug-cosmetic products, the use in the Drug Facts labeling is attributed only to the drug component. See § 201.66(c)(4).
(c)(5)	Warning(s)	Warning information appears in a specific order, under the heading Warnings, as applicable. Most warnings follow specific subheadings, as described in (c)(5)(i) through (c)(5)(x).

directions for use, but also information regarding who should (or should not) use these products, which despite their accessibility, do carry risks. This is especially important for older adults (Wogalter & Dietrich, 1995).

1.4 Older Adults and Medication Use

One of the largest challenges for drug manufacturers is ensuring safe and effective medication use (Roumie & Griffin, 2004). Since older adults (aged 75-85) tend to use medications of all types (including around 47.2 % of OTC drugs in the United States (Qato et al., 2009)). In addition to the other reasons previously discussed, increased per capita use for older adults (for both prescription and OTC products) results further enhances the likelihood of an ADR occurrence for this population.

Based on a recent study by Oscanoa et al. (2017) older adults are four times more likely to experience an ADR than their younger counterparts. As a result, we targeted participants 65 and older for our work. The creation of labels that are more likely to be noticed by this vulnerable population is an important aspect when attempting to prevent ADRs that result from drug/diagnosis, drug/drug interactions in complex medical regimens (Albert et al., 2014).

Although multiple strategies are required to mitigate the likelihood of an ADR, when OTCs are considered as part of the mix, one strategy that is employed is labeling. Although multiple sources of information can be utilized when selecting and using an OTC, studies have suggested that frequently labeling is the sole source of information accessed by the consumer (Brass & Weintraub, 2003). As such, labeling is a crucial strategy in the prevention of adverse effects related to OTC medication use (Roumie & Griffin, 2004). In order to improve labeling, empirical studies should be done (Brass & Weintraub, 2003)(Roumie &

Griffin, 2004)(Catlin et al., 2012)(Bix et al., 2010).

In an attempt to develop OTC labels that garner attention to information critical to the safe and effective use of OTCs, particularly for older adults, we leveraged insights from a review of research related to a successful strategy for food labeling.

1.5 Nutrition Facts Panel

Most packaged food products sold in the US (and the labeling of the same) fall under the regulatory authority of the FDA (meat and alcohol are regulated by Agencies within the Department of Agriculture and the Treasury, respectively (Meat Inspection Act 1906, n.d.)(Federal Alcohol Administration Act, 1935)(Alcoholic Beverage Labeling Act, 1988)).

The formatting and content of nutritional information required for most packaged food sold in US commerce, called the Nutrition Facts Panel (NFP), is found in regulations that are authorized by the Nutrition Labeling and Education Act (NLEA)(Waxman, 1990).

Nutrition labeling generally takes the form of a rectangular box referred to as the Nutrition Facts Panel (NFP) which appears to the right of the Principal Display Panel (PDP), the face that is "customarily displayed during retail (Fair Packaging and Labeling Act, 1966).

The primary intention of the NFP is to provide consumers with consistent and objective nutrition information regarding food they are considering for purchase (Kessler, Mande, Edward, Schapiro, & Feiden, 2003).

Similar to the Drug Facts Label (DFL), required on most OTC drugs in the US, the nutrition facts panel (NFP), follows mandates for both information content and formatting requirements for the information published by the FDA (21 CFR 201.60). Like the DFL, the NFP has different headings; these include servings per container, serving size, calories (per serving), and percent daily values (and grams) for varied nutrients and vitamins.

The original intention behind the NLEA, and enacted in the form of the NFP, was to provide a uniform standard for nutrition information which would assist consumers making nutritional comparisons between products by providing accurate, standardized information related to the nutritional components for the products that they consider for purchase (Balentine, n.d.).

1.6 Front of Package on Labels

Dietary choices are commonly indicated as a single factor among many that contribute to chronic diseases, including: stroke, diabetes, heart disease and obesity (Kromhout, Menotti, Kesteloot, & Sans, 2002)(Astrup, 2001)(Members of WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases, 2003). One approach to reducing the prevalence and impacts of these serious diseases is to promote strategies that encourage consumers to choose healthier products (Nijman et al., 2007).

As with ADRs and OTCs, labeling has been seen as a strategy that can be used to provide information at the point of selection and consumption of foods with the potential to influence healthier choices and consumption practices. Just as the use of labeling for OTCs is employed as a mitigation strategy for ADRs, labeling for food products is one technique that is used to facilitate appropriate choices, and healthy portions. A relatively recent development within food labeling is the use of a “Front of Pack” (FOP) strategy, whereby portions of the more comprehensive nutrition information from the NFP is also provided on the package’s front. Generally, the components included in FOP strategies are closely affiliated with chronic diseases (e.g. salt- hypertension; sugar- diabetes; fat and saturated fat- heart disease).

Hodgkins et al. classify FOP labeling in three categories: directive, non-directive and semi-directive (Hodgkins et al., 2012). The non-directive labels leave the burden of assessment of the information's meaning to the consumer by listing truncated section of the nutrition information from the more comprehensive nutrition information on the package front. One such example, is the Guideline Daily Amount- (GDA), one of the early, non-directive FOPs used in the UK; incidentally, this approach has now been replaced by the Reference Intake (RI standard). When overlaid with an ordinal assessment (e.g. color, or icon indicating that the product had a relative "level" of a given nutrient), these non-directive systems become semi-directive. From our previous example, when the GDA FOPs included a color overlay, they were referred to as a "traffic light system".

Specifically, green was applied for nutrients levels that were low; yellow for moderate and red for high amounts of a given component of the product. By contrast, directive labels make an assessment regarding some aspect of the product (e.g. the "heart safe" seal or "healthy tick")(L. Bix, Sundar, Bello, & Peltier, 2015). Scott and Worsely (1994) remind us that the presence of an FOP of any type does not preclude the ability of the consumer to access more complete information, or back-of-pack (BOP); the Nutrition Facts Panel (NFP) in the United States, allowing consumers to access more data about the products under their consideration (Scott & Worsley, 1994).

Feunekes et al. investigated the important role of FOP nutrition labelling in choosing healthier products among consumers in diverse countries (Feunekes, Gortemaker, Willems, & Kommer, 2008). Their work suggests that while shopping, it is easier and less time-consuming for consumers to make purchase decisions when simpler FOPs (like Healthier choice tick, smileys and stars) are used compared to those FOPs that merely present

truncated information (i.e. the non-directive formats)(Feunekes et al., 2008).

Researchers have also investigated how the position of nutrition information impacts the likelihood that consumers will attend to it. A study by Grunert & Wills shows that users are less likely to see nutrition information on the side or back of the package compared to FOPs (Grunert & Wills, 2007), but they are likely to view nutrition information that appears on the package's front (Graham & Jeffery, 2011). Shiyanbola et al. had similar findings in their investigation of prescription labels; they found a consumer preference for placement of drug information on the front of pill bottles (Shiyanbola et al., 2014).

Many researchers indicate that the simplified designs which appear on the front-of-package are more noticeable than the more complete sets of information that appear elsewhere (e.g. back of the package (BOP) or on its side)(An Agreed Public Health Position, 2009)(Wansink, 2003)(Grunert & Wills, 2007)(Kleef, Trijp, Paeps, & Ferna, 2007).

In addition, Smith et al. measured four versions of FOP labels on food products; specifically: "(1) Control : no front-of-package information (zero icons), (2) Some information : Calories only (one icon), (3) More information : Calories+nutrients to limit (saturated fat, sodium and sugars)(four icons), and (4) Most information : Calories+nutrients to limit (saturated fat, and sugars) and nutrients to encourage (protein, fiber, vitamin A, vitamin C, calcium, iron, or folate)(five to seven icons) on third version plus nutrients to encourage (five to seven icons)"(Smith et al., 2014).

Given that the design and formatting of the Drug Facts Label (DFL) for OTCs was largely based on the Nutrition Facts Panel (NFP) (OTC Drug Fact label FDA, 2015), and studies (L. Bix, Bello, Auras, Ranger, & Lapinski, 2009)(Ryan & Costello-white, 2017)

suggest the DFL to be poorly attended by people, we postulated that the FOP strategy might also be an effective way to increase consumer attention to some of the critical information found in the DFL.

We leveraged findings from the literature on food labeling to create a novel, FOP for OTC drugs. The literature regarding food labeling suggests that the use of FOP labels result in faster (and increased)(Becker et al., 2017) attention to nutrition-related in information, better and more accurate cross product comparisons (Grunert & Wills, 2007) and, ultimately, more healthful product selections (Bix et al., 2015) to develop a novel FOP (Becker et al., 2017) for OTC drugs.

To test the effect of our novel FOP on the attention of older consumers viewing the labels of OTC medications we leveraged a change detection method from the field of visual psychology. This method is traditionally used to examine the visual attention of people viewing scenes. Herein, we apply it to assess the efficacy of four label types (the standard OTC (1) No FOP label and no highlight (2) No FOP with highlighted (3) FOP with highlighted and (4) FOP without highlighting) at garnering attention to critical information.

1.7 Change Detection method for evaluating packaging

First proposed by Rensink, Regan & Clark in 1997, the change detection methodology has been extensively studied to develop a fundamental understanding of attention (Stevens & Bavelier, 2012)(Knudsen, 2007) but, more recently, has been employed as an applied tool to assist in understanding the visual saliency of critical elements of labels.

Labeling studies employing the technique have examined the efficacy of varied strategies for use with food (Gaschler, Mata, Störmer, Kühnel, & Bilalić, 2010)(Becker et al., 2017)(Becker, Bello, Sundar, Peltier, & Bix, 2015)(B. L. Bix et al., 2010), medical devices

(Seo, 2014) and drugs (Dehenau, Becker, Bello, Liu, & Bix, 2016).

During a change detection method, also called a "flicker task" two images, an original image (sample one) and a slightly modified image (sample two) appear in series with a blank, gray field interleaving. A modification to sample one is made to create sample two and this modification can be any size and type. The four screens display in a repeated series (grey field, sample one, grey field, sample two), yielding a "flickering appearance until the participant, who has been instructed to find the change in the image as quickly as possible, locates the difference.

Participants signal identification of change location by inputting a keystroke on the computer running the test. If the change is not detected within an allotted timeframe determined by the experimenter, the trial is recorded as a "timeout" (Rensink, Regan, & Clark, 1997). As such, there are generally two resultant variables for these experiments, the proportion of participants that successfully locate a change prior to timing out (a binary variable- accuracy) and the time to successfully locate a change (continuous variable-time).

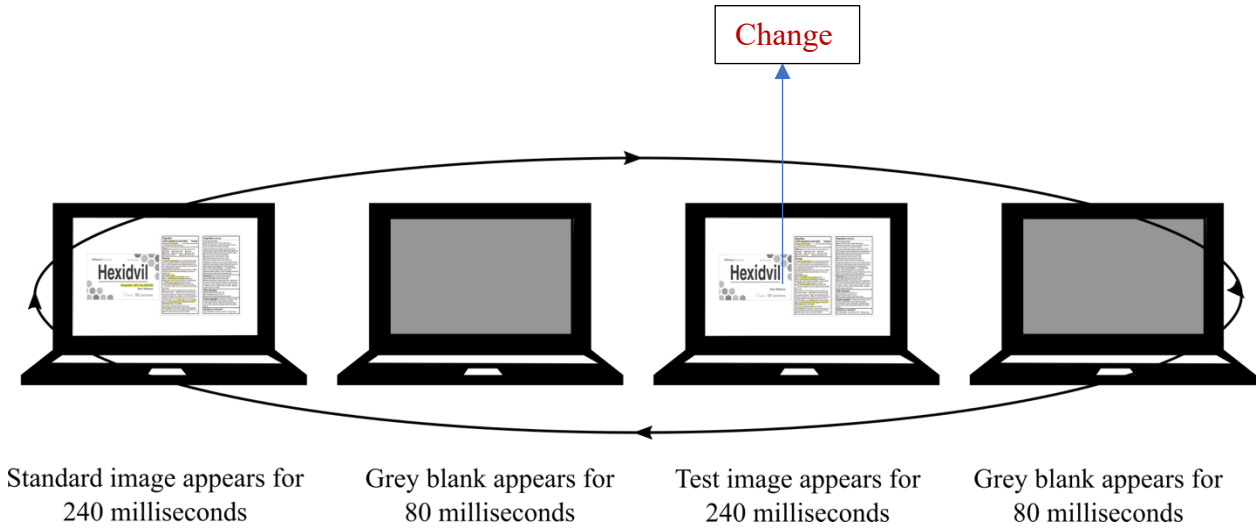


Figure 1- Iterative loop of standard and test images (timing and method first proposed by (Rensink et al., 1997))

Thus, change detection testing requires the participants to attend and encode the change into a more durable form of working memory (Rensink et al., 1997)(Becker, Pashler, & Anstis, 2000)(Becker & Pashler, 2002). Due to this attention dependency, a good indication of the time when attention first selects an object is the time required to detect a change. Subsequently, faster detection of the change means early attention to the change property.

This can improve our understanding regarding the viewer's 'attention scan path' (Rensink et al., 1997)(Simons & Rensink, 2005).

Reviewed studies suggest that the use of an FOP for food products is an effective tool for garnering attention. Herein, we proposed to use a flicker change detection method to evaluate the attention of older people, at increased risk for ADRs, to test the efficacy of an FOP strategy as applied to OTCs using E-Prime software.

CHAPTER 2 – STUDY GOALS

2.1 Goals of the Study

The overarching goal of this study was to investigate how the addition of a novel, Front of Pack (FOP) label and highlighting of information critical to safe and effective product use impacts consumer attention when viewed by older adults (65+) examining OTC drug labels. Specifically, we hypothesized that:

- Older adults would be more accurate and faster in finding changes to a FOP than comparable changes to a STD.
- Older adults would be more accurate and faster in finding changes to highlighted information than comparable changes that were not highlighted.

CHAPTER 3 – METHODS

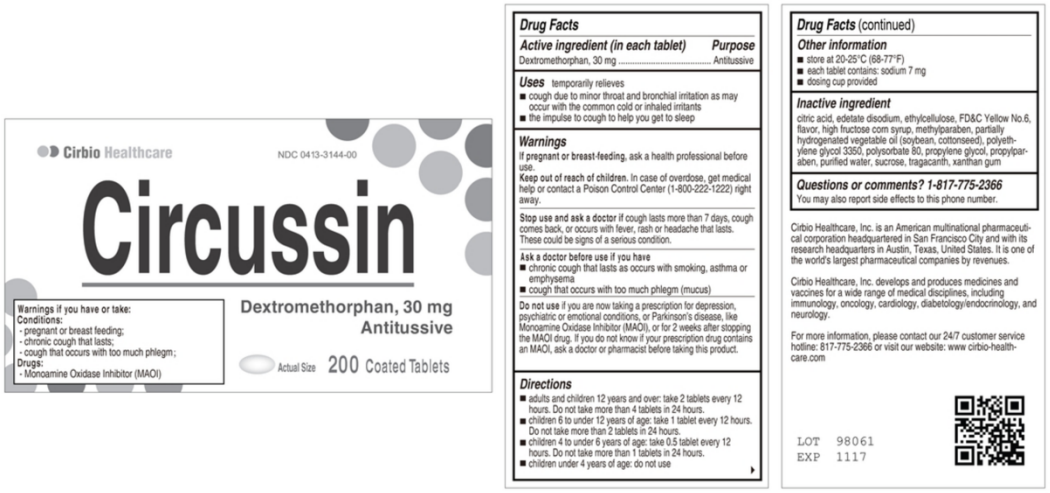
3.1 Test Study

In support of these objectives, we utilized the change detection methodology (discussed previously). During this method, called a "flicker task" two images (an original and modified) and gray screen, flickering for eighteen seconds or until the time ran out. We using version 3 of E-prime software (Pennsylvania, USA (Tools Psychology Software, n.d.)). Timings and method were based on those developed by Rensink et al. 1997, and the study was performed in accordance with methods reviewed and approved by the MSU IRB under the number x17-922eD.

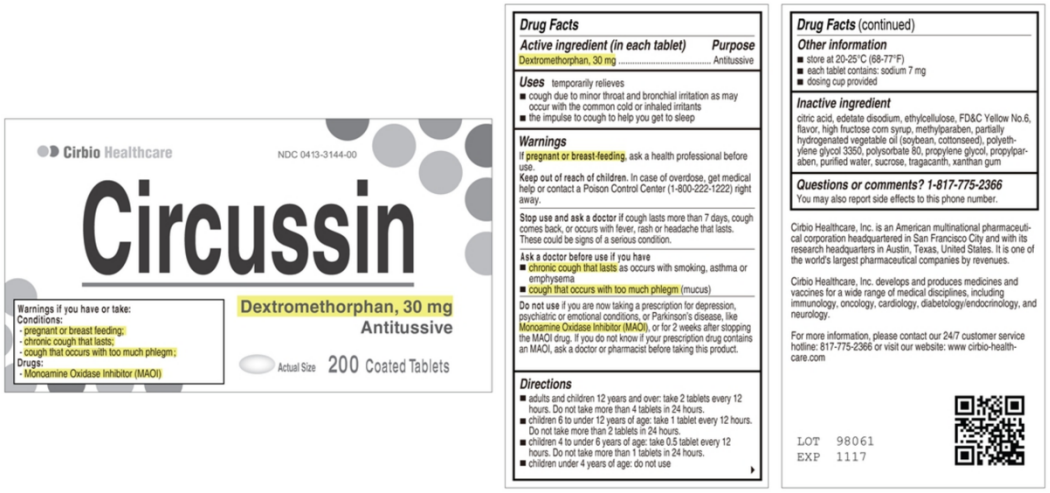
Stimulus materials were created utilizing Adobe Illustrator software in support of study objectives. Stimulus images were comprised of three black and white mock brands created by the research team and used in previous studies (Liu, 2016). All stimulus images' dimensions were 1920x1080 (with resolution of 226.97 ppi). Brand names used were: Hexidvil, Circussin, and Recantac (Appendix 8-19). Designs were carefully created such that each of the mock brands was from a different class of drugs; namely, pain relief/fever reducer, antitussive and acid reducer, respectively. Each brand consisted of a different (single) active ingredient (Hexidvil-Ibuprofen (IBU), Circussin-Dextromethorphan (DEX) and Recantac-Ranitidine (RAN)). Each brand was created in four different treatments (FOP present/Highlighted; FOP absent/Highlighted; FOP absent (Standard label)/Highlighted; FOP absent (Standard label)/not highlighted). Study participants were asked to complete a total of 56 trials for each of the mock brands (each brand was presented in the four design treatments and changes occurred at different locations for each of the trials- details to follow), for a total of 168 trials per participant.

