

## FUNCTIONALITY OF DRUG LABEL WARNINGS DEFINED POST-MARKETING BY USER EXPERIENCE

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User experience with medicines is essential knowledge for successful drug product development. In the US medical therapies must be shown, prior to approval, to be safe and effective when used according to directions in OTC labels or Rx labeling. They must also be positioned to be competitively attractive to consumers in terms of their inherent value. User experience in the development phase and throughout the lifecycle of a medical therapy also helps shape these considerations. Without strong evidence on user experience with the medical therapies, the product is vulnerable to competition, and from a safety standpoint the patient and consumer may be disadvantaged with respect to their own self-care. This Commentary focuses on user experience with the drug product label and associated labeling, as these government-approved elements of the drug product are most often the most accessible to patients and consumers<sup>†</sup> in their day to day medication-related self-care.

### DEFINING USER EXPERIENCE WITH A MEDICAL THERAPY USING VALUE ATTRIBUTES

Meaningful and valuable user experience with a product is defined as the interaction of six value attributes that determine whether in the consumer's eyes the product information is useful, usable, desirable, findable, accessible and credible<sup>1,2</sup>. Morville depicted user experience as a honeycomb diagram with the six value attributes surrounding a central cell termed 'valuable'. Morville's conception of user experience was originally defined for web site architecture, but it has direct applicability to medicine labels, as shown in Table 1.

<sup>†</sup> In this article, the term consumer is used as a general term to include those who approach their own health problems through self-care and no physician supervision, as well as those who are under a physician's supervision and who are using self-care approaches to manage their disease and other health-related issues.

**Table 1: Defining the Six Attributes of User Experience for Web Sites and Medicine Labels\***

Attribute	Applied to Websites	Application to Medicine Labels*
<b>Useful</b>	Content should be original and fulfill a need.	Content should be similar for drug products of the same class, to the extent possible, and should support the need for safe and effective use of the product.
<b>Useful</b>	Site must be easy to use.	Labels/labeling should be easy to read and easy to understand.
<b>Desirable</b>	Image, identity, brand, and other design elements are used to evoke emotion and appreciation.	Design elements should evoke appreciation for effective application of readability principles.
<b>Findable</b>	Content needs to be navigable and locatable onsite and offsite.	Label/labeling information should be easy to find, before product use to aid selection and during use for proper self-administration and correct action steps in case of a serious emergent side effect.
<b>Accessible</b>	Content needs to be accessible to people with disabilities	Label/labeling content should be written with consideration for those having lower health literacy.
<b>Credible</b>	Users must trust and believe what you tell them	Label/labeling statements must not be false or misleading, and based on sound scientific and medical evidence.

As a distillation of Morville’s concept of use experience, the medication user’s experience with a medicine label is to a greater or lesser extent both meaningful and valuable depending on:

- Need fulfillment (i.e. appropriate selection of the product for the condition and user-perceived in-use safety and effectiveness);
- Functionality (i.e. easy to read, easy to understand, easy to find information);
- Appearance (i.e. as this contributes to credibility such as a visually pleasing layout of required label information);
- Credibility (i.e. based on sound science, which can be translated as government-approved).

Among these four characteristics, functionality stands out as different. For need fulfillment and credibility, government consideration of results from preclinical and clinical studies support intended use at recommended dosages, and this is managed in a highly structured review processes by government agencies. Appearance, once a neglected component of user experience with labeling, has more recently been transformed by the adoption of label/labeling content and format regulations (e.g., OTC Drug Facts Label, Physician’s Labeling Rule for the content and format of Rx Full Prescribing Information)<sup>3,4</sup>.

Drug label functionality, however, has potential to significantly impact appropriate, safe and effective product use. Yet, it is not routinely measured across all medicines in the U.S. Label comprehension, self-selection, and actual use studies are used to support certain OTC New Drug Applications as

a pre-market approval measure of readability (easy to read/understand), appropriate selection of the product for its intended use, and in-use adherence. However, non-NDA'd OTCs such as aspirin and acetaminophen and NDA'd OTCs approved before implementation of the OTC Drug Facts Labeling Rule (e.g., ibuprofen) have had only limited assessment of their label functionality in the government approval and product surveillance processes. Further, literature reviews yield relatively few germane peer-reviewed publications by independent researchers assessing how to make the OTC Drug Facts Label even better.

For prescription drug labeling in the U.S., there are routinely no functionality studies on physician use of the Full Prescribing Information (FPI). This is particularly important in relation to FPI Section 17 on 'Patient Counseling' which provides detailed counseling information that is written in the grammatical imperative (e.g., the patient shall be informed...). Another concerning example is how FPI content on drug safety information is used by physicians in making judgements about off-label use and in conveying safety information to patients. For patients, label comprehension studies on Rx drugs are routinely not done, so there is little actual understanding of the user experience with the various Rx labeling components (i.e. physician counseling information based on Section 17, or not; Medication Guides, retail drug monographs handed out at the point of dispensing medicines)

### **Core Questions**

These considerations beg certain questions. Should there be closer attention to research on user experience with drug product labeling across a broader spectrum of labeling information and consumer experience? That broader range might include not only the free-range OTC consumer making self-selection and in-use self-care decisions, but also use of medication labeling by, for example: (a) chronic disease patients who mainly engage in self-care for their disease and medication management<sup>††</sup>; and (b) their physicians who are making decisions for product selection for labelled and off-label use of medications.

