



Interface Analysis Associates

6800 Redwood Retreat Rd. Gilroy, CA 95020

Labeling of Drug Vial Ferrules and Cap Overseals:

Executive Summaries



Anthony D. Andre, Ph.D., CPE

Founding Principal,

Interface Analysis Associates

April 2010

Executive Summary – Human Factors Literature Review

About This Report

This report represents an objective human factors analysis of the USP proposal (revised November 2009) for the labeling on drug vial ferrules and cap overseals. The proposal seeks to limit the labeling statements on ferrules and cap overseals in an effort to make serious (i.e., “critical for the presentation of imminent life-threatening situations”) cautionary statements more salient. If no cautionary statement, as defined above, is necessary, the top surfaces of the ferrule and cap must remain blank (*Pharmacopeial Forum, Vol. 36(1) [Jan.-Feb.2010]*). Prior to this analysis, we at Interface Analysis Associates have had no involvement in the development of ferrule or cap overseal labeling, nor did we have any pre-disposition or bias on this issue. We do not benefit in any way from this proposal either being adopted or dismissed. This analysis attempts to provide a human factors perspective that appears absent from the impetus and context of the USP proposal. Further, through a health care provider survey that we carried out in January 2010, we provide needed data pertaining to this proposal; data that the FDA has indicated would be beneficial. Our objective was to analyze known human factors research standards and guidelines as they pertain to the proposal and to identify human factors scientific evidence that either supports or refutes the proposal and its underlying premises.

Qualifications

Interface Analysis Associates (IAA) is a human factors and ergonomics consultancy in business since 1993. We have extensive experience in the health care domain covering design, evaluation, research and usability testing services for over 20 different health care/medical/drug clients. IAA is led by Dr. Anthony D. Andre, CPE, who also serves as an Adjunct Professor of Human Factors and Ergonomics at San Jose State University and is the President-Elect of the Human Factors and Ergonomics Society. Dr. Andre has conducted research and published on many of the human factors topics that are germane to any analysis

of the USP proposal, and is well-versed in the human factors literature relevant to the USP proposal.

Disclosures

IAA was engaged by CAPS, the Consortium for the Advancement of Patient Safety (<http://www.caps-edu.org/>). The CAPS representatives asked IAA to provide a human factors analysis of the USP proposal. IAA, in turn, proposed to conduct a human factors literature review in order to identify data and guidelines as they pertain to the issues and directives of the proposal. In addition, IAA proposed to obtain data and feedback from health care providers (nurses, physicians, anesthesiologists, CRNAs, pharmacists, pharma techs and med techs) who routinely handle drug vials. While it is publicly known that CAPS does not agree with the proposal to limit printing and other types of messaging on ferrules and cap overseals (see www.caps-edu.org), they did not ask IAA to support their position. Rather, since it appears that little, if any, human factors data was explicitly used to substantiate the USP proposal and/or known to the FDA on this specific labeling issue, CAPS asked IAA to conduct an objective analysis of human factors data relevant to the proposed standard. This document represents a report of the findings of these two activities.

While we performed our literature review in an unbiased manner, this report is more focused on presenting theory, data, guidelines and information that potentially refutes or contradicts the USP proposal. This is because maintaining the status quo (and in the absence of data that undermines the USP proposal) will result in the proposal being adopted by default. With any human factors analysis of a medical device or health care procedure, it is assumed that there is some merit in the proposed design. The focus, therefore, turns to identifying potential risks that might suggest that the proposed design will cause more harm than good or produce unintended negative consequences. Indeed, when validating a medical device design for FDA approval, the primary focus is always on identifying and mitigating risks under plausible worst-case scenarios.

Methods

The following methods were used to perform our analysis and to inform the conclusions and dispositions presented in this report.

- We conducted an extensive review of the human factors literature on the topics of ferrule and cap overseal labeling, warnings guidelines, drug labeling, expectancy theory, Gestalt processing, attention theory, communication theory, signal detection theory and more.
- We conducted a search of incidents related to drug delivery errors in the context of common ferrule and cap overseal messages (cold chain management, drug name, drug concentration, dosage instructions, counterfeit drug, etc...).
- We contacted representatives of the USP and FDA and inquired about the research, data, incidents, standards or guidelines that served as the foundation for the proposal. We did not receive any response from the six individuals we emailed.