Both the formats, the FOP and the STD, had common elements; specifically, each had a principal display panel (PDP) and a drug facts label (DFL) with information that was specific to the mock brand (tied to the active ingredients mentioned previously). As such, changes to the stimulus material could occur on the Principal Display Panel (PDP), which might or might not have an FOP, or the DFL for any of the four test treatments (FOP/non-highlighted, FOP/highlighted, STD/non-highlighted, STD/highlighted) (see figures 2 and 3).

We considered three pieces of information as critical to the safe and effective use of OTCs; namely: The Active Ingredient (AI); Drug-Drug interactions (DD1) and Drug/Diagnosis interactions (DD2). To provide an example of the types of changes that occurred in drug/drug and drug diagnoses warnings, please see Figure 4 which shows changes to the Hexidivl product, containing the active ingredient Ibuprofen. Comparing A to B (within Figure 4) represents the change that occurred in the critical information in the DFL relating to the active ingredient. A comparison of C to D (within Figure 4) represents the critical information (DD2) that represents the drug diagnosis information and E to F (within Figure 4) references critical changes to DD1 (Drug drug interactions). These changes were part of the critical trials that each participant conducted (see Figure 6) and were presented in accordance with Rensink's methods (Rensink et al., 1997) depicted in Figure 1.

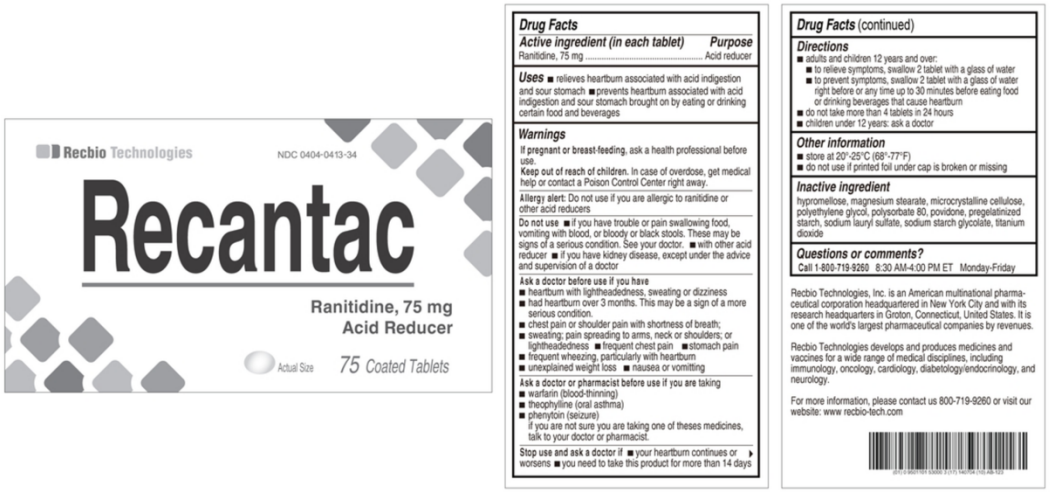


(a)

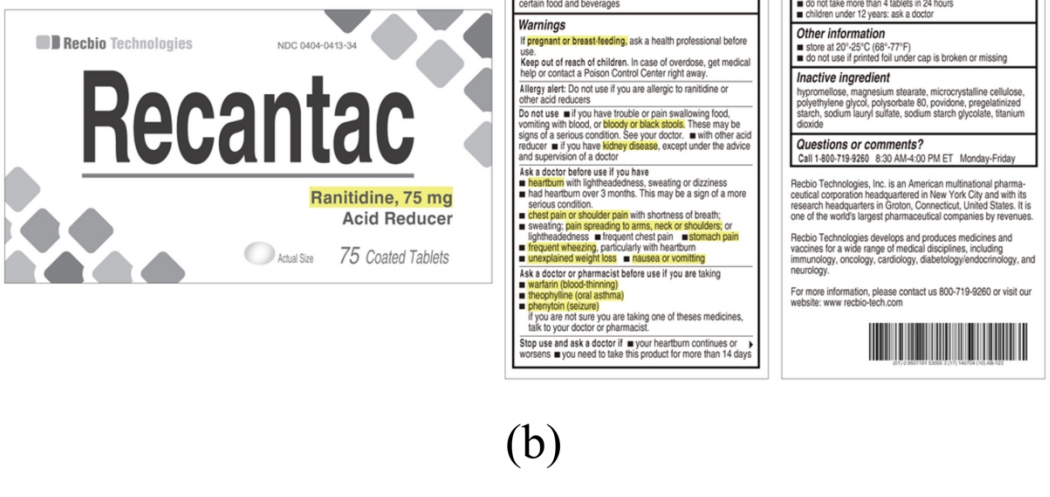


(b)

Figure 2- Image (a) shows FOP/non-highlight and Image (b) shows FOP/highlight

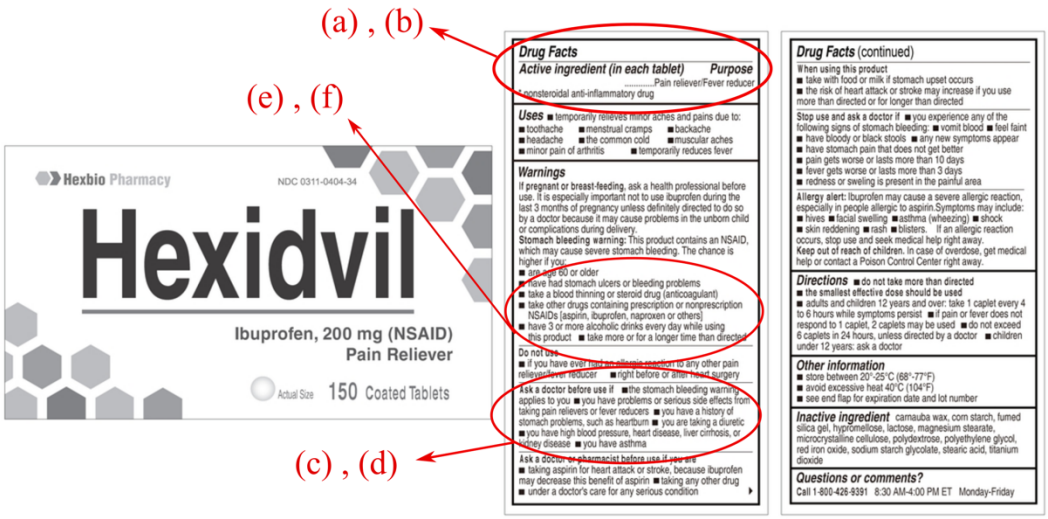


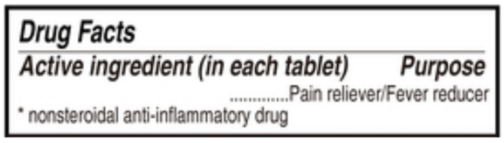
(a)



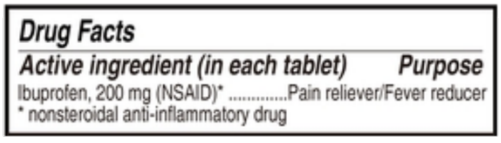
(b)

Figure 3-Image (a) shows STD/non-highlight and Image (b) shows STD/highlight

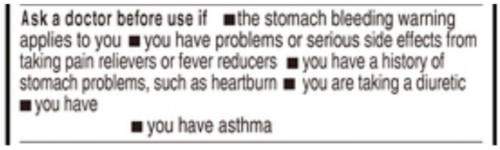




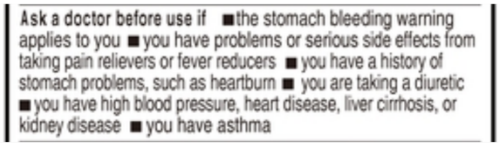
(a)



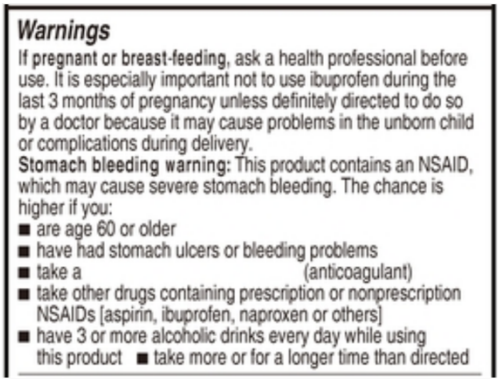
(b)



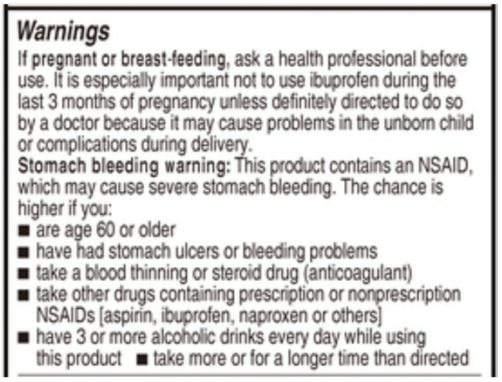
(c)



(d)



(e)



(f)

Figure 4-Image (a) & (b) show change in AI, Image (c) & (d) show change in DD1, and Image (e) & (f) show change in DD2

Changes that occurred in the stimulus materials were classified as critical and non-critical. We considered changes in information tied to the safe and effective use of the products as critical. Specifically, any changes to the active ingredient (AI), drug-drug interaction (DD1; e.g. do not take this drug if you are currently taking aspirin or other blood thinning products), drug- diagnosis (DD2; e.g. do not take this drug if you have been diagnosed with high blood pressure) (see figure 4), were considered as “critical changes”; changes that occurred to other information within the stimulus were considered non-critical.

It is important to note that the AI appeared on both the PDP and the DFL for all treatments, as such, it was also important that the model and statistics consider the location of the change. Specifically, some changes to the critical information could occur in the AI that appeared on the PDP (this information appeared regardless of the presence of a FOP) or in the DFL (as depicted in Figure 4). By contrast DD1 and DD2 do not normally appear on the PDP but do appear in the DFL. As a result, changes in DD1 and DD2 only appeared in the PDP in the conditions where a FOP was present. In order to properly consider this, the information relating to the location of the change had to be coded into the data. Figures 2-4 provides insight into the coding related to the highlighted trials. Changing in the trials is can occur by (1) highlight text in one picture and the other does not have same highlight text or (2) the portion of the information is disappearing in the modified image.

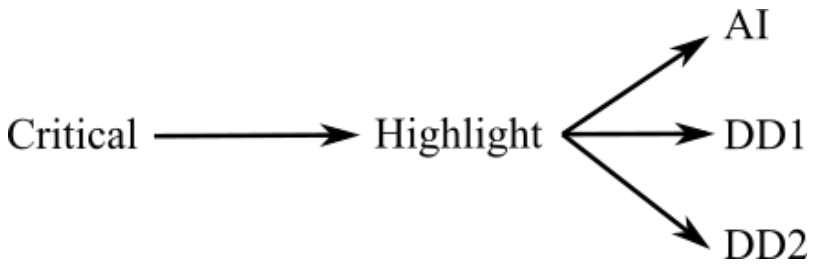


Figure 5- Classification of Critical trails

Figure 6 provides an overall perspective on the trials that each participant conducted. Within the 56 trials composed of a single brand, 30 contained a front of the pack (FOP) label and 26 were comprised of standard (STD) labels. The FOP was designed such that it contained truncated critical information from the DFL that related to drug/drug or drug diagnosis interactions (AI was not included in the FOP as that critical information is already present on all package fronts. Also, as you can see in the Figure 6, we cannot have STD label and changing location is on front of panel (PDP) and DD1 or DD2 is changing. Because if we do not have a FOP, we do not have any information relating to either of those pieces of information on front of package.

All changes that occurred in the critical information related to DD1 and DD2 were matched in size and text regardless of whether they occurred in the FOP or in the DFL. (Appendix 10). For the changes in the AI, the sizes were presented as they would be in a commercial scenario; as a result, text presenting the AI on the PDP was larger than it was on the DFL.

To minimize the potential effect of run order fatigue, the order of trials was randomized by E-prime software for each participant.

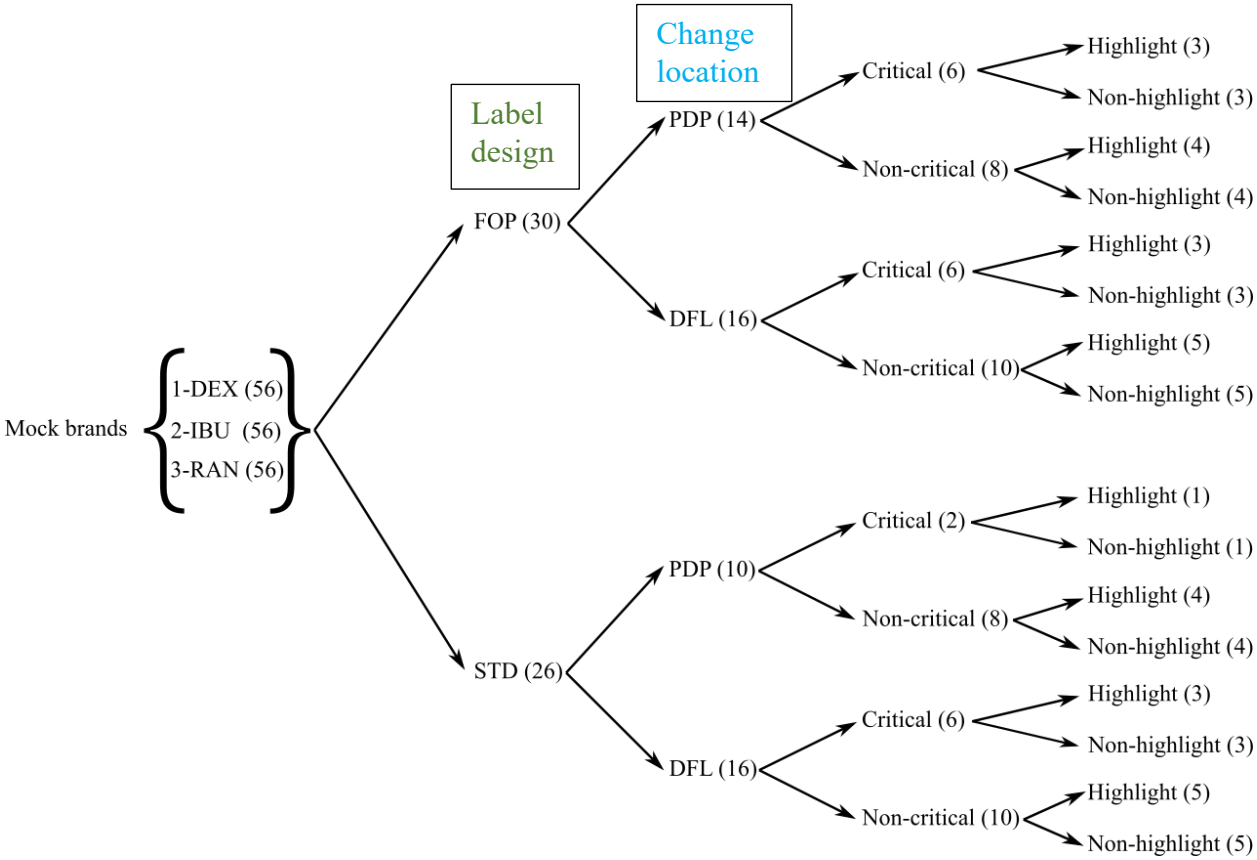


Figure 6- Classification of 168 trials conducted by each participant

3.2 Recruitment

Participants were recruited using the SONA software system, word of mouth communication, and distribution of approved fliers to willing participants to recruit their friends. The SONA system is an online system, where interested parties register to receive notification of available studies; additionally, the system can also assist with participant scheduling, though we did not use this feature. The platform enables participants to read a summary of research, including the inclusion/exclusion criteria, location of the research and information regarding incentive. Interested, eligible parties were instructed to contact the research team by phone or email to schedule a time for testing.

3.3 Participants

To participate in this study, participants had to:

- Be at least sixty-five years of age
- Not be legally blind
- Have used OTC drugs during the past 6 months
- Have NO history of seizure
- Have the ability to come the HUB lab at the Michigan State University, where the research was conducted.

In exchange for their participation, subjects were provided a $60 cash incentive, and, when needed, a two-hour parking permit. All participants underwent an informed consent process which required a written consent form (See Appendix 1 - consent form (approved under MSU IRB x17-922eD).

As part of the informed consent process, participants were informed that they were able to discontinue or opt out of any portion of the test at any time, and that they would still receive the incentive of sixty dollars. No identifying information was collected; as a result, not even the research team was able to tie collected data to participant identity. Data was tracked by participant number only.

After informed consent was obtained, participants provided basic demographic information such as gender, age, highest level of education, ethnicity, income, etc. in a survey that was administered to them on paper (See Appendix 2). Participants were further characterized with a series of pre-tests (see Appendix 4, 5, and 6) before starting the change detection testing. Prior to these tests they were asked if they used glasses for reading and,

if so, they were asked wear them during the pretest and change detection testing.

3.4 Pre-tests

The pre-tests contained three separate parts; namely, a near-point visual acuity test, a test of health literacy and a test of color vision. The pre-tests and the change detection testing were held in the room 159, the Healthcare, Universal Design, Biomechanics lab (HUB) in the School of Packaging at Michigan State University.

3.4.1 Near-Point Visual Acuity

The visual acuity testing measured participants' near-point visual acuity using a card from Bernell (Mishawaka, IN a division of Vision Training Products, INC). The researcher placed the visual acuity card approximately 16 inches from the participants' eyes under standard room illumination in the HUB lab and instructed the participant to read the lowest line on the card that they were able. Specifically, they were instructed with the following verbiage, "I want you to hold this card at about 16 inches from your eyes and try to read the lowest line on this card that you are able."

The line they read completely correctly was scored as indicated on the card with values ranging from 20/20 (lowest line) to 20/800 (Appendix 4).

3.4.2 Health Literacy

To estimate participants' health literacy we employed the Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R); REALM-R is a technique widely used to identify people at risk for poor literacy (Bass III, Wilson, & Griffith, n.d.).

The card contains eleven words: fat, flu, pill, allergic, jaundice, anemia, fatigue, directed, colitis, constipation, and osteoporosis (See Appendix 5). In accordance with standard procedures for this test, the first three words in the list were not scored, but used to improve

participant confidence and decrease test anxiety (Aging & Foundation, n.d.).

Standard instructions for examiners collecting this data are to:

"Put an x next to the scored trials where subjects did not correctly pronounce the word and a checkmark next to those that were correctly indicated."

Participants were asked to read aloud the eleven words on the REALM-R cards. The number of words they read correctly was scored as eight to zero; eight representing correct pronunciation for all words scored, seven for those whom read seven of the eight words correctly, etc. As indicated by standards procedure, participants receiving a score of 6 or less were coded as "at risk" for poor health literacy.