Additionally, given that a health policy decision often represents a population-based 'best projection' at a snap-shot in time, user experience with the tangible results of that projection (e.g., a reformatted FPI) takes time to fully understand the in-use functionality of that projection. This begs a further question. In cases where there are persistent safety issues associated with a use of a medical therapy, should there be a zero-based look at the functionality of the entire label/labeling or specific sections (e.g., OTC Drug Facts Label) or sections of labeling (e.g., Section 17 FPI), to determine if it is optimally designed with appropriate content to achieve its intended purpose?

### **Case Example**

OTC acetaminophen is used as a case example, because of its narrow therapeutic index, persistence as a leading cause of acute liver failure and liver transplantation in the U.S., and long history of progressive regulatory changes to labeling and dosage. Since 1977 there have been six

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<sup>††</sup> Most patients are not under direct supervision of a physician for their chronic disease. For example, a diabetes patient likely sees his/her physician once or twice a year for an hour or less, therefore being on their own during the vast majority of waking hours to manage their diabetes and associated medicines.

major changes to the acetaminophen label, mainly related to expanding warnings against unsafe use and the dangers of overdose.

A review of the OTC Drug Facts label shows an accretion of label statements information over time, which diminished focus in the view of researchers assessing the current label on readability principles (including this author; see the June issue of the *Therapeutic Innovation and Regulatory Science* journal.)<sup>5</sup>. Further, there are no publicly-available label comprehension studies on the OTC Drug Facts Label for acetaminophen. There is also no regulatory requirement for companies to undertake or publish research using well-designed label comprehension studies, since acetaminophen is an OTC ingredient marketed in the US under the monograph system of the OTC Review and not the product-specific requirements of the New Drug Application process.

Using methodology derived from FDA guidelines on label comprehension studies, researchers compared the current label to a revised label. The revised OTC label included: a revised warning heading, 'Liver damage warning'; early signs/symptoms of overdose; earlier placement of directions to seek medical help in the event of possible overdose, and various other content/format reorganization. Among other queries about label information on mocked-up current and revised cartons, a scenario-based question was used to assess label usability. The scenario was derived from Poison Control Center experience and the literature, and allowed study participants to role play the action they would take to help manage a potentially serious emergent drug safety issue related to liver injury.

While the study was not designed to include lower health literacy patients, the researchers found that the current and revised OTC Drug Facts label (ODFL) were comparable in terms of ease of reading and ease of understanding, indicating the revised label met current standards for these attributes for the general population. Overall the revised ODFL was preferred over the current label, with significant differences shown for new information including headers (e.g. 'liver damage warning'), early signs of overdose, and altered format (i.e. earlier placement of the action statement to seek medical help; reorganization of information to improve usefulness), usefulness for first time use, directions for overdose and prevention, and amount of information. Also, the proportion reporting the correct intended action when viewing the revised label was statistically greater than the proportion using the current label. The study was approved by the University of California San Francisco Institutional Review Board.

In summary, a relatively low cost study with reasonably fast turn-around found that research-based user experience with an OTC Drug Facts Label relating a critical public health problem was improved in relation to an essential element of the label – i.e. intended action in response to a potentially serious emergent drug safety issue pertaining to liver damage. Further, similar to another published study on the OTC ibuprofen allergy alert<sup>6</sup>, early signs and symptoms of the emergent side effect were included where currently they are absent. The principles and findings of that study had additional connotations for the OTC acetaminophen label as a result of FDA recently adding an allergy alert based on emergent cases of an association between acetaminophen and Stevens Johnson Syndrome.

## Implications

Label functionality is not a static phenomenon, and research should be encouraged in the spirit of continuous product improvement so that user experience with the medication label is optimized. The government decision to approve the acetaminophen Drug Facts Label was made on what it considered to be reasonable decisions on available information. Considerable time has passed since that approval, and an independent review of that label (i.e. in the context of other OTC analgesic labeling and other research) indicated that: information on early symptoms of emergent liver problems was absent; there was potentially a better placement of certain information; and the liver warning heading was not consistent with the organ-specific warning headings for aspirin and ibuprofen.

Since it is virtually impossible to prospectively study user experience with the OTC Drug Facts Label in real-time for serious and less common conditions, the label comprehension model for improving warnings relating to serious side effects of medicines can serve as a reasonable approach with acceptable cost and with rapid turn-around for regulatory agencies, companies and independent researchers interested in improving the likelihood that product labels and labeling will be used to help improve medication safety.

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