Dear FDA and USP representatives.

As a human factors practitioner and consultancy owner, who often aids clients in their instructional and labeling issues, I have read with interest your proposed new standard. I have a few questions about both the impetus of the proposed standard, and the practicality of interpreting it, that I hope some of you can clarify for me (and ultimately for my many drug/medical clients).

- Did any particular incidents or MAUDE/Medwatch type reports, directly attributable to ferrule or cap overseal labeling, contribute to this proposal?
- Do you know of any scientific literature or human factors studies that support the proposal?
- Do you have examples of commonly used allowable cautionary statements beyond the two you provide ("warning-paralyzing agent", "dilute before using")?
- Do you have example of commonly printed ferrule/cap overseal statements that would no longer be allowed? Common messages I have seen include:
 - Store Frozen"
 - "Refrigerate"
 - Drug name
 - Drug concentration
 - Cytotoxic
 - Multidose
 - Administer over 30-60 minutes
 - For IV only

Thank you in advance,

Tony Andre

- We posted a request for information pertaining to this issue, an example of which is shown below, on various professional web forums. Our objective was to tap the human factors and health care research communities in order to locate any research that had been conducted on ferrule and cap overseas labeling.

The screenshot shows a LinkedIn interface. At the top, it says 'Basic Account: Upgrade' and 'Welcome, Tony Andre, Ph.D., CPE'. Below that is the LinkedIn navigation bar with 'Home', 'Profile', 'Contacts', 'Groups', 'Jobs', 'Inbox (15)', and 'More...'. The main content area shows the profile of Tony Andre, Ph.D., CPE, with a 'YOU' tag. His title is 'President Elect, Human Factors and Ergonomics Society'. Below his profile is a discussion post titled 'Messages/Warnings on Drug Vial Caps and Ferrules' with the text: 'Is anyone aware of any research on messages/labels/warnings that are printed on the caps (cap overseals) or ferrules of drug vials?'. The post was posted 19 hours ago and has a 'Delete discussion' link.

- We conducted an online survey of health care providers (nurses, physicians, anesthesiologists, CRNAs, pharmacists, pharma techs and med techs) who routinely handle drug vials. The survey was promoted to numerous organizations, forums and websites around the country. The purpose of the survey was to collect data on a variety of issues relevant to the USP proposal such as: frequency of use of ferrule/cap printing; importance and value of ferrule/cap messages; drug delivery incidents related to ferrule/cap messages; opinion on restriction of ferrule/cap messages; pros and cons of USP proposal; statements, warnings and messages they prefer to see on ferrules and cap overseals; and more. The findings from this survey are presented in a companion document to this report.

Summary of Findings and Disposition

We understand and appreciate the objective of the USP proposal. There is merit in wanting the most serious cautionary statements to be most easily perceived, understood and acted upon by health care providers who handle drug vials. However, the proposed method is not the most effective way to achieve this objective, from a human factors perspective. More importantly, the present USP proposal is potentially fraught with serious negative “side effects.” Further, the

USP proposal contradicts the current trend of providing additional redundant layers of protection in line with principles of resilience engineering. For example, layers of information have been added to, not subtracted from, vials containing the drug Heparin (see image below). As one survey participant stated, “I don't think there is such a thing as NON-ESSENTIAL information which acts as additional safety measure on any medications, injectable or other types.”



Heparin drug vial with and without outer label wrap.

Today, only a minority of drug vials have messages printed on the ferrule or cap overseal. When a message does exist, it is usually limited to one topic (e.g., “Must Dilute”). Hence the issue of overcrowding, which has been identified as relevant to the main drug vial label, is less relevant to this specific space on the drug vial. Further, since there are no standards that limit the types of messages printed on the top surface of ferrules and caps, there is not a prior expectation for the existence of a message or its particular type. As our survey results point out, some health care providers notice and make use of ferrule/cap messages and some (purposely) do not. For those who do utilize these messages, they typically state the value of having an extra layer of error prevention. As one survey participant stated, “Redundancies are designed to protect patients and providers from errors.”