3.4.3 Color Differentiation Ability

Following the assessment of participant health literacy, we examined participants' ability to perceive color using a series of color vision test cards based on the concept introduced by Japanese ophthalmologist Shinobu Ishihara in 1917 (Levine & Beveren, n.d.)(See Appendix 6). These cards contain 24 plates with sets of colored dots, some of which contain numbers, others not.

Participants were instructed to view each of the color perception circles printed in the test sheets and, say aloud, any number that they were able to detect. In the event they were not able to decipher a number, they were instructed to say "pass." Responses were recorded in tabular form (See Appendix 7) as a rough estimate of the ability of participants to view color.

If participants read at least 13 plates correctly, results were recorded as "Normal color vision". Participants with 9 or fewer correct responses were recorded as having "Red-Green Deficiencies", and participants who read only one number (usually the first plate) were indicated as at risk for color blindness and recorded as "Total Color Blindness and

Weakness".

3.5 Change Detection Testing

As mentioned previously, change detection testing was conducted using E-prime software; testing took place at one of three workstations set up, side by side within room 159 Packaging. Each workstation was comprised of a Dell computer laptop with a 13-inch screen containing an Intel® Core™ i5-7440HQ CPU @ 2.80GHz and 16.0 GB of installed memory Ram and 238 GB memory. Each ran a 64-bit Operating System and had a screen resolution of 1920 * 1080. The E-prime code for this project contained 172 trials; specifically, each participant began with four example trials intended to familiarize them with the testing technique, providing them the opportunity to clarify questions prior to starting the test and then continued with the 168 trials previously discussed (see Figure 6).

3.6 Test

To begin, the researcher transferred all information collected on the demographic sheet into the participant's assigned computer (Appendix 3-7). This included: participant number, computer number, subject's sex, age, ethnicity, maximum education successfully achieved, native language, near point visual acuity score, REALM-R health literacy score, and color differentiation ability. Researchers asked each participant to sit in a chair in front of computer laptop station. At this point the screening criteria related to seizure history was reiterated, and the participant was seated in front of the computer screen, where the following information appeared:

"Do you have a history of seizures?

If so, we ask that you do not participate in the experiment. Instead please inform the experimenter that you are not able to continue.

If you have no history of seizures, please hit a button to continue."

Once the participant had advanced past the final screening for seizures, a welcome screen explaining the experiment appeared as:

"Welcome to the experiment!

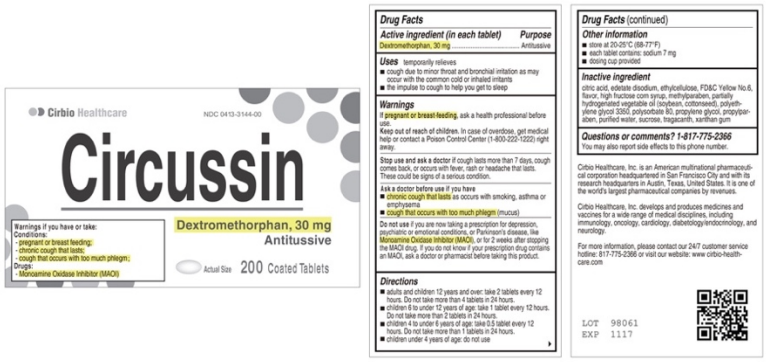
You will see two images separated by a brief blank. The images are identical except for one change. Your task is to detect the change. As soon as you see the change, press the space bar. Then the cursor will appear. Use the mouse to click on the location where the change occurred. The task is timed until you hit the space bar. Using the mouse to indicate the change location is not timed. If you fail to find the change within 18 seconds, the trial will time out. Please hit the space bar to begin a few practice trials…"

Directly following these instructions, the researcher worked with participants as they engaged four example trials of the test, which were intended to familiarize them with the experiment. Prior to engaging these four trials, participants were also instructed with the following text:

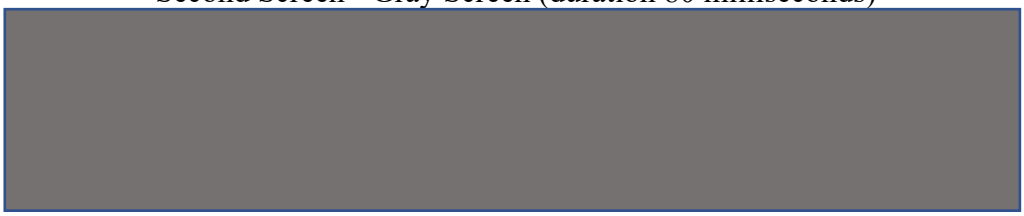
"try to find the change that appears in the image, or 'flickering' as quickly as possible. You can indicate that you have found this by hitting the space bar. After this point, you will need to use the mouse to click the area where the change appeared."

Testing was comprised of three blocks composed of fifty-six trials, with participants having the opportunity to take a break between trial blocks. During these times, they were offered water, and the opportunity to rest. Participants were instructed that they could restart the testing at any time by pressing the space bar.

First Screen (duration 240 milliseconds)

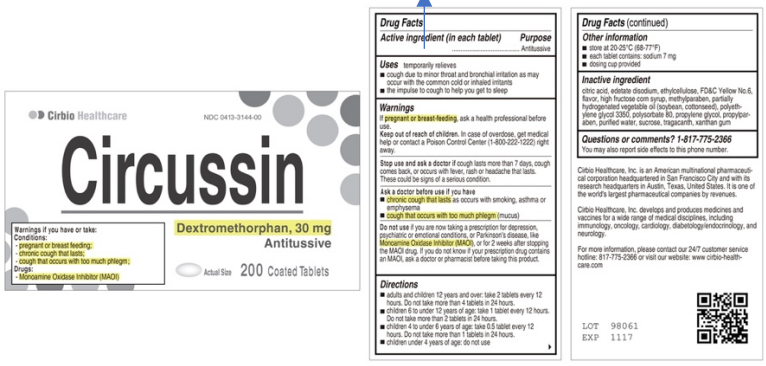


Second Screen - Gray Screen (duration 80 milliseconds)



Third Screen (duration 240 milliseconds)

Change



Forth Screen- Gray Screen (duration 80 milliseconds)

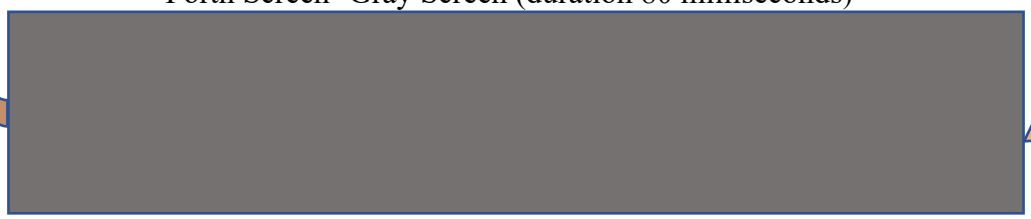


Figure 7- Example of change Detection Image Cycle for FOP type (different on highlight)

3.7 Statistical Methods

This study focuses primarily on the effects of two variables. The first, label design, compares the FOP design of label and non-FOP (STD) for sixty critical trials (see Figure 6); the second examines the effect of highlighting. Two dependent/resultant variables from the experiment were analyzed: (1) the proportion of people that were able to successfully identify the critical change prior to timing out at 18 seconds (a binary variable), and (2) the time it to them to correctly identify the change (a continuous variable).

The independent variables used in the study's final model were: education level, age, ethnicity, sex, label design (FOP or standard), change location (where the change occurred, either on the PDP or the DFL), highlighting (present and absent), change type (identifying which type of critical information was changing- the active ingredient AI, drug drug interaction DD1 and drug diagnosis DD2), and ingredients (IBU, RAN and DEX).

3.8 Binary Results (Proportion of correct responses)

We used a generalized linear mixed model to assess the influence of different variables of interest (see aforementioned) on the probability of correctly identifying changes to critical information prior to timing out at 18 seconds. The independent variables included were label type (2 levels- FOP and Standard), change location (PDP and DFL), highlighting (present or absent, change type (changed occurred in active ingredient, drug drug interaction-DD1 or drug diagnosis DD2), ingredient (Ibuprofen, Ranitidine or Dextromethorphan), education (at five levels), participant age, sex (male, female). Trial order and the participant themselves were also included as random effects. To begin, all possible variables in the model and two-way and three-way interactions between the variables that are most of interest (such as label

type crossed with highlighting, each at two levels) and (label type, highlight and location change).

This resulted in the following interactions terms being included in the model as improving: Label design x highlight x change location, change type x label design x highlight, and change type x highlight x change location. Models were run using R software (version 3.6.1, Vienna, Austria).

The data is binary in format (correctly detected yes/no); results are interpreted in terms of the probability of correctly detecting the change in terms of log odds. The log odds are defined as follow:

$$\log\left(\frac{P}{1-P}\right)$$

Where p is the probability of correctly detecting the change. As the log odds increase, the probability of detecting the changes increases; conversely, as the log odds decrease the probability of detecting the change decreases.

3.9 Continuous Results (Time to correct selection)

For all the critical trials that were correctly identified prior to time out, we used linear mixed model with log-transformed time to correct response as the dependent variable for the model. The process for this model was similar to that used in determining the binary model employed for the probability data. To assess the validity of normality assumptions, we residual plots and normal probability plots were visually inspected first with the non-transformed data, and then with data that had undergone transformation until it was determined that normality assumptions were adequately fulfilled. In the residual plot with the original data, there is low variability at the beginning/end points and high variability in the middle, suggesting a failure to meet model assumptions. As a result, data were log

transformed prior to use with the linear model. To account for minor non-constant variance in the data, Tukey's methods and Satterthwaite's degree of freedom was used to adjust the degrees of freedom.

The final model included the independent variables: education (at five levels), age, sex (male and female), ethnicity (white and nonwhite), ingredients (IBU, RAN, DEX), Label design (FOP present and absent) x highlight (present and absent) x change location (PDP or DFL) , change type (changed occurred in active ingredient, drug drug interaction-DD1 or drug diagnosis DD2) x label type (FOP present or absent) x highlight, change type x highlight x change location.

Post- hoc tests were conducted in order to perform pairwise comparisons related to the research objectives.

CHAPTER 4 – RESULTS AND DISCUSSION

4.1 Characterization of Participant Population

A total of 60 people aged 65 and older participated. Results of participant characterizations are presented in Figures 9-13. Twenty-three of the participants were male and thirty-seven of them were female (Figure 9).

4.1.1 Participant Demographics

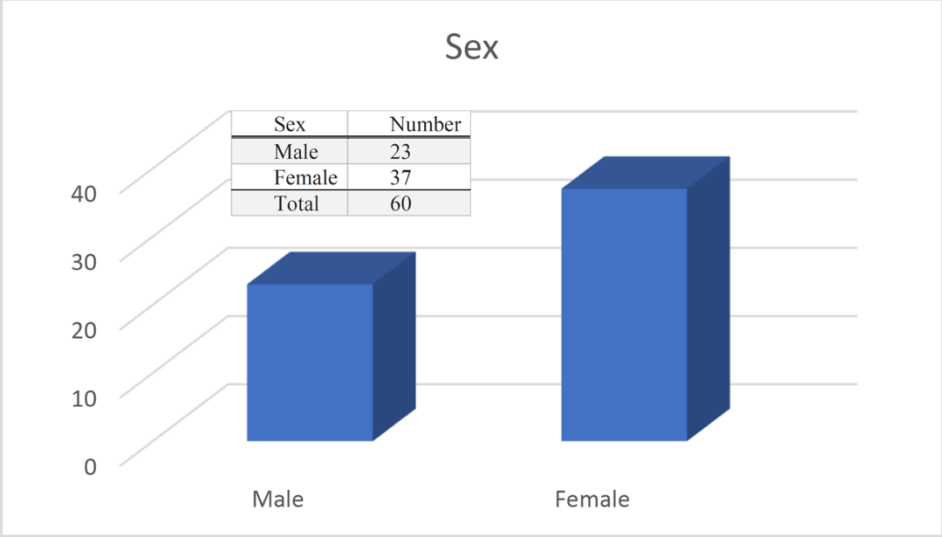


Figure 8- Subject Sex

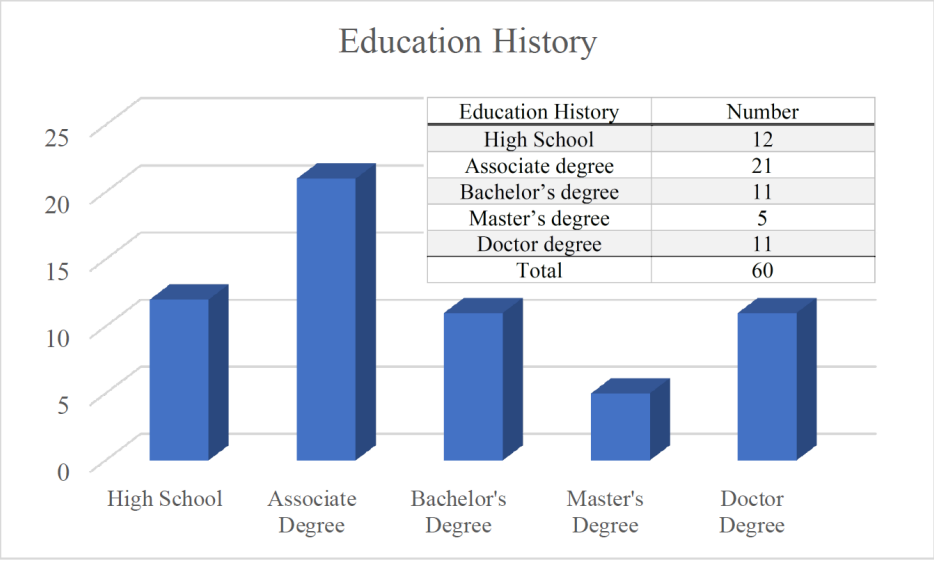
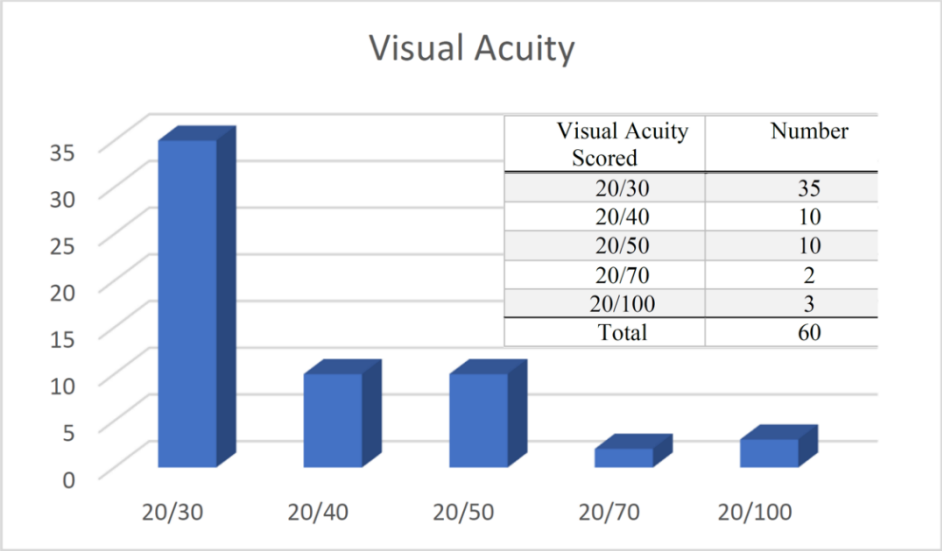


Figure 9- Education History

The sample collected through the campus-offered SONA system was highly educated; the majority of participants had a bachelor's degree or beyond. Of the 60 participants recruited, the primary language for the vast majority (58) was English, with one native speaker of Spanish and the other Arabic.

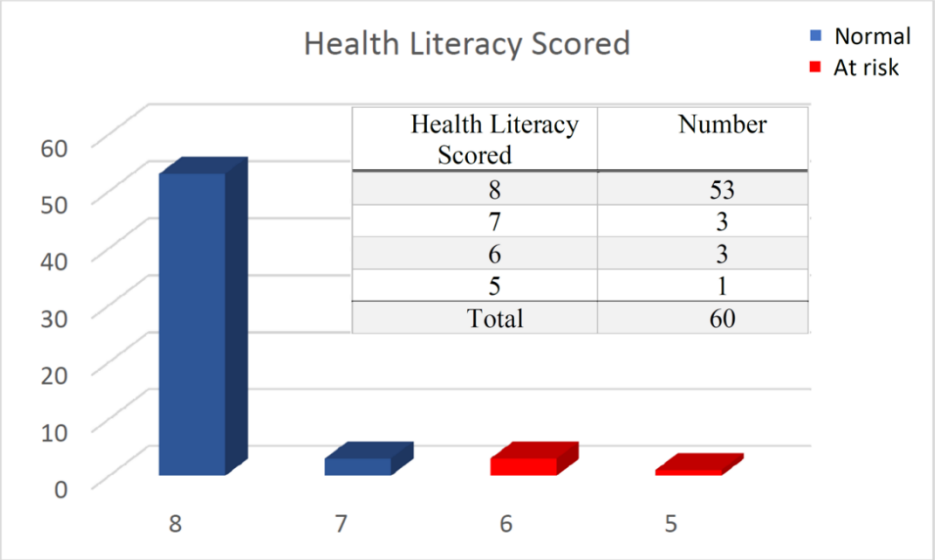
Figure 10 presents the frequency of results relating to the near point visual acuity testing of the 60 participants. All participants had some degree of vision loss at close range according to the results from the near point visual acuity testing. Not a single participant tested to have 20/20 vision, with even the most visually capable participants testing at 20/30 or lower (see Figure 10).



Visual Acuity Scored	Number
20/30	35
20/40	10
20/50	10
20/70	2
20/100	3
Total	60

Figure 10-Visual Acuity

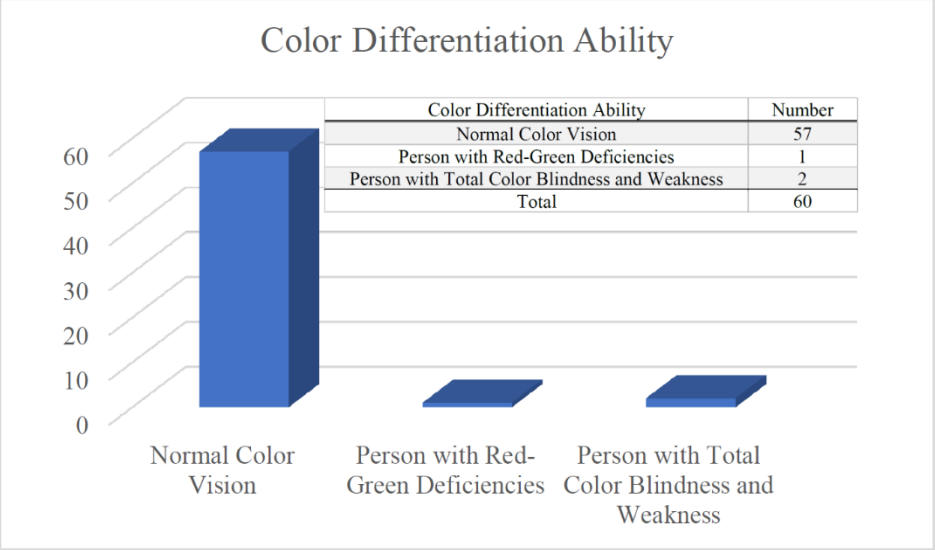
The education level of the sample paralleled the results of the REALM-R test, which assessed health literacy. Four participants tested at risk for poor health literacy (pronouncing six or less of the provided words correctly), while fifty-six participants did not have an indication of difficulty according to test results (meaning they read 7 or 8 of the words correctly).



Health Literacy Scored	Number
8	53
7	3
6	3
5	1
Total	60

Figure 11-Health Literacy

Participants were also characterized by their ability to view color. Figure 12 presents the frequency of people who were suggested to have anomalies in their ability to see color.



Color Differentiation Ability	Number
Normal Color Vision	57
Person with Red-Green Deficiencies	1
Person with Total Color Blindness and Weakness	2
Total	60

Figure 12-Color Differentiation Ability

4.2 Results Related to Probability of Successful Detection

Independent variables that were determined to improve the model fit for the binary response, proportion of correct responses, are indicated in table 2, effects those that reached a level of significance (α=0.05) are presented in bolded text.

Table 2- Overall result for the probability of successful detection

Variables	Mean Estimate	Standard Error	Test Statistic	P-Value
Education (associate degree-high school)	-0.42081	0.44892	-0.937	0.348568
Education (bachelor's degree- high school)	-0.45185	0.39909	-1.132	0.257549
Education (master's degree-high school)	-0.31756	0.46648	-0.681	0.496023
Education (Doctoral Degree-high school)	-0.01528	0.60673	-0.025	0.979902
Age	**-0.58714**	**0.13359**	**-4.395**	**1.11e-05**
Ethnicity (Hispanic- White)	-1.07551	0.77730	-1.384	0.166464
Ethnicity (African Americans- White)	-0.30883	0.44837	-0.689	0.490967
Sex	0.09899	0.29674	0.334	0.738689
Ingredient (RAN-IBU)	**-0.31675**	**0.09878**	**-3.207**	**0.001343**
Ingredient (DEX-IBU)	0.18974	0.09921	1.913	0.055807
Label Design	-0.42699	0.24026	-1.777	0.075531
Highlight	**0.84779**	**0.25293**	**3.352**	**0.000803**
Change location	**0.71115**	**0.25024**	**2.842**	**0.004485**
Change Type (DD1-AI)	**-1.09677**	**0.24433**	**-4.489**	**7.16e-06**
Change Type (DD2-AI)	**-1.57902**	**0.25312**	**-6.238**	**4.43e-10**
Label Design x Highlight	0.37422	0.35551	1.053	0.292508
Label Design x Change location	0.45845	0.35252	1.301	0.193429
Highlight x Change location	**1.23276**	**0.43126**	**2.859**	**0.004256**
Label Design x Change Type (AI-DD1)	0.27721	0.34570	0.802	0.422626
Label Design x Change Type (DD2-AI)	0.47442	0.35566	1.334	0.182232
Highlight x Change Type (DD1-AI)	0.46795	0.35259	1.327	0.184444

Table 2-(cont'd)

Highlight x Change Type (DD2-AI)	**0.86789**	**0.35805**	**2.424**	**0.015355**
Change Location x Change Type (DD1-AI)	**-0.75170**	**0.35060**	**-2.144**	**0.032029**
Change location x Change Type (DD2-AI)	**-0.88583**	**0.35739**	**-2.479**	**0.013190**
Label Design x Highlight x Change Location	**-1.42299**	**0.57543**	**-2.473**	**0.013402**
Label Design x Highlight x Change Type (DD1-AI)	-0.24861	0.49802	-0.499	0.617642
Label Design x Highlight x Change Type (DD2-AI)	-0.63480	0.50372	-1.260	0.207594
Highlight x Change Location x Change Type (DD1-AI)	-0.53205	0.51485	-1.033	0.301413
Highlight x Change location x Change Type (DD2-AI)	-0.40726	0.51830	-0.786	0.432007

As you see in the table 2, with p values greater than α=0.05, there is no evidence that education level affected the ability to detect a change prior to timing out at 18 seconds. The same was true when sex and ethnicity of participants of participants were considered. Unlike other participant characteristics, results did suggest a significant impact of age on the probability of getting a correct response; specifically, as age increases, the likelihood of detecting the change prior to time out decreases, as indicated by the negative mean estimated probability (p=1.11e-05).

The result of all variables of interest and pairwise comparisons which suggest significance are explored below in order to better interpret results. As mentioned in the Statistical Methods Tukey's test was utilized with a confidence level of 0.95 (alpha is 0.05).

4.2.1 Effect of Label Design

In contrast to our first hypothesis, that the presence of an FOP label would lead to more accurate detection of changes, our data does not suggest a significant difference in the ability

to detect changes in FOP treatments when they were compared to those without an FOP (STD; P=0.07)(see Table 3). The negative value of the mean estimate of the log odds (-0.42699) suggests that treatments absent an FOP had a lower probability of successful detection than those where the FOP was present. Although the directionality of this response is as we anticipated in our hypothesis, it doesn't rise to the level of a significant effect.

Table 3-Pairwise difference of Label Design in first model

Pairwise	Mean Estimate	Standard Error	Test Statistic	P-Value
Label Design (FOP absent and present)	-0.42699	0.24026	-1.777	0.075531

The other primary design element that we proposed to examine was that of highlighting of critical information. Specifically, we hypothesized that by highlighting information critical to the safe and effective use of an OTC, older adults would be able to detect changes more accurately (a higher proportion prior to time out) and more quickly). The following section explores the role of highlighting.

4.2.2 Effect of Highlight

Tables 4-7 present statistical results while controlling for a variety of factors (change location, change type, etc.). All comparisons suggest a positive effect of highlighting on the ability to successfully detect a change prior to timing out. Specifically, the pairwise comparisons of the mean estimates of the log of probability of comparisons in all tables (4-7) result in a negative, which means the probability of correct response in the absence of highlighting is less than in present of it. Also, p-value is significant so we can conclude the participants are better at detecting trials that incorporate highlighting than those that do not.

Table 5 presents the results of the pairwise comparison related to highlighting while

Table 4-Pairwise differences of Highlight across all treatments

Pairwise	Mean Estimate	Standard Error	Test Statistic	P-Value
NonHL-HL	-1.44	0.14	-10.248	**<.0001**

controlling for change location. Specifically, we can see that the benefits of highlighting the text on the probability of finding the change prior to timeout hold regardless of whether or not the changes occur in the DFL or the PDP. The fact that the difference of the estimates is slightly larger in the PDP treatments suggest that the benefit may be greater when it occurs to information of the PDP, though this comparison was not tested statistically.

Table 5- Interaction of Change Location and Highlight in first model

Comparisons of the Effect of Highlighting within a Location Change	Mean Estimate	Standard Error	Test Statistic	P-Value
DFL				
NonHL- HL	-1.33	0.104	-12.829	**<.0001**
PDP				
NonHL- HL	-1.54	0.259	-5.944	**<.0001**

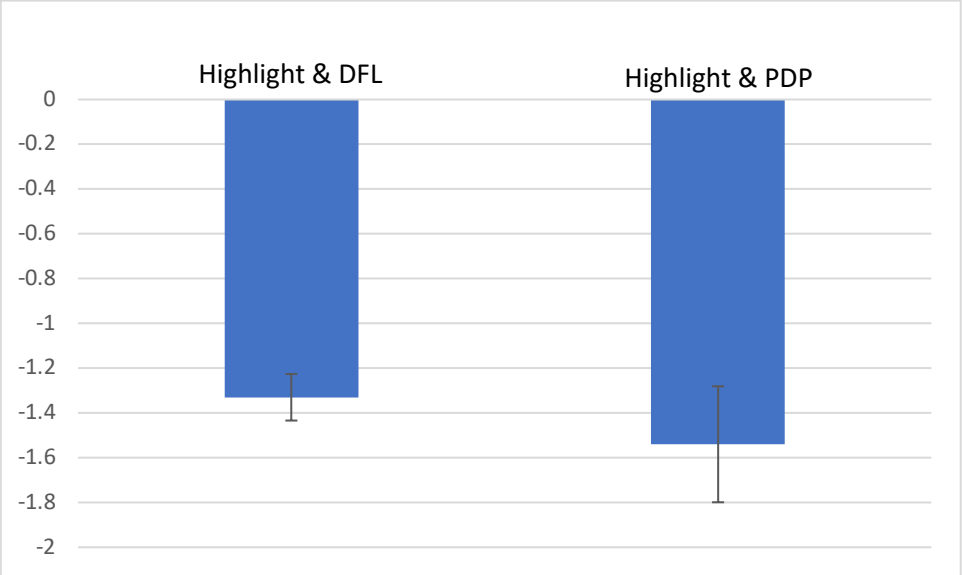


Figure 13- Comparisons of the Effect of Highlighting within a Location Change

Table 6 investigates the benefit of highlighting while controlling for the type of information that is involved in the change. As with all the previous comparisons investigating highlighting, the p-value is significant for all three change types (changes in the active ingredient, changes in the drug drug contraindications or changes in the drug diagnosis warnings). Anecdotally we can make a comparison of the size of the resultant differences and see that DD2 appears to derive the most benefit (largest difference; =1.64) from the presence of a highlight, as compared with DD1 or AI, though these were not compared for statistical significance.

Table 6-Interaction of Highlight and Change Type

Comparisons of Highlighting by Change Type	Mean Estimate	Standard Error	Test Statistic	P-Value
Change type = AI				
NonHL- HL	-1.30	0.146	-8.896	**<.0001**
DD1				
NonHL- HL	-1.37	0.225	-6.102	**<.0001**
DD2				
NonHL- HL	-1.64	0.229	-7.187	**<.0001**

As with all other comparisons that have been made with the highlighting, a review of Table 7, suggests that this people are significantly more likely to find the highlighted changes across label designs and change locations for all comparisons at α=0.05. A review of the differences suggests that this benefit is largest when the changes occur on the PDP of a standard label (i.e. without the FOP; -2.213). By contrast, when the FOP is present, the benefit is greatest when highlighting is added to the DFL (-1.373) and relatively small in the PDP (-0.869). This could be interpreted as suggesting that the FOP is drawing attention to the package front already, and as a result, highlighting does not enhance attention as greatly as it

does when the FOP is absent. That said, these differences were not assessed for significance and further study is needed.

Table 7-Interaction between Highlight and Change Location and Label Type

Comparisons of Highlighting within Change Location by Label Design	Mean Estimate	Standard Error	Test Statistic	P-Value
DFL, STD				
NonHL- HL	-1.293	0.146	-8.86	**<.0001**
PDP, STD				
NonHL- HL	-2.213	0.506	-4.37	**<.0001**
DFL, FOP				
NonHL- HL	-1.373	0.145	-9.441	**<.0001**
PDP, FOP				
NonHL- HL	-0.869	0.15	-5.805	**<.0001**

4.2.3 Effect of Location Change

The following tables summarize the investigation of effects specific to change location. The mean estimates of differences between the logs of probability for all the tables 8-11 is negative, which means the probability of identifying a change prior to timing out when changes happen on the PDP is higher than those that occur in the DFL. Table 8 provides an overarching assessment which suggests that participants are better at detecting the trials which the change occurs on the primary display panel compare when occurs on the drug fact label.

Table 8-Pairwise difference of Location Change in first model

Pairwise	Mean Estimate	Standard Error	Test Statistic	P-Value
DFL-PDP	-0.499	0.139	-3.578	**<0.0003**

Table 9 shows compares the location of the change (DFL Vs. PDP) for treatments that were highlighted and those that were not. Within each condition of highlighting, results are

significant ((α≤0.05). The presence of highlighting exacerbates this location difference (with a larger difference occurring in the probability of detecting changes in the PDP as compared to the DFL in highlighted treatments (-0.603) as compared to those in non-highlighted treatments (-0.395)).

Table 9-Interaction of Change Location and Highlight

Comparing Change Location for an effect of Highlighting	Mean Estimate	Standard Error	Test Statistic	P-Value
Non-Highlight				
DFL-PDP	-0.395	0.177	-2.227	**0.0259**
Highlight				
DFL-PDP	-0.603	0.215	-2.805	**0.005**

We investigate the effect of change location by change type (Active Ingredient, Drug/Drug interactions, vs Drug/Diagnosis interactions) in Table 10. These results suggest that the difference is only significant as it relates to AI (p<.0001) with the AI change to the PDP being more likely to be detected than when it appeared on the DFL (as indicated by the negative difference between the probability logs -1.201). By contrast, DD1 (Drug Drug contraindications p=0.4145) and DD2 (p= 0.6227) did not achieve any indication of a significant difference. This suggests that the information on the FOP (DD1 and DD2 presented in FOP formats) did not enhance attention to critical information.

Table 10-Interaction of Change Location and Change Type

Comparing Change Location for an effect by Change Type	Mean Estimate	Standard Error	Test Statistic	P-Value
AI				
DFL-PDP	-1.201	0.146	-8.25	**<.0001**
DD1				
DFL-PDP	-0.183	0.225	-0.816	0.4145

Table 10-(cont'd)

DD2				
DFL-PDP	-0.112	0.227	-0.492	0.6227

Table 11 investigates the three-way interaction that occurred between highlighting x label design x change location. As was suggested in the previous discussion related to change type, the effect of change location is impacted by the type of change that is happening. Within the standard label (no FOP) for non-highlighted trials, no evidence of significance was present when changes in the DFL were compared with the PDP (P=0.6081); by contrast, for this same label (STD- no FOP) in the highlighted condition, a significant difference was noted in the ability to correctly identify changes prior to timing out (P=0.0092), whereby participants were more likely to find changes in the PDP that were highlighted than those in the DFL (as indicated by the negative difference in the probability estimates -1.085). Conversely, in the results that investigate the FOP labels, people are statistically significantly more likely to find changes in the PDP than the DFL *for non-highlighted treatments* (P<.0001), but no evidence of location effect is present in the highlighted treatments (P=0.4189).

Table 11-Interaction of Highlight, Label Design and Change Location

Comparisons of Change Location by Highlight and Label Design	Mean Estimate	Standard Error	Test Statistic	P-Value
Non-Highlight, STD				
DFL-PDP	-0.165	0.322	-0.513	0.6081
Highlight, STD				
DFL-PDP	-1.085	0.417	-2.604	**0.0092**
Non-Highlight, FOP				
DFL-PDP	-0.624	0.145	-4.305	**<.0001**
Highlight, FOP				
DFL-PDP	-0.12	0.149	-0.808	0.4189

4.2.4 Effect of Ingredient

Table 12 depicts, the difference in the log probability of mean estimates for the pairwise comparisons related to the brands that we created. As with previous tables, a positive value indicates that the probability of a successful detection is higher for the first brand then the second, a negative mean estimate suggest that the second had a higher probability of successful detection. For example, the first comparison (IBU-RAN) is significant (P=0.0038), the positive mean estimate of the differences indicates that the probability of a successful detection is higher for Ibuprofen (IBU) than Ranitidine (RAN), participants were better at detecting the change in IBU compare to RAN. Also, the difference in the mean estimates for the third row has a negative value (-0.506) which means the probability of correct response for DEX is significantly higher than RAN and the p-value is significant, so participants were better at detecting changes in DEX compare to RAN.

Table 12- Pairwise differences of ingredients in binary model

Pairwise Comparisons of Ingredients/Brands	Mean Estimate	Standard Error	Test Statistic	P-Value
IBU-RAN	0.317	0.0988	3.207	**0.0038**
IBU-DEX	-0.190	0.0992	-1.913	0.1351
RAN-DEX	-0.506	0.0992	-5.108	**<0.0001**

4.3 Results Related to the Time to Successful Detection

Results were also analyzed to investigate the time to successful detection (a continuous variable) as a dependent variable. In this model we used Tukey's test with Satterthwaite's degrees (to adjust the degree of freedom) of freedom and confidence level of 0.95 (α=0.05). Table 13 lists the fixed effects serving as independent variables and interactions. Effects that reached a level of significance are presented in **bolded** text.