Image from www.caps-edu.org showing representative variety of cap overseal messages in use today.

Now, let us imagine a future where the USP proposal is in place. In this situation, a smaller number of vials will have any form of message printed on the top surface. These messages will appear on a variety of cap colors and in a variety of contrasting text colors. Health care providers will have an expectation that all high-risk/volatile drugs will have cautionary messages on the ferrule and cap overseal. But, of course, this is not true. That is because the USP proposal attempts to specify the types of messages permitted on ferrules and cap overseals. It does not, however, require that any high-risk drug have a cautionary message presented on these surfaces. Thus, in this future scenario, some high-risk drug vials will be absent any message on the top surface. By restricting and specifying what messages can be presented on the top surface of ferrules and caps, an unintended and negative interaction will occur whereby health care providers will make false assumptions about unlabeled (on the top ferrule and cap surfaces) vials. Building a specific expectation or perception, through regulation, can result in disastrous effects when that expectation or perception is violated.



Image from www.caps-edu.org showing representative cap overseal messages per the USP proposal.

Perhaps an equally important future scenario to discuss is the most common one that describes a given health care provider's interaction with a single drug vial. After all, once a pharmacist selects a drug vial from among many, or once a nurse obtains a drug vial from a specific drawer in a drug cart, the labeling of concern is now absolute with respect to that one vial. One has to ask: If, under the USP proposal, the vial ferrule and cap overseal are blank, with no information of any kind, how is the health care provided aided? In other words, for the vast majority of drugs where current ferrule and cap overseal labeling provides useful information, an added line of defense or critical warnings, what is the value of this information now being removed?

Another potential flaw in the USP proposal is that it assumes that what they define as "cautionary messages" can be determined a priority based solely on the volatility of the drug. In truth, even the most benign drug can be dangerous when given in the wrong dose, used in the wrong concentration, administered with the wrong method of input or is counterfeit. As one survey participant stated, "All medications should be considered dangerous drugs."

As expected, our survey results demonstrate that some health care providers do not notice and/or make use of ferrule or cap overseal labeling. As one survey participant stated, "I pop off the cap first thing, without even looking at it. The cap usually ends up in the trash or falling on the floor." With even fewer drug vials having any form of message, this type of behavior will actually increase, not decrease, if the USP proposal goes into effect. It is equally important to point out that from a human factors design perspective, using the presence and absence of text messages to signify a warning message is perhaps the weakest form of salience coding. It is well established by human factors research that changes to the global properties of a product, such as shape or color, are more likely to be noticed or processed pre-attentively than changes to the local properties of a product (such as text), which require focused attention. The combination of a lower overall message event rate and a low salience form of message coding

will actually produce a reduction in the likelihood that a cautionary message is noticed or processed. A better approach to the valuable objective of making high-risk cautionary messages more salient and producing a “pop-out” effect would be to code all such messages in a unique color amongst vials with all other important but less imminent life-threatening messages. The USP proposal is using the absence of information to affect the salience of presented information. This is a known flawed approach. As one survey participant stated “I'm grateful for any information included with medication that will increase safety.”

The survey data, much like the human factors literature reviewed in this report, shows support for the general objective of the USP proposal, but not for the specific implementation plan for achieving this objective. For example, a large majority of the health care provider respondents stated that enhancing the saliency of critical cautionary warnings should be accomplished through a unique color or symbol, rather than the removal of ferrule and cap overseals labeling from what are deemed less life-threatening drugs.

Finally, it should not go without saying that the language of the proposal is inconsistent and vague. For example, in the four paragraphs that make up this proposal, the messages in question are referred to as “important safety messages,” “cautionary labeling statements,” “critical safety messages,” “cautionary statements” and “safety related instructions.”

Consequently, the proposal as written is somewhat non-deterministic. A given drug manufacturer cannot precisely determine if a desired statement does or does not meet the requirements of the proposal. Interestingly, the USP proposal does not explicitly list all (or the most common) known ferrule and cap overseal messages and identify which are allowed and which are prohibited per the proposed standard.