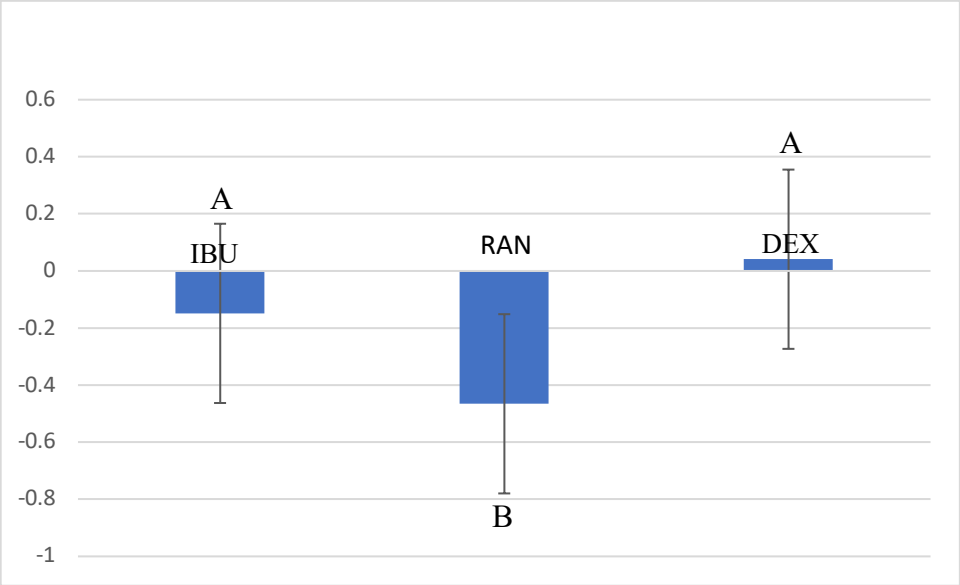


Figure 14-Pairwise comparison between different brand

Table 13-Overall result for the Time to Successful Detection

Variables	Mean Estimate	Standard Error	Test Statistic	P-Value
Education (associate degree-high school)	2.388e-01	9.889e-02	2.415	**0.02066**
Education (bachelor's degree-high school)	1.457e-01	8.754e-02	1.664	0.10432
Education (master's degree-high school)	3.152e-01	1.018e-01	3.095	**0.00374**
Education (Doctoral Degree-high school)	3.379e-01	1.313e-01	2.575	**0.01432**
Age	-2.076e-03	3.124e-02	-0.066	0.94727
Ethnicity (Hispanic- White)	4.121e-01	1.730e-01	2.383	**0.02205**
Ethnicity (African Americans- White)	1.861e-01	1.009e-01	1.844	0.07230
Sex	**-1.889e-01**	**6.549e-02**	**-2.884**	**0.00640**
Ingredient (RAN- IBU)	3.159e-02	3.168e-02	0.997	0.31883
Ingredient (DEX- IBU)	-2.564e-02	3.025e-02	-0.848	0.39672
Label Design	6.921e-02	8.105e-02	0.854	0.39320
Highlight	-9.886e-02	7.354e-02	-1.344	0.17904
Change location	**-5.455e-01**	**7.442e-02**	**-7.329**	**3.43e-13**
Change Type (DD1-AI)	**5.164e-01**	**8.958e-02**	**5.764**	**9.60e-09**
Change Type (DD2-AI)	**5.991e-01**	**9.833e-02**	**6.093**	**1.34e-09**
Label Design x Highlight	-3.328e-02	1.066e-01	-0.312	0.75505

Table 13-(cont'd)

Label Design x Change Location	1.334e-01	1.070e-01	1.247	0.21269
Highlight x Change location	-1.586e-01	9.832e-02	-1.613	0.10688
Label Design x Change Type (DD1-AI)	3.840e-02	1.302e-01	1.849e+03	0.476807
Label Design x Change Type (DD2-AI)	-8.193e-02	1.400e-01	-0.585	0.55847
Highlight x Change Type (DD1-AI)	-5.267e-02	1.149e-01	-0.458	0.64687
Highlight x Change Type (DD2-AI)	-1.871e-01	1.219e-01	-1.534	0.12513
Change Location x Change Type (DD1-AI)	**-5.176e-01**	**1.257e-01**	**-4.118**	**3.99e-05**
Change Location x Change Type (DD2-AI)	**-2.866e-01**	**1.857e+03**	**-2.133**	**0.03307**
Label Design x Highlight x PDP	2.145e-03	1.416e-01	0.015	0.98792
Label Design x Highlight x Change Type (DD1-AI)	-1.029e-01	1.657e-01	-0.621	0.53462
Label Design x Highlight x Change Type (DD2-AI)	1.707e-01	1.744e-01	0.979	0.32757
Highlight x Change Location x Change Type (DD1-AI)	**3.478e-01**	**1.618e-01**	**2.150**	**0.03170**
Highlight x Change Location x Change Type (DD2-AI)	1.446e-01	1.699e-01	0.851	0.39490

4.3.1 Effect of Label Design

Table 14 provides a global comparison of the label designs of interest (FOP present and absent) in support of our first hypothesis (an FOP label would enhance attention to critical information as measured by time to successfully detect changes. Across all types of changes, there is no evidence of a difference in the time to successfully detect changes (P=0.39320). That said, the positive difference (6.921e-02) when the mean estimates are compared suggests that in FOP absent conditions (STD) time to successful detection is slightly higher than the time that it took to detect changes in FOP present conditions.

Table 14- Pairwise difference of Label Design in second model

Pairwise	Mean Estimate	Standard Error	Test Statistic	P-Value
Label design (FOP absent and present)	6.921e-02	8.105e-02	0.854	0.39320

4.3.2 Effect of Highlight

When the effect of highlighting on time to detect is investigated across all treatments (Table 15) there is no evidence of a significant effect (P=0.17904). The slight negative value in the difference suggests, the difference in the mean estimates of the time to correct response for highlighted trials was slightly higher than non-highlight.

Table 15- Pairwise differences of Highlight in second model

Pairwise	Mean Estimate	Standard Error	Test Statistic	P-Value
NonHL-HL	-3.328e-02	1.066e-01	-0.312	0.17904

However, by further investigating the three-way interaction between highlighting change type and location we can begin to better understand the efficacy of our design strategy, and overall we can conclude that highlighting significantly decreases the time to successful detection when the change is in AI in the DFL (P=0.0309); AI in the PDP (<0.0001); DD1 in the DFL (P=0.0006) and DD2 in the DFL (P=0.0017). The treatments where highlighting did not provide evidence of a significant effect involved those that were in the FOP (DD1, PDP (P=0.8191) and DD2 in the PDP (P=0.0924)).

4.3.3 Effect of Location Change

As was the case with our probability results, Table 17 suggests that the location of the change significantly impacts that time to successful detection (P<0.0001). The difference in

Table 16-Interaction of Label Design, Highlighting and Change Type

Comparisons of Highlighting by Change Type and Change Location	Mean Estimate	Standard Error	Test Statistic	P-Value
AI, DFL				
NonHL- HL	0.1155	0.0535	2.16	**0.0309**
AI, PDP				
NonHL- HL	0.273	0.0467	5.847	**<.0001**
DD1, DFL				
NonHL- HL	0.2196	0.0637	3.447	**0.0006**
DD1, PDP				
NonHL- HL	0.0294	0.1285	0.229	0.8191
DD2, DFL				
NonHL- HL	0.2172	0.0693	3.135	**0.0017**
DD2, PDP				
NonHL- HL	0.2302	0.1367	1.684	0.0924

estimates of the mean log response times is positive, this suggests that across all changes that occur in the DFL there is a larger mean log response time than those in the PDP (as indicated by the positive difference of the mean estimate (0.744). One my conclude that people have a tendency first attend information on the PDP as compared to other segments of the packaging.

Table 17-Pairwise difference of PDP and DFL in second model

Pairwise Comparison of Change Location	Mean Estimate	Standard Error	Test Statistic	P-Value
DFL-PDP	0.744	0.0406	18.327	**<0.0001**

Table 18 evaluates the three-way interaction that occurred involving change location x highlighting x change type. In these comparisons, when the difference in the log for response times of the mean estimates is positive, it suggests that the time to successfully detect a

change in the PDP is less than DFL. The p-values are significant for all comparison conditions, so participants are quicker to detect changes in the front panel compared with changes in the DFL regardless of the condition related to highlighting or the type of information that is changing (AI, DD1 or DD2).

Table 18- Interaction of Label Design, Highlight and Change Type

Comparison of Change Location by Highlighting and Change Type	Mean Estimate	Standard Error	Test Statistic	P-Value
Non-Highlight, AI				
DFL-PDP	0.479	0.0543	8.817	**<.0001**
Highlight, AI				
DFL-PDP	0.636	0.0467	13.62	**<.0001**
Non-Highlight, DD1				
DFL-PDP	0.996	0.1123	8.869	**<.0001**
Highlight, DD1				
DFL-PDP	0.806	0.0904	8.922	**<.0001**
Non-Highlight, DD2				
DFL-PDP	0.765	0.1218	6.284	**<.0001**
Highlight, DD2				
DFL-PDP	0.778	0.0938	8.294	**<.0001**

4.3.4 Effect of Change Type

Table 19 provides the differences of the mean estimates of the log times comparing the change types. Results suggest that changes to active ingredient are successfully detected more quickly than either DD1 or DD2 (<0.0001). There was no evidence of a significant difference in the amount of time to successfully detected changes when trials composed of DD1 and DD2 were compared (P=0.1342)(see Figure 15).

That said, it is important to remember that the AI that appeared on the PDPs was not size matched to the AI that appeared on the DFL, likely leading to faster changes at this location.

Table 19-Pairwise differences of change type in the second model

Pairwise Comparisons of Change Type	Mean Estimate	Standard Error	Test Statistic	P-Value
AI-DD1	-0.3117	0.0400	-7.795	**<0.0001**
AI-DD2	-0.4002	0.0426	-9.397	**<0.0001**
DD1-DD2	-0.0885	0.0462	-1.917	0.1342

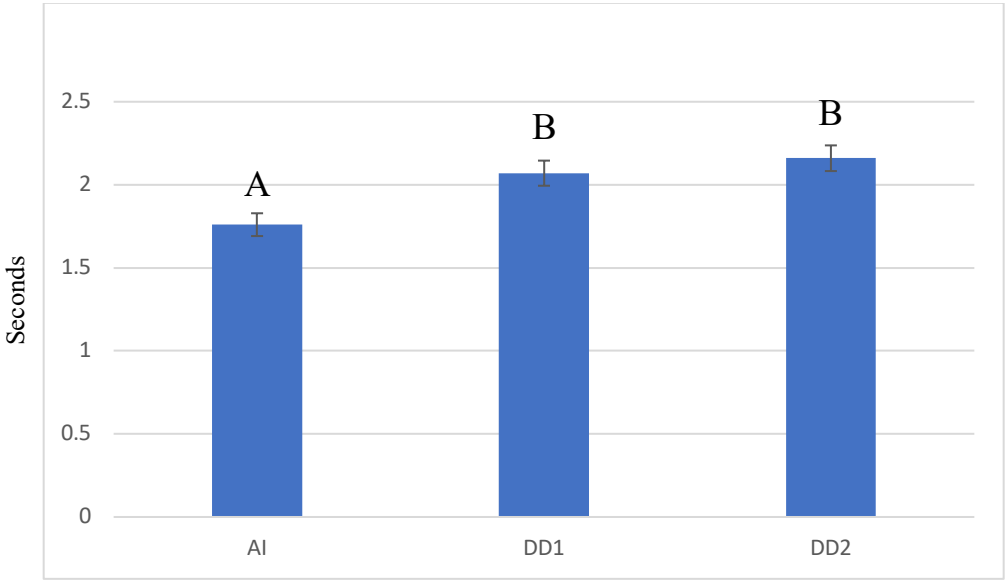


Figure 15-Pairwise comparison between different change type

By contrast, DD1 and DD2 were size matched in both locations (DFL and PDP- present in FOP designs only). As such, exploring by location is an important next step when analyzing the effects Change Type. Table 20 provides comparisons of the differences of the mean estimates of the log times for the comparisons of Change Type by highlighting and change location. Significant differences were found: (1) in Non-highlighted changes in the DFL when comparing AI and Drug/drug as well as drug/ diagnosis ($p<.0001$). That is that on the DFL, when in non-highlighted treatments, changes to the AI were more detected faster than those to either DD1 or DD2. No evidence of a difference was noted when changes in drug/drug and drug/diagnoses were compared (for nonhighlighted changes in the DFL).

When comparing the log times to successful detection on the PDP in non-highlighted conditions, only AI compared to DD2 rise to the level of significance (P=0.0448) with the negative value suggesting people were faster in detecting changes to the AI than those to DD2. It important to note that this comparison would only be made with FOP treatments as the standard treatment did not have DD1 or DD2 appear on the PDP. The highlighted trials resulted in a more consistent result than the non-highlighted trials (discussed immediately previously). Specifically, for each comparison of the log time to detect active ingredient vs DD1 and DD2 was significant at α=0.05, where the active ingredient was detected faster regardless of whether the change took place on the DFL or the PDP, although the difference in the effect of the type of information was more pronounced in the DFL than in the PDP.

Table 20-Interaction of Change Location, Highlighting and Change Type

Comparisons of Change Type by Highlighting Condition and Change Location	Mean Estimate	Standard Error	Test Statistic	P-Value
Non-Highlight, DFL				
AI-DD1	-0.5356	0.0654	-8.191	**<.0001**
AI-DD2	-0.5582	0.0705	-7.917	**<.0001**
DD1-DD2	-0.0226	0.0771	-0.293	0.9538
Non-Highlight, PDP				
AI-DD1	-0.018	0.1054	-0.171	0.9841
AI-DD2	-0.2716	0.1137	-2.389	**0.0448**
DD1-DD2	-0.2536	0.125	-2.03	0.1054
Highlight, DFL				
AI-DD1	-0.4315	0.0512	-8.434	**<.0001**
AI-DD2	-0.4564	0.0521	-8.753	**<.0001**
DD1-DD2	-0.025	0.0542	-0.461	0.8895
Highlight, PDP				
AI-DD1	-0.2616	0.0883	-2.962	**0.0087**
AI-DD2	-0.3145	0.091	-3.455	**0.0016**
DD1-DD2	-0.0528	0.0981	-0.539	0.8522

4.4 Discussion

Contrary to our hypothesis that the use of a novel FOP would enhance attention to critical information and the time it took to detect the same, our results (Table 3&14) did not suggest that the presence of an FOP, as compared to a STD label, significantly affected the attention to, or time to detect critical information for OTC products when tested with adults 65 and older. That said, it is important to note that our stimulus treatments were in a flattened format, automatically exposing the viewer to the information present in the DFL. In real-world contexts, participants would have had to rotate the package to have access to the DFL; as a result, our experiment is a conservative test of our hypothesis. Further, the directionality of our results suggests that people were more accurate (Table 3) and faster (Table 14) in FOP treatments than standard, but that the difference did not rise to a level of significance. Additionally, there is a clear indication that participants tended to preferentially attend information on the PDP (Table 8), which continues to show promise for the strategy. We positioned the FOP at the far-left side of the package. It is possible that repositioning of the FOP within the PDP could result in stronger strength of signal. Future work is recommended.

Our results regarding highlighting suggest it to be a promising strategy for garnering the attention of older adults. Although Figure 16, which depicts the average response time for successful detection for highlighted versus non-highlighted trials, collapsed across all conditions, (6.72415365 seconds for highlighted compared to 7.45347917 seconds for those without highlights) does not indicate significance. It is imperative to look at the nuances of this data to get a better understanding of the effect.

When compared globally (across all other effects) results suggest that older adults were significantly more likely to highlighted detect changes (Table 4) but not significantly faster

(Table 15) in finding the change in the highlight compare to non-highlight (across all other factors). More nuanced looks at the interactions (as in Table 16 which investigates that the three way interaction between label design x highlight and change type) suggest highlighting to be significantly beneficial for all combinations of information type (AI, DD1 and DD2), the both locations (PDP and DFL) with one exception, when the information changes in the FOP (those changes involving the PDP with DD1 and DD2).

Results suggest that highlighting of critical information may be a promising avenue for garnering attention to important information related to the safe and effective use of OTC products. Further work to evaluate the efficacy of the FOP approach, including the effect of placement within the PDP is recommended.

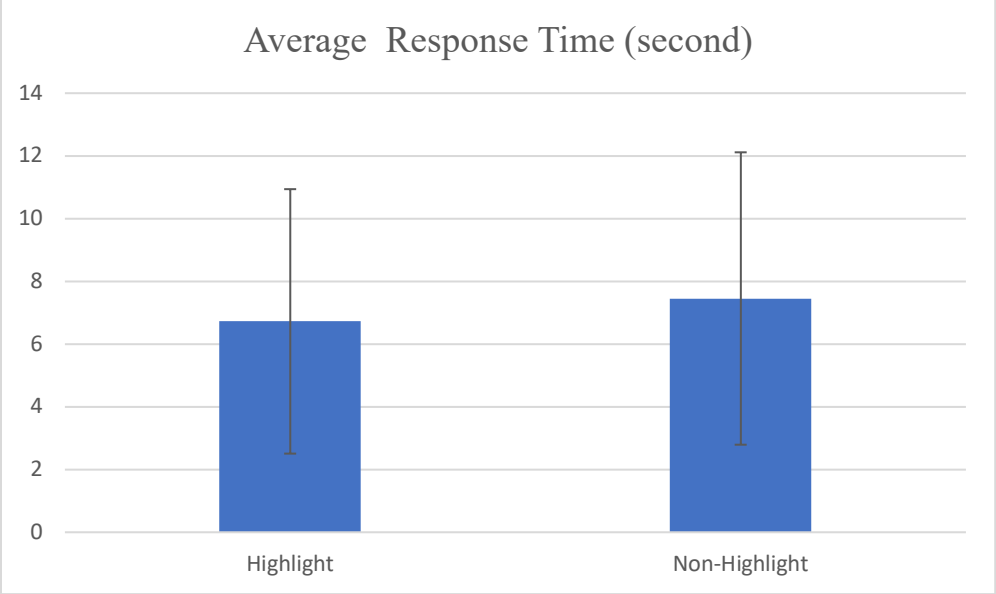
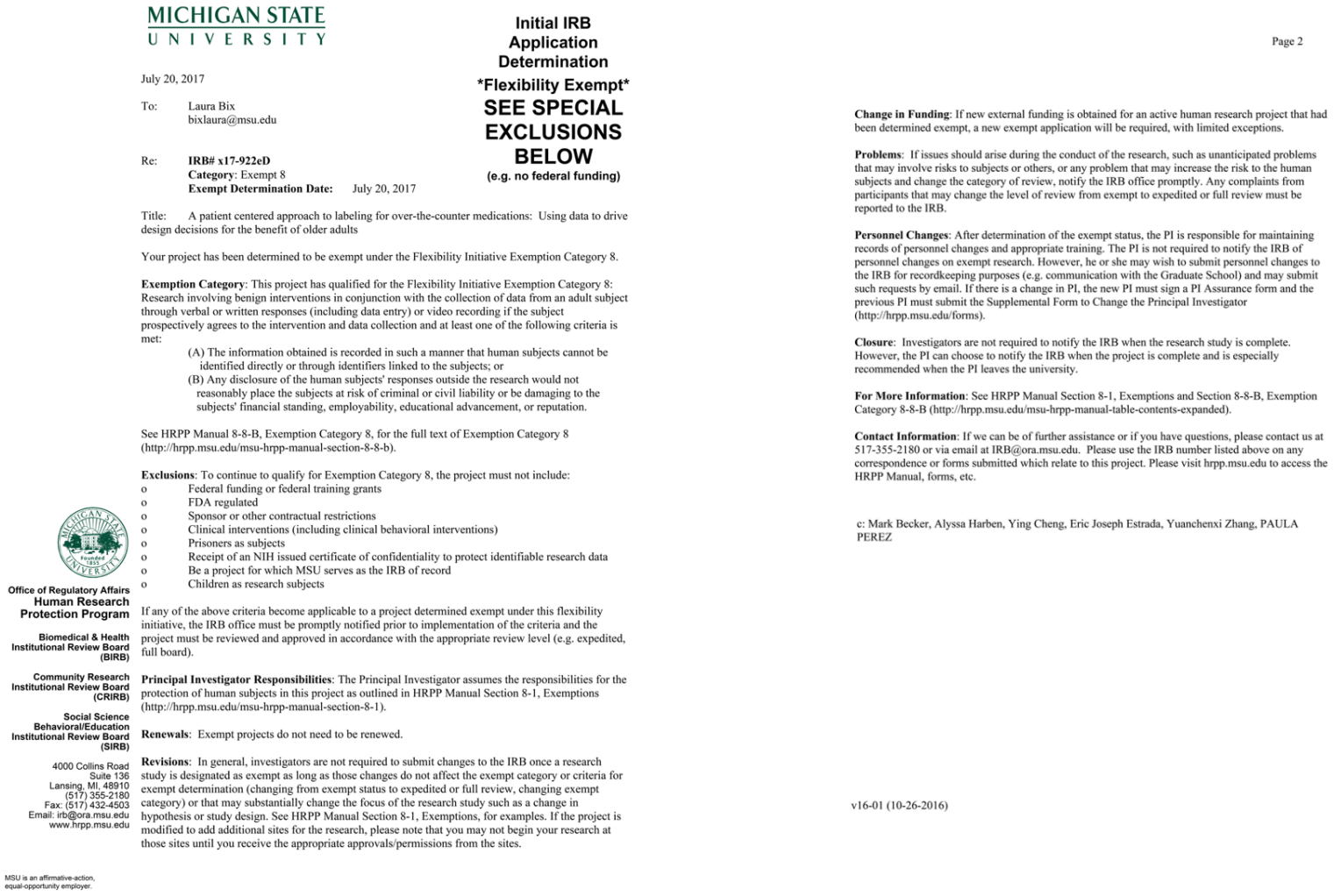


Figure 16-Average Response Time for Highlight and non-Highlight trials

APPENDICES

APPENDIX A-Initial IRB Application Determination



MICHIGAN STATE UNIVERSITY

Initial IRB Application Determination
Flexibility Exempt
SEE SPECIAL EXCLUSIONS BELOW
(e.g. no federal funding)

July 20, 2017

To: Laura Bix
bixlaura@msu.edu

Re: **IRB# x17-922eD**
Category: Exempt 8
Exempt Determination Date: July 20, 2017

Title: A patient centered approach to labeling for over-the-counter medications: Using data to drive design decisions for the benefit of older adults

Your project has been determined to be exempt under the Flexibility Initiative Exemption Category 8.