Indeed, our health care provider survey showed that those who handle drug vials vary greatly in their definition of what is cautionary and their highly desired content for ferrule and cap overseal labeling. Many expressed high value in labeling statements that would likely be prohibited or restricted under the USP proposal. Another example of the problem in

interpreting what is, and what is not, a critical safety message is highlighted by the growing problem of counterfeit drugs. For example, a recent article in the *Washington Post*, titled “Officials fear toxic ingredient in Botox could become terrorist tool,” discusses the influx of fake botox in the US (<http://www.washingtonpost.com/wp-dyn/content/article/2010/01/24/AR2010012403013.html>). Relevant to the USP proposal, the article states that investigators fear that the counterfeit Botox may be more potent, if not deadly, than approved Botox. It describes several instances where fake Botox entered the US market, including a 2004 case where four people were left paralyzed. Yet, under the USP proposal, since approved Botox is not normally a dangerous drug requiring life-threatening critical safety messages, any labeling (name, message, symbol, watermark) on the ferrule or cap overseal used to thwart counterfeiters would likely be prohibited.

Conclusion

This report presents a large volume of data, though we found no studies directly pertaining to drug vial ferrule or cap overseal labeling. This suggests a need for research on this topic prior to changes in the standards that govern such labeling. What can be gleaned and applied from the literature on labeling, warnings, message design and medication errors suggests that the current approach is likely to be less effective in its key objective of making critical cautionary messages more salient to health care providers, and more importantly, is likely to introduce unintended negative consequences. The collective effects of the USP proposal will likely result in producing a ferrule and cap overseal labeling problem that does not necessarily exist today.

Executive Summary – Health Care Provider Survey

CAPS, the Consortium for the Advancement of Patient Safety, contracted with Interface Analysis Associates (IAA) to conduct Human Factors analyses and research on the issue of drug vial ferrule and cap overseal labeling in the context of the recent proposal to limit such labeling made by the United States Pharmacopeia (USP). This report presents the results of one phase of this effort: a health care provider (HCP) survey covering various issues related to ferrule and cap overseal labeling. To the best of our knowledge, this is the first survey of its kind.

What Did We Do?

We conducted the survey to gather objective and quantifiable data as to how ferrule and overseal labels are used and valued. In addition, we attempted to gather opinions directly aimed at USP proposal elements and assumptions. To achieve this objective, we targeted health care providers who routinely handle drug vials (during receipt, storage, and injection preparation or injection administration), such as registered nurses, physicians, anesthesiologists, physician assistants, medical assistants, pharmacists, CRNAs and pharmacy technicians.

The survey was conducted online using a web-based survey tool called “Survey Monkey” (www.surveymonkey.com) and was distributed via: email to RNs, pharmacists and pharmacy technicians from our in-house database; online postings to a number of national and state physician, nurse, pharmacist and CRNA associations, unions, mail groups, forums and websites (e.g., Nurses Associations, California Physician Assistant Committee for the Department of Consumer Affairs, LinkedIn.com, Federation of Pharmacy Networks, etc.); as well as general postings to advertising web sites, such as Craigslist.org and Backpage.com. CAPS members were not provided access to the survey.

Participants were not paid to complete the survey, but a donation of \$.50 was made to either the Red Cross or Humane Society for each completed survey (choice of organization made by respondent on the last item of the survey).

We conducted an initial survey that yielded approximately 300 responses. This survey was followed up with a micro-survey in order to obtain clarification on three questions in the original survey that were deemed vague or poorly worded. This latter survey yielded approximately 250 responses, from both previous respondents and new respondents.

What Did We Find?

The responses of the 328 HCPs who participated in the main survey are highly variable. Some HCPs notice and make use of ferrule/cap over seal messages, while others do not. Some support the objectives and/or approach of the USP proposal, while others do not. At the very least, the lack of a consensus set of responses to support the USP proposal, and the overall variation in responses, suggest that this is a highly contextual and complicated issue, which the somewhat terse and uni-dimensional USP proposal does not seem to address. Collectively, it is fair to say that the survey data shows support for the general objective of the USP proposal, but not for the specific implementation plan for achieving this objective.