Exemption Category: This project has qualified for the Flexibility Initiative Exemption Category 8: Research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses (including data entry) or video recording if the subject prospectively agrees to the intervention and data collection and at least one of the following criteria is met:

(A) The information obtained is recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects; or
(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

See HRPP Manual 8-8-B, Exemption Category 8, for the full text of Exemption Category 8 (http://hrpp.msu.edu/msu-hrpp-manual-section-8-8-b).

Exclusions: To continue to qualify for Exemption Category 8, the project must not include:
- Federal funding or federal training grants
- FDA regulated
- Sponsor or other contractual restrictions
- Clinical interventions (including clinical behavioral interventions)
- Prisoners as subjects
- Receipt of an NIH issued certificate of confidentiality to protect identifiable research data
- Be a project for which MSU serves as the IRB of record
- Children as research subjects

If any of the above criteria become applicable to a project determined exempt under this flexibility initiative, the IRB office must be promptly notified prior to implementation of the criteria and the project must be reviewed and approved in accordance with the appropriate review level (e.g. expedited, full board).

Principal Investigator Responsibilities: The Principal Investigator assumes the responsibilities for the protection of human subjects in this project as outlined in HRPP Manual Section 8-1, Exemptions (http://hrpp.msu.edu/msu-hrpp-manual-section-8-1).

Renewals: Exempt projects do not need to be renewed.

Revisions: In general, investigators are not required to submit changes to the IRB once a research study is designated as exempt as long as those changes do not affect the exempt category or criteria for exempt determination (changing from exempt status to expedited or full review, changing exempt category) or that may substantially change the focus of the research study such as a change in hypothesis or study design. See HRPP Manual Section 8-1, Exemptions, for examples. If the project is modified to add additional sites for the research, please note that you may not begin your research at those sites until you receive the appropriate approvals/permissions from the sites.

Page 2

Change in Funding: If new external funding is obtained for an active human research project that had been determined exempt, a new exempt application will be required, with limited exceptions.

Problems: If issues should arise during the conduct of the research, such as unanticipated problems that may involve risks to subjects or others, or any problem that may increase the risk to the human subjects and change the category of review, notify the IRB office promptly. Any complaints from participants that may change the level of review from exempt to expedited or full review must be reported to the IRB.

Personnel Changes: After determination of the exempt status, the PI is responsible for maintaining records of personnel changes and appropriate training. The PI is not required to notify the IRB of personnel changes on exempt research. However, he or she may wish to submit personnel changes to the IRB for recordkeeping purposes (e.g. communication with the Graduate School) and may submit such requests by email. If there is a change in PI, the new PI must sign a PI Assurance form and the previous PI must submit the Supplemental Form to Change the Principal Investigator (http://hrpp.msu.edu/forms).

Closure: Investigators are not required to notify the IRB when the research study is complete. However, the PI can choose to notify the IRB when the project is complete and is especially recommended when the PI leaves the university.

For More Information: See HRPP Manual Section 8-1, Exemptions and Section 8-8-B, Exemption Category 8-8-B (http://hrpp.msu.edu/msu-hrpp-manual-table-contents-expanded).

Contact Information: If we can be of further assistance or if you have questions, please contact us at 517-355-2180 or via email at IRB@ora.msu.edu. Please use the IRB number listed above on any correspondence or forms submitted which relate to this project. Please visit hrpp.msu.edu to access the HRPP Manual, forms, etc.

c: Mark Becker, Alyssa Harben, Ying Cheng, Eric Joseph Estrada, Yuanchenxi Zhang, PAULA PEREZ

v16-01 (10-26-2016)

Office of Regulatory Affairs
Human Research Protection Program

Biomedical & Health Institutional Review Board (BIRB)

Community Research Institutional Review Board (CRIRB)

Social Science Behavioral/Education Institutional Review Board (SIRB)

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MSU is an affirmative-action, equal-opportunity employer.

Figure 17- Initial IRB Application Determination

Appendix B-Consent Form

Michigan State University
School of Packaging/Department of Psychology
Study Title: A Patient Centered approach to labeling for over-the-counter medications: Using data to drive design decisions for the benefit of older adults
INSTRUCTIONS AND RESEARCH CONSENT FORM

You are being asked to participate in a research project. Researchers are required to provide a consent form to inform you about the study, to convey that participation is voluntary, to explain risks and benefits of participation, and to empower you to make an informed decision. You should feel free to ask the researchers any questions or concerns you may have during the experiment.

1. **PURPOSE OF RESEARCH:** You are being asked to participate in an experiment to investigate how well the formats of different OTC drug labels work.

2. **TO PARTICIPATE IN THIS STUDY YOU MUST:**
   a. Be 65 years or older
   b. Have NO HISTORY OF SEIZURE
   c. Not legally blind
   d. Manage your own medications
   e. Have purchased or used OTC drugs within the last 12 months
   f. Have transportation to Michigan State University, where testing will occur

2. WHAT YOU WILL DO: If you agree to participate in this study, the following events will take place. We will ask you to answer some basic questions about yourself. Your visual acuity, and your ability to see color will be tested; we will also test you for familiarity with medical terms. You will sit in front of a computer screen. On the computer screen, a test image (a label) continuously alternates with the same image, slightly altered, with a gray screen in between. This image-blank-test-blank will loop, resulting in a "flickering" at the place of alteration until you press the space bar, indicating that you have found the change. You will then be asked to use a mouse to point and click on the place where you saw the flickering of the image. If you are unfamiliar, unable or uncomfortable with using the mouse to click, you can point to the location of the change and the research team will do this for you. If you cannot find the change within the time the allotted time (30 seconds per label), the software will move you to the next trial in the test. This process will repeat for a series of trials. The research should take no more than 1 hour of your time. In exchange for your participation in this study, you will receive $60.

3. **POTENTIAL BENEFITS:** There will be no direct benefit to you from these procedures. However, it is our goal to understand what factors make certain parts of a label more noticeable than others so that we can develop labels that provide important information to people in ways that they are likely to see it.

4. **POTENTIAL RISKS:** We will ask you to read aloud a series of words used by medical people. It is possible that you may not be familiar with these words and this would be embarrassing. You can skip any words you are unsure of.

There is a possible risk of seizure associated with viewing flashing images; as a result, if you have a history of seizure, you are not eligible to participate. If you are injured as a result of your participation in this research project, researchers from Michigan State University will assist you in obtaining emergency care, if necessary, for your research-related injuries. If you have insurance for medical care, your insurance carrier will be billed in the ordinary manner. As with any medical insurance, any costs that are not covered or in excess of what are paid by your insurance, including deductibles, will be your responsibility.

The University's policy is not to provide financial compensation for lost wages, disability, pain or discomfort unless required by law to do so. This does not mean that you are giving up any legal rights you may have.

In the event that you are uncomfortable with any of the tasks, you may elect to skip a portion of the study, or discontinue altogether.

5. PRIVACY AND CONFIDENTIALITY: The data for this project will be tied to subject number, not name. Although the researchers, research staff, and the Institutional Review Board will have access to the data, neither the researchers nor anyone else will be able to link your data to you. Participant confidentiality will be protected to the maximum extent allowable by law. Paper records will be kept in Dr. Bix's office for as long as required by publishers or at least three years after the study closes whichever is longer; digital records will be housed on computers in our laboratories (Psychology and Packaging). Data would be provided (deidentified) to publications that deemed it a necessary part of due diligence and is also accessible to the IRB.

6. YOUR RIGHTS TO PARTICIPATE, SAY NO, OR WITHDRAW: Participation in this research is completely voluntary. Refusal to participate will involve no penalty or loss of benefit. You may also refuse to answer particular questions. You may change your mind at any time, for any reason, and withdraw without penalty or loss of compensation.

7. COSTS AND COMPENSATION FOR BEING IN THE STUDY: You will receive $60 in exchange for your participation in this study.

8. CONTACT INFORMATION FOR QUESTIONS AND CONCERNS: If you have any concerns or questions about this research study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher (Laura Bix, PhD 448 Wilson, 114 Packaging East Lansing MI 48824 517 355-4556 bixlaura@msu.edu)

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Road, Ste. 136, Lansing, MI 48910.

9. DOCUMENTATION OF INFORMED CONSENT: I voluntarily agree to participate in the study.

_____ Signature _____ Date

You will be provided with a copy of this consent form for your records.

Figure 18- Consent Form

Appendix C-Research Questionnaire Form (Data collection)

Change Detection Questionnaire, School of Packaging, Michigan State University

Research Questionnaire Form Subject #: _____

Section A. Demographic Survey

1. **Sex: _____**
2. **Age:__**_____
3. **What is your ethnicity?**

☐ White, non-Hispanic ☐ American Indian/Alaskan Natives

☐ Asian or Pacific Islanders ☐ Hispanic

☐ African Americans, non-Hispanic ☐ Others: _____

4. **What is the highest level of education you have completed?**

☐ Middle School ☐ Bachelor Degree

☐ High School ☐ Master Degree

☐ Associate Degree ☐ Doctor Degree

5. **What is your native language?**

☐ English ☐ Spanish ☐ French ☐ Russian ☐ Chinese

☐ Japanese ☐ Others: _____

1 | 6

Figure 19-Research Questionnaire Form (Data collection)

Appendix D-Near Point Visual Acuity card

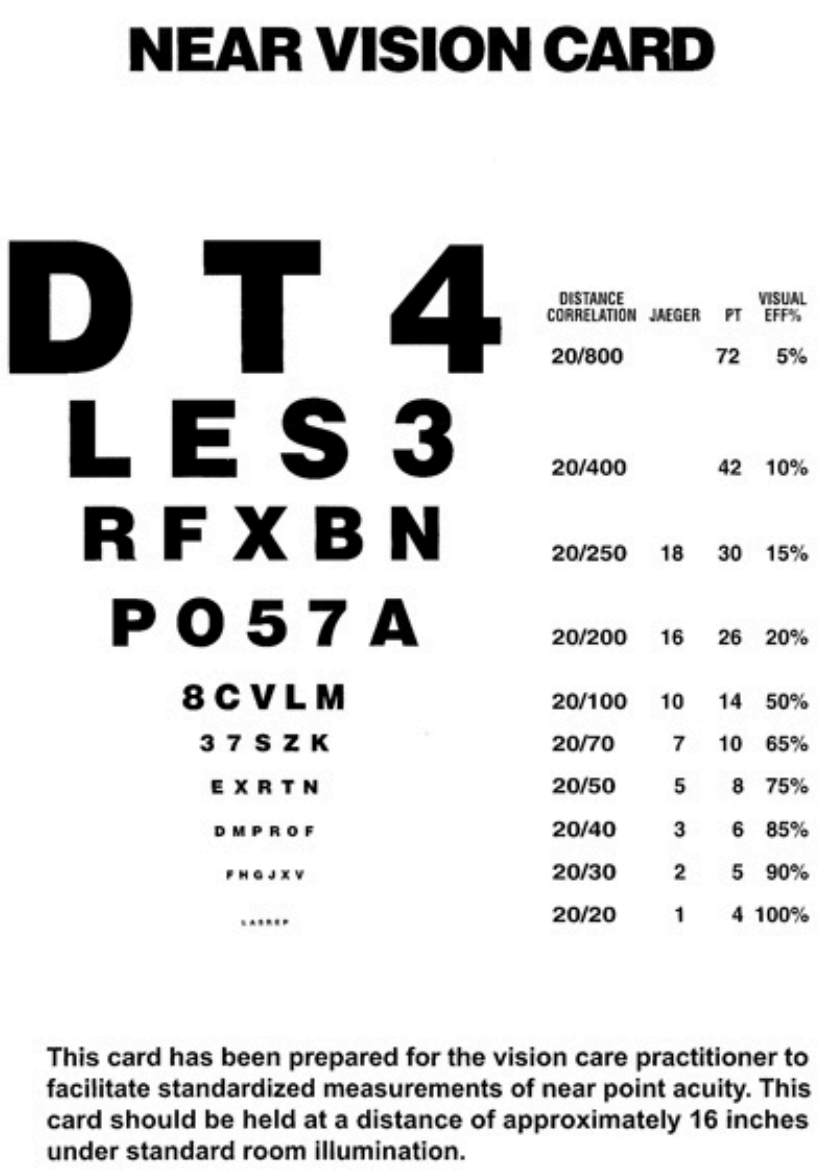


Figure 20-Near Point Visual Acuity card

Appendix E-REALM-R Card

Change Detection Questionnaire, School of Packaging, Michigan State University

Part II. REALM-R Examiner Record

Put an x next to the scored trials where subjects did not correctly pronounce the word and a checkmark next to those that were correctly indicated.

fat		fatigue	____
flu		directed	____
pill		colitis	____
allergic	____	constipation	____
jaundice	____	osteoporosis	____
anemia	____		

Fat, Flu, and Pill are not scored. We have previously used a score of 6 or less to identify patients at risk for poor literacy.

Score: _____

Figure 21-REALM-R Card

Appendix F-Color Differentiation Ability

Figure 22-Color Differentiation Ability

Appendix G-Table for Color Differentiation Ability

Change Detection Questionnaire, School of Packaging, Michigan State University

Answers to each plate

Plate	Normal Person	Person with Red-Green Deficiencies				Person with Total Color Blindness and Weakness
1	12	12				12
2	8	3				X
3	29	70				X
4	5	2				X
5	3	5				X
6	15	17				X
7	74	21				X
8	6	X				X
9	45	X				X
10	5	X				X
11	7	X				X
12	16	X				X
13	73	X				X
14	X	5				X
15	X	45				X
		Protan		Deutan		
		Strong	Mild	Strong	Mild	
16	26	6	(2) 6	2	2 (6)	
17	42	2	(4) 2	4	4 (2)	

The mark X shows that the plate cannot be read. Blank spce denotes that the reading is indefinite. The numerals in parenthesis show that they can be read but they are comparatively unclear.

As assessment of the readings of plates 1 to 15 determines the normality or defectiveness of color vision.

If 13 or more plates are read normally, the color vision is regarded as normal.

If only 9 or less than 9 plates are read normally, the color vision is regarded as deficient.

However, in reference to plates 14 and 15, only those who read the numerals 5 and 45 and read them easier than those on plates 10 and 9 are recorded as abnormal readings.

It is rare to find a person whose recording of normal answers is 14-16 plates. An assessment of such a case requires the use of other color vision tests, including the anomaloscope.

Figure 23- Table for Color Differentiation Ability

Appendix H-Example of Hexidvil-STD-Critical-PDP-Change in AI-Non-Highlight

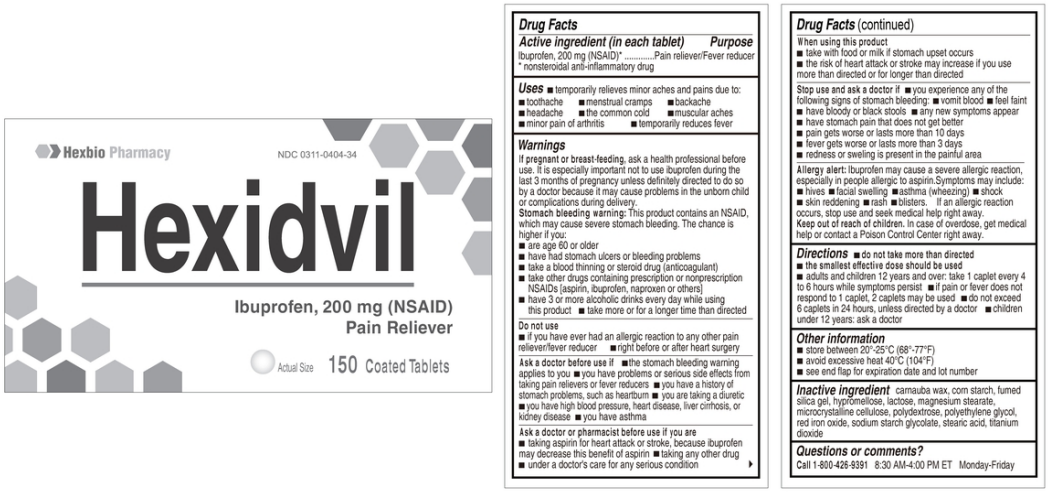


Figure 24-Example of Hexidvil-STD-Critical-PDP-Change in AI-Non-Highlight

Appendix I-Example of Hexidvil-STD-Critical-DFL-Change in AI-Highlight

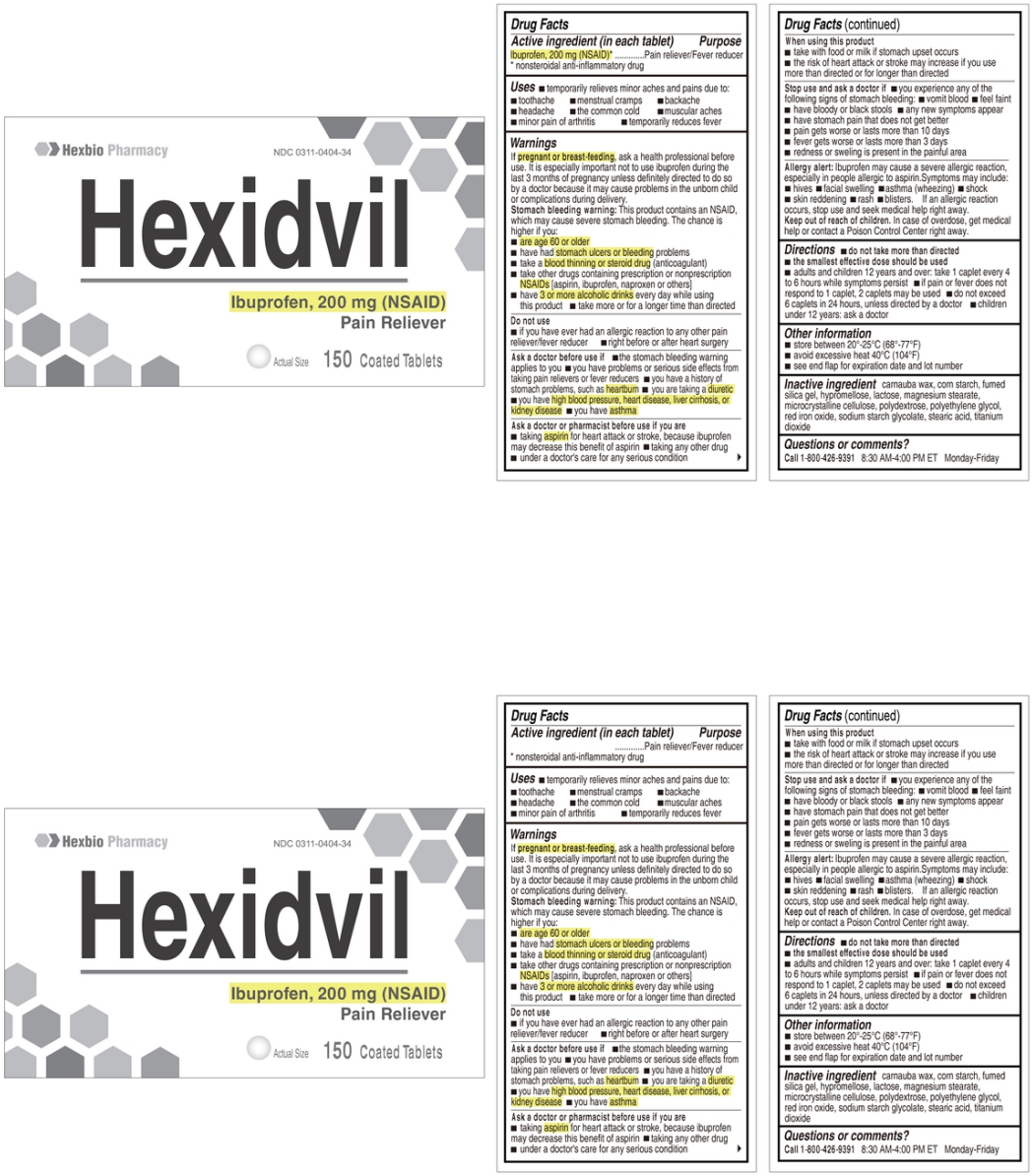
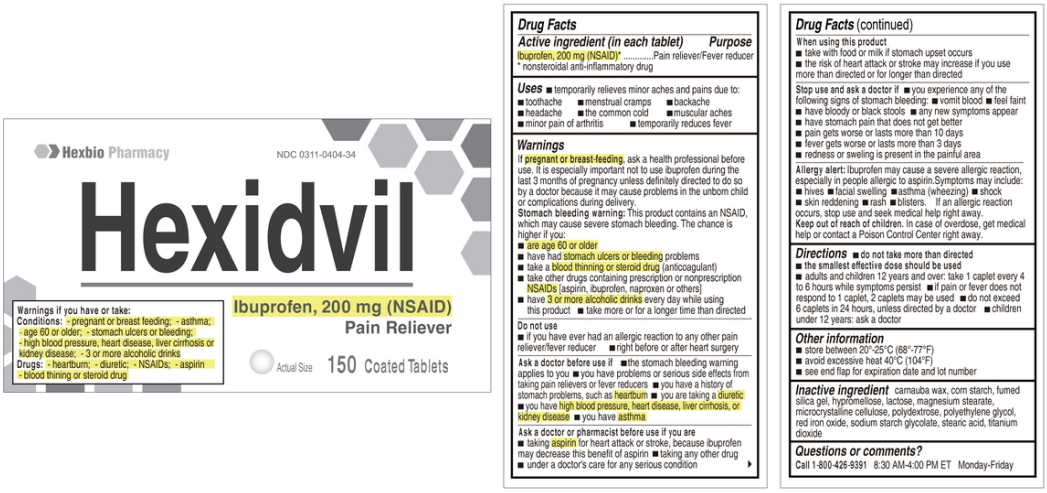


Figure 25-Example of Hexidvil-STD-Critical-DFL-Change in AI-Highlight

Appendix J-Example of Hexidvil-FOP-Critical-DFL-Change in DD1-Non-Highlight

Figure 26- Example of Hexidvil-FOP-Critical-DFL-Change in DD1-Non-Highlight

Appendix K-Example of Hexidvil-FOP-Critical-DFL-Change in DD2-Highlight



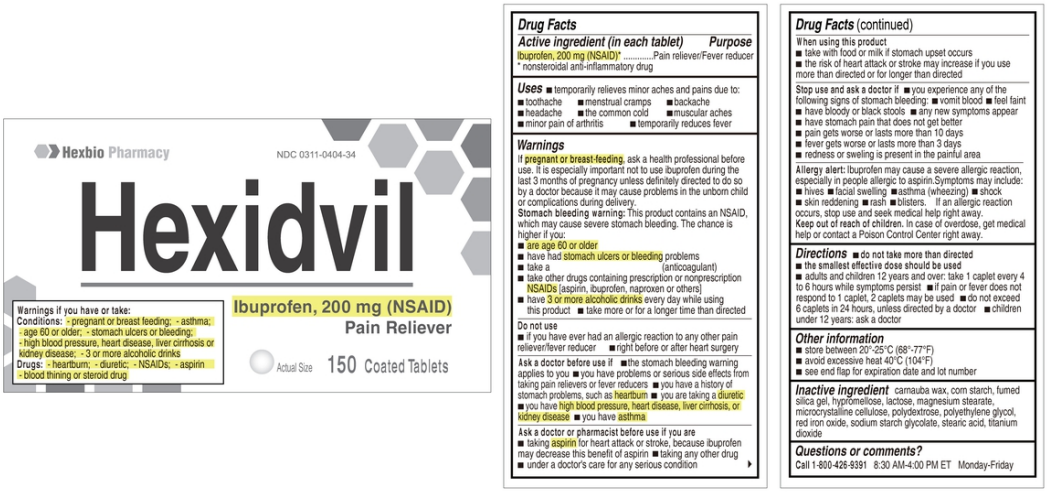
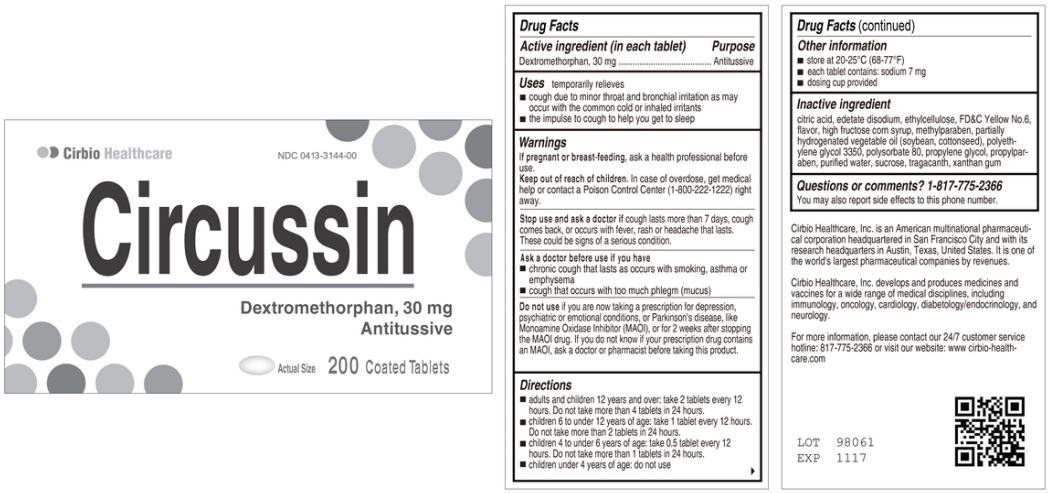


Figure 27-Example of Hexidvil-FOP-Critical-DFL-Change in DD2-Highlight

Appendix L-Example of Circussin-STD-Critical-PDP-Change in AI-Non-Highlight



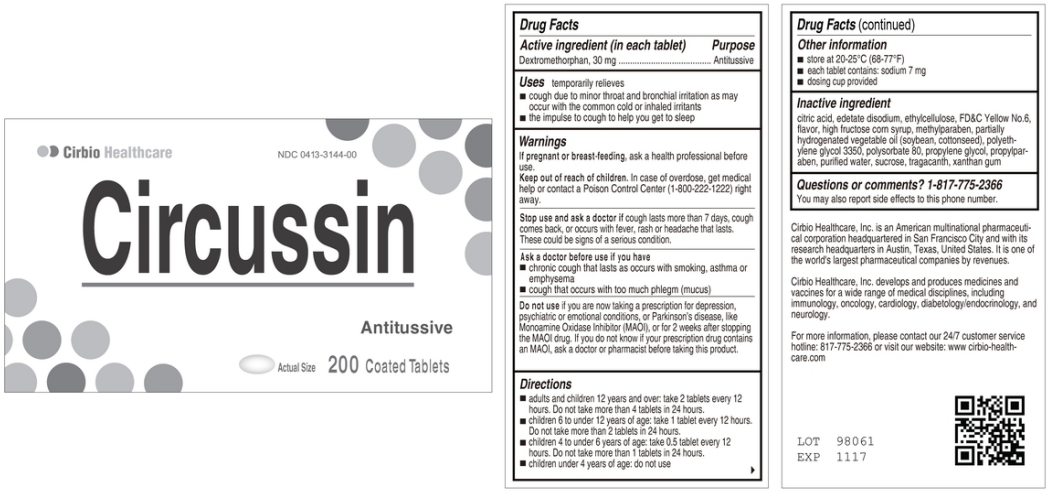
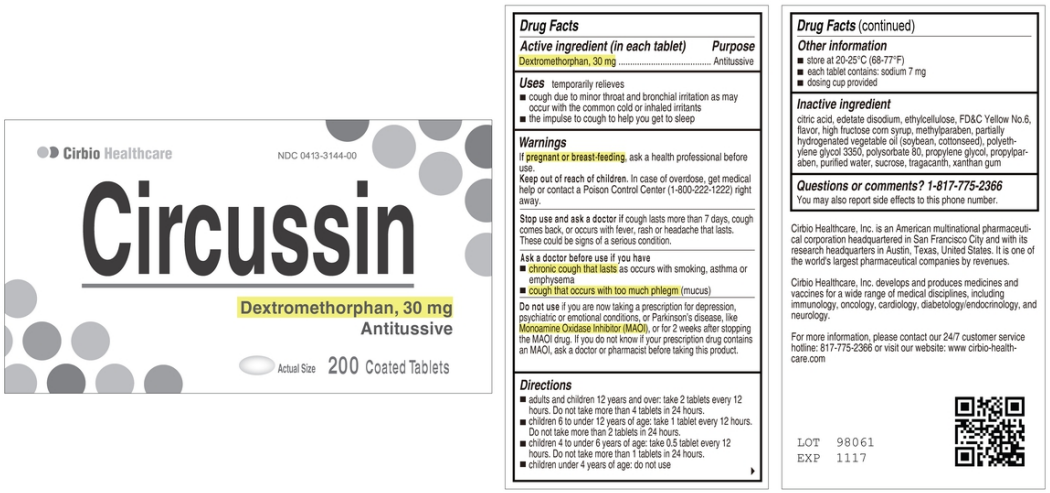


Figure 28-Example of Circussin-STD-Critical-PDP-Change in AI-Non-Highlight

Appendix M-Example of Circussin-STD-Critical-PDP-Change in AI-Highlight



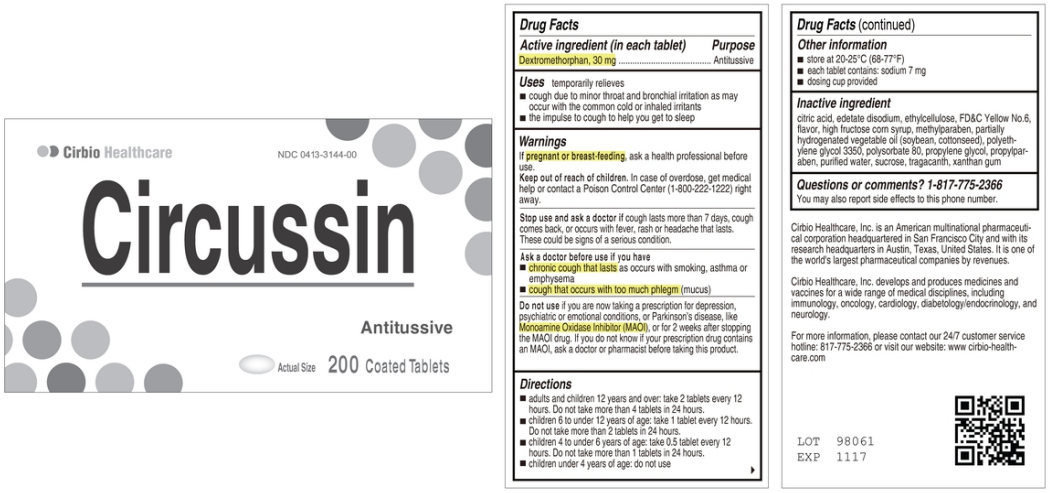
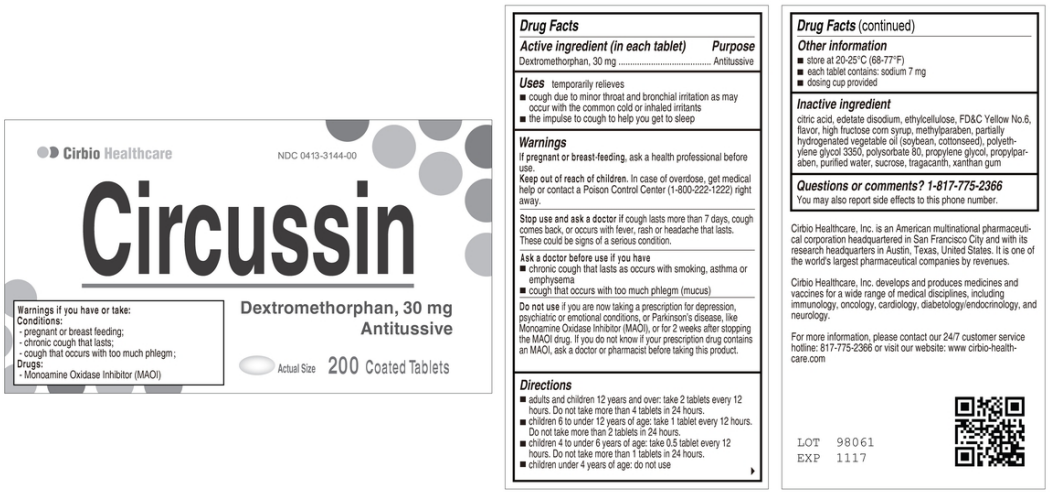