Some specific findings of note are listed below:

- Many respondents stated that the top surface is too small for readable text. This suggests that basing an approach to making cautionary warnings more salient on the presence or absent of ferrule or cap text might be a flawed approach.
- Some of the messages that would likely be prohibited or restricted by the USP proposal were highly valued by the respondents. For example, in Section 4- Q6 & Q13, many respondents cited the drug name, concentration, dose, expiration date and storage information as one of the most valuable purposes for ferrule/cap over seal labeling. Further, when asked to rate the value of certain categories of messages on ferrules and cap over seals the drug name/concentration were almost as highly rated as cautionary warnings, with 75% rating drug name/concentration as somewhat or very high value (Section 4 – Q7). In addition, dosage messages were rated by 54% as somewhat or very high value (Section 4 – Q7). When asked to specifically rate the importance of anti-

counterfeiting information on ferrules and cap overseals, 38% rated it as somewhat or extremely important (Section 5 – Q2). When asked to specifically rate the importance of cold chain management messages on ferrules and cap overseals, 43% rated it as somewhat or extremely important (Section 6 – Q2). When asked to specifically rate the importance of dose information messages on ferrules and cap overseals, a majority (58%) rated it as somewhat or extremely important (Section 7 – Q1). When asked to specifically rate the importance of point-of-use instructions on ferrules and cap overseals, a majority (74%) rated it as somewhat or extremely important (Section 8 – Q1).

- In the follow-up survey, when presented with the idea of certain ferrule/cap overseal messages being prohibited (such as drug name, cold chain information, anti-counterfeit information), an overwhelming majority of respondents (74%) stated that “it would be harmful to eliminate most of these messages.”
- In the follow-up survey, when presented with the idea of certain ferrule/cap overseal messages being prohibited, an overwhelming majority of respondents (80%) stated “Yes” to the question “*Do you see the potential for increased medication errors due to the removal of messages related to dosing instructions, anti-counterfeiting measures, cold-chain storage, potency/concentration, population, etc.?*”
- No respondents cited a single example, or described a causal incident, where ferrule or cap overseal labeling was overcrowded (Section 4 – Q15).
- The majority of respondents stated that a prevalence of ferrule/cap overseal labeling would NOT lead to a decline in their perception of, or complacency with, ferrule and cap overseal labels (Section 4 – Q17).
- When asked if ferrule and cap overseal labeling should be restricted, more respondents said “yes” than “no.” In the follow-up survey many respondents stated that standards setting agencies, drug companies and HCPs should all be involved in identifying useful labeling approaches. Those who opposed restricting ferrule/cap labeling typically referred to the value of redundancy and the cost of losing information. Some specific comments include:

- “Knowledge and information is power.”
 - “Information enhances patient safety.”
 - “Not restricted, yet standardized.”
 - “Information needs to be present so that errors can be prevented.”
 - “For safety and guide.”
 - “Way too many restrictions turning us into manual robots; should be encouraging intelligence, rather than laying on more restrictions.”
 - “While certain persons may ignore all printed messages, I believe most health care personnel appreciate the extra precautions that the printed messages provide. In the fast-paced world of health care, any assistance to the providers is useful to slow us down and make us think before administration of any medication.”
 - “There is more important information that would be lost.”
 - “Inconsistent if limited to only a select few.”
 - “While I feel labeling on the ferrules or cap can provide important warnings to the administrator of the drug, the actual size of the print is often very small and difficult to see. But, until there is enough research done to determine what labeling is most effective, info should not be restricted.”
- When asked which of two ways is the ideal method for making cautionary warnings more salient the majority of respondents (69%) agreed with the statement, *“Present life-threatening messages in a unique color and with a unique symbol/icon, but allow other safety related messages to remain on the ferrules and cap overseals,”* while only 31% agreed with the statement, *“Eliminate all other, non-life threatening forms of messages from ferrules and cap overseals.”* The latter represented the USP proposal