Figure 29-Example of Circussin-STD-Critical-PDP-Change in AI-Highlight

Appendix N-Example of Circussin-FOP-Critical-PDP-Change in AI-Non-Highlight



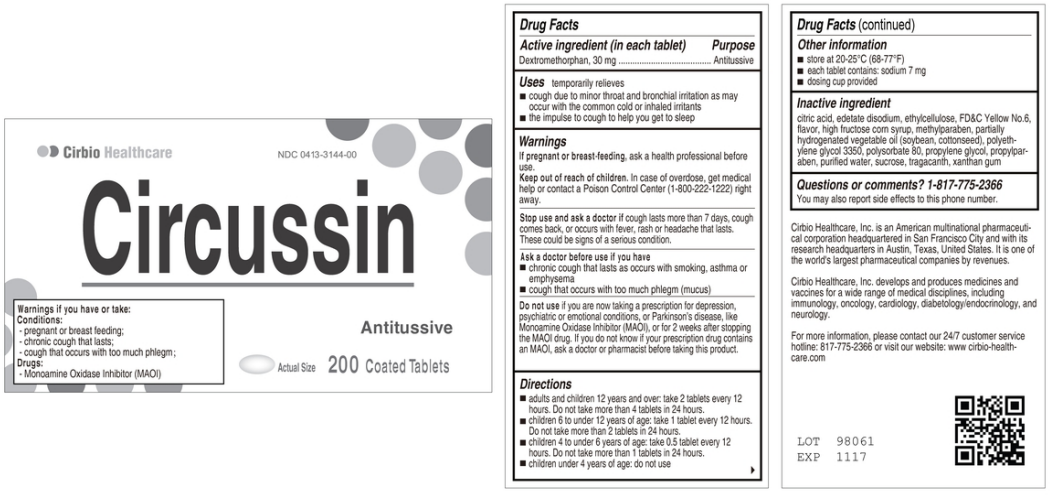


Figure 30-Example of Circussin-FOP-Critical-PDP-Change in AI-Non-Highlight

Appendix O-Example of Circussin-FOP-Critical-DFL-Change in DD1-Highlight

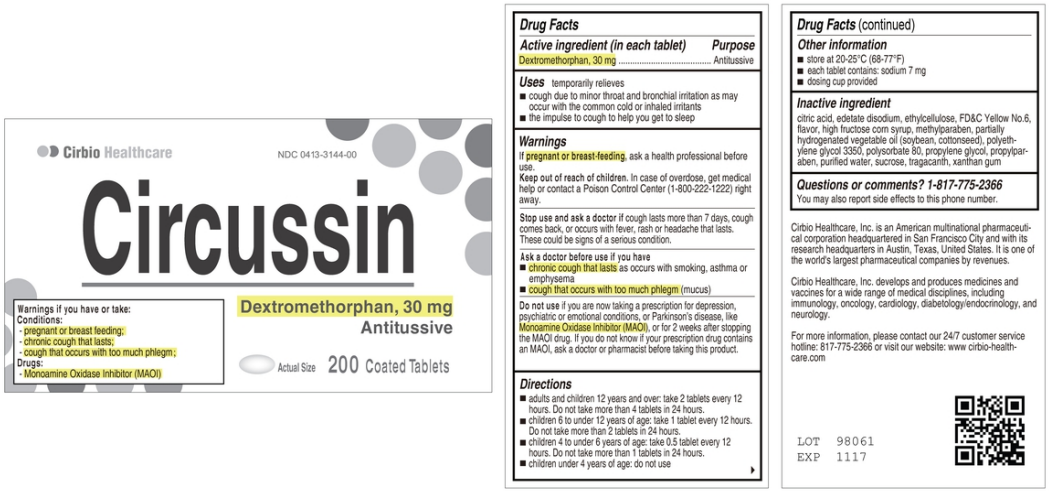


Figure 31-Example of Circussin-FOP-Critical-DFL-Change in DD1-Highlight

Appendix P-Example of Recantac-STD-Critical-DFL-Change in DD2-Non-Highlight

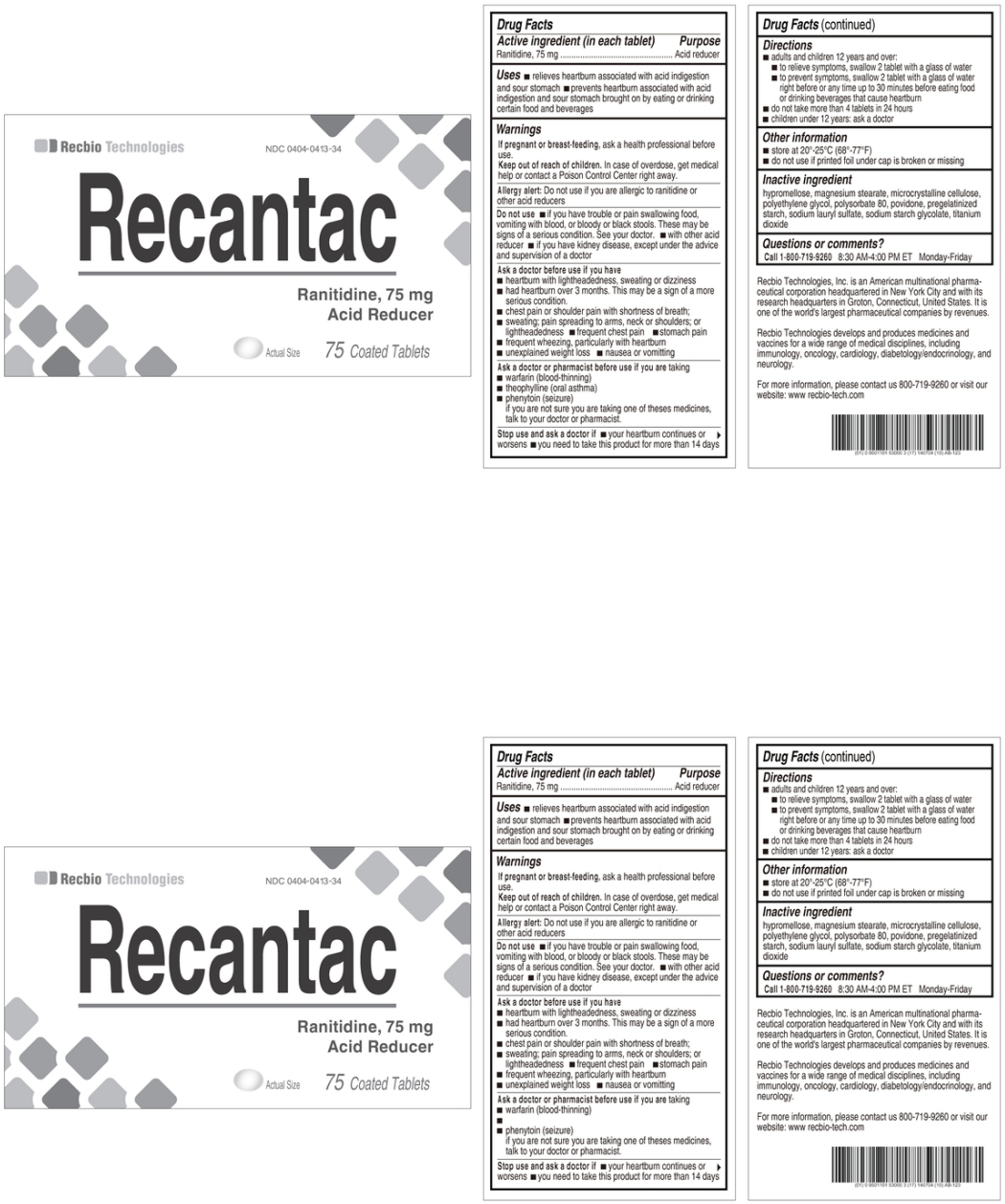
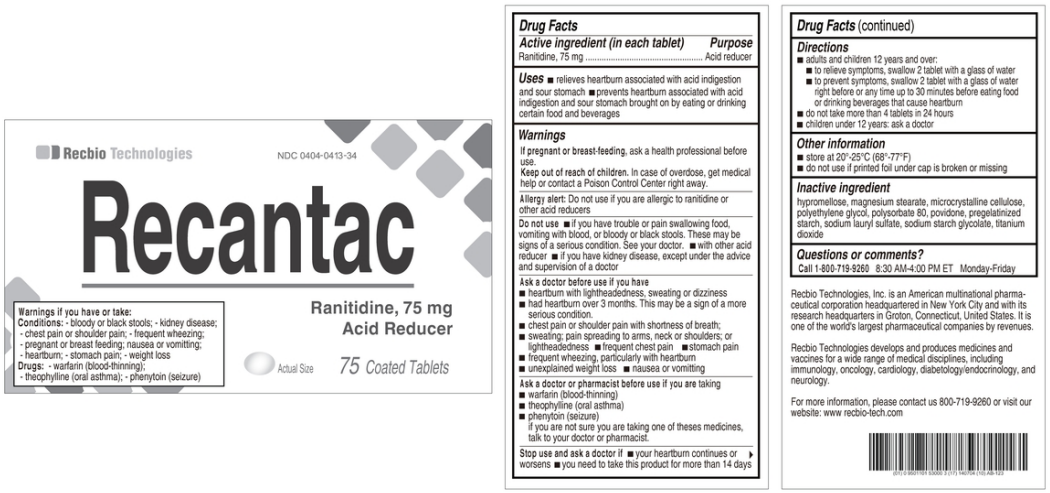


Figure 32- Example of Recantac-STD-Critical-DFL-Change in DD2-Non-Highlight

Appendix Q-Example of Recantac-STD-Critical-DFL-Change in AI-Highlight

Figure 33- Example of Recantac-STD-Critical-DFL-Change in AI-Highlight

Appendix R-Example of Recantac-FOP-Critical-DFL-Change in DD2-Non-Highlight



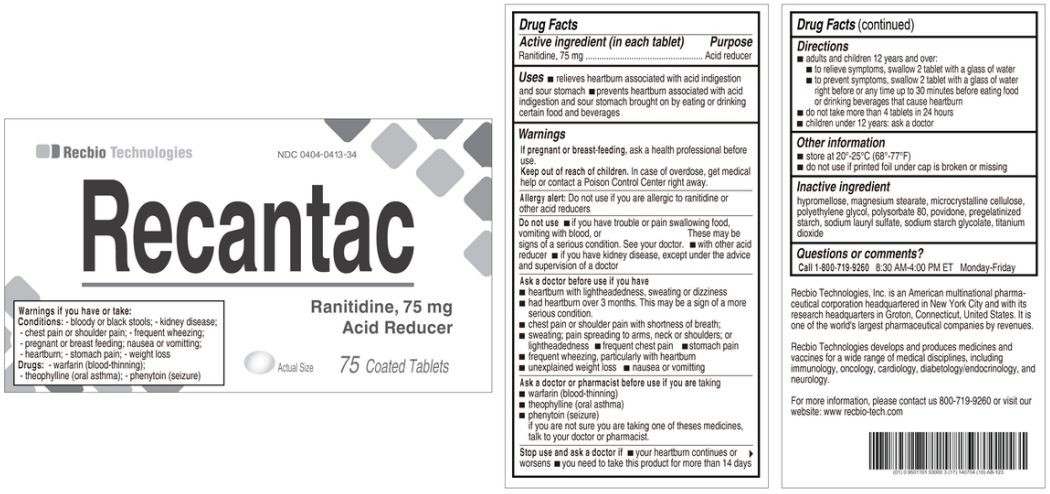


Figure 34-Example of Recantac-FOP-Critical-DFL-Change in DD2-Non-Highlight

Appendix S-Example of Recantac-FOP-Critical-PDP-Change in DD1-Highlight

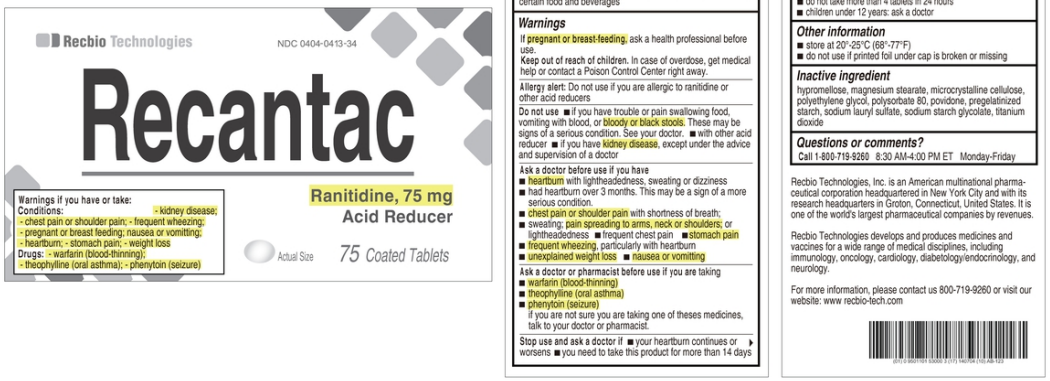


Figure 35-Example of Recantac-FOP-Critical-PDP-Change in DD1-Highlight

Appendix T-Average time that each participant answers the trials

In the table below, you can see the average and standard deviation time that each participant answers the trails:

(Milliseconds look up significant figure and we do not need lots of digit after.)

Table 21-Average time that each participant answers the trials

Subject	Average of time in seconds	Standard deviation of time in seconds
1	7.390578947	5.126036632
2	6.25026087	5.054352771
3	6.389363636	4.00560523
4	6.163595745	4.443962718
5	6.487219512	4.084368602
6	6.584484848	4.393289998
7	6.425130435	3.51428711
8	6.907	4.583958042
9	6.377066667	3.112127157
10	2.228363636	0.85608157
11	6.658787234	4.58249205
12	7.631086957	5.758538687
13	6.719478261	4.412721093
14	8.370761905	5.283273416
15	4.26175	4.300608078
16	5.64114	3.857159958
17	8.351555556	3.481085934
18	8.004130435	4.407643849
19	6.697641026	4.565979214
20	7.664083333	4.386352304
21	6.98528125	4.915396103
22	6.665310345	4.763362611
23	9.963636364	1.828774359
24	6.485117647	4.178877532
25	7.420105263	4.930268919
26	6.800325	3.587115836
27	6.794511628	3.985163397
28	7.692142857	3.819242592
29	7.500452381	4.320582172
30	9.06425	3.087808319
31	5.765814815	3.758648878
32	8.497333333	3.675107578

Table 24 (cont'd)

33	7.536809524	5.158519212
34	6.3163	3.786948506
35	6.543413793	4.760022355
36	7.471047619	5.008300607
37	6.930804348	3.828771254
38	5.570388889	3.381140393
39	7.429194444	4.093876311
40	9.389305556	4.693962242
41	10.7485	5.087275402
42	6.483765957	4.06747445
43	5.3638	3.524312845
44	4.840214286	2.930228648
45	6.411458333	2.917521878
46	8.108166667	4.775426033
47	11.88688462	5.119991245
48	9.127097561	4.763124598
49	6.3705	3.533643648
50	6.147266667	2.963730377
51	9.120369565	5.441074258
52	5.245605263	2.896638905
53	4.829347826	3.738630737
54	6.675192308	3.975304195
55	5.048166667	4.418939892
56	8.033117647	3.821687821
57	8.322173913	5.502439686
58	6.43945	2.438822181
59	5.809941176	3.137129609
60	7.540756098	4.085788062

The average time for the all participants is 7.00961331 seconds.

Appendix U-Number of correct answers for sixty participants

In the table below, you can see the number of the correct answer for each participant. Depend on the 60 participants that did the test, the average of the trials that answered correctly is about 70, which is less than half of all trails (168). These numbers are for the all trails, and for critical trails the average is about 33.

Table 22-Number of correct answers for sixty *participants*

Subject	Number of hit for all trials	Number of hit for all critical trials
1	59	38
2	47	23
3	112	44
4	125	47
5	76	41
6	81	33
7	99	46
8	107	49
9	57	30
10	25	11
11	87	47
12	45	23
13	55	23
14	60	42
15	25	12
16	123	50
17	15	9
18	39	23
19	65	39
20	41	36
21	40	32
22	69	29
23	14	11
24	83	51
25	82	38
26	86	40
27	65	43
28	23	14
29	98	42
30	12	8

Table 25 (cont'd)

31	64	27
32	87	24
33	53	21
34	101	40
35	68	29
36	73	42
37	113	46
38	87	36
39	93	36
40	63	36
41	77	30
42	113	47
43	40	15
44	85	42
45	67	24
46	67	24
47	57	26
48	80	41
49	15	8
50	120	45
51	87	46
52	104	38
53	93	46
54	87	26
55	7	6
56	96	34
57	78	46
58	55	20
59	33	17
60	92	41

Appendix V-Total number of correct responses for men and women for difference condition of the labels

Table 23- Total number of correct responses for men and women for difference condition of the labels

Condition of the Label	Total Number of Men Answers	Total Number of Women Answers
Critical-FOP-PDP-AI-HL	56	94
Critical-FOP-PDP-AI-NonHL	54	70
Critical-FOP-PDP-DD1-HL	43	53
Critical-FOP-PDP-DD1-NonHL	27	43
Critical-FOP-PDP-DD2-HL	33	53
Critical-FOP-PDP-DD2-NonHL	21	35
Critical-FOP-DFL-AI-HL	43	82
Critical-FOP-DFL-AI-NonHL	31	54
Critical-FOP-DFL-DD1-HL	39	67
Critical-FOP-DFL-DD1-NonHL	19	37
Critical-FOP-DFL-DD2-HL	36	61
Critical-FOP-DFL-DD2-NonHL	13	34
Critical-STD-PDP-AI-HL	64	102
Critical-STD-PDP-AI-NonHL	48	75
Critical-STD-DFL-AI-HL	48	79
Critical-STD-DFL-AI-NonHL	34	66
Critical-STD-DFL-DD1-HL	36	71
Critical-STD-DFL-DD1-NonHL	20	41
Critical-STD-DFL-DD2-HL	37	68
Critical-STD-DFL-DD2-NonHL	16	30

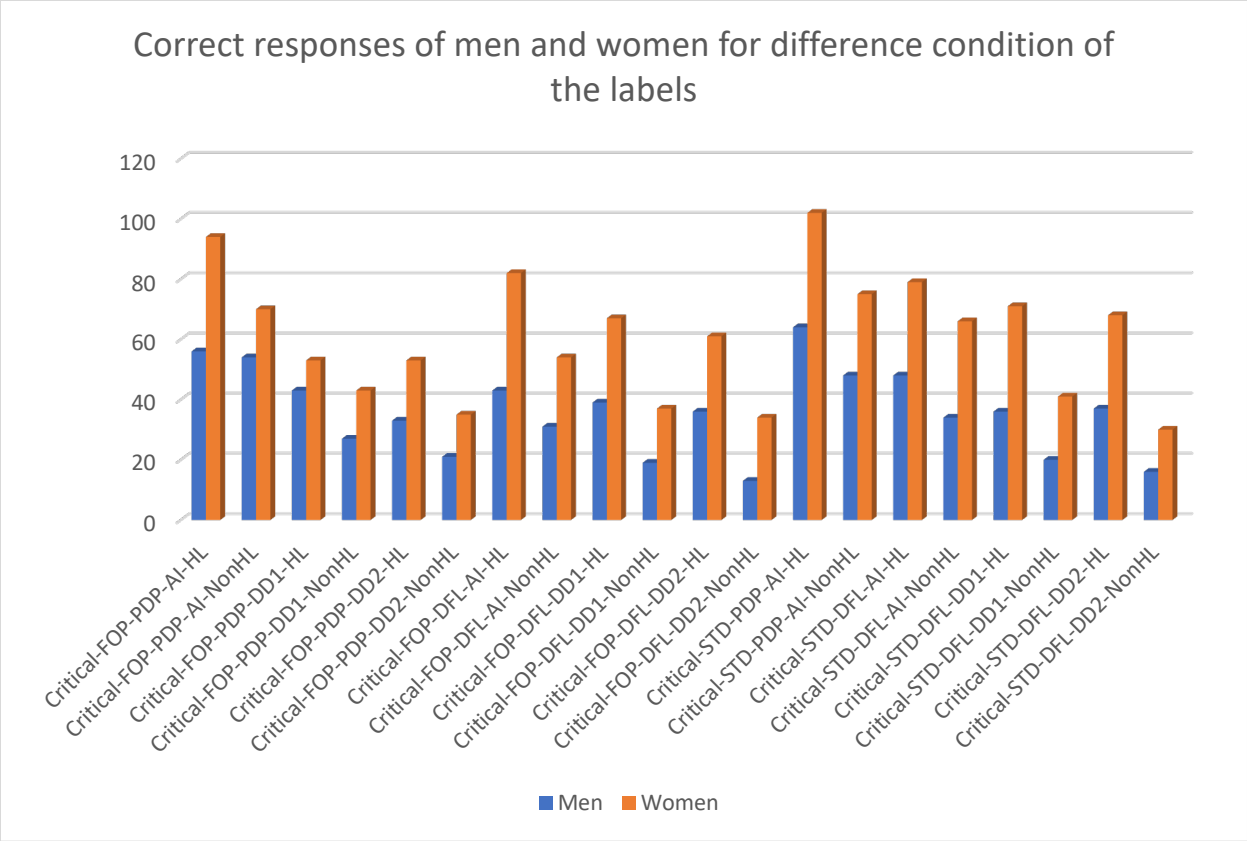


Figure 36-Correct response of men and women for different condition of the labels

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BIBLIOGRAPHY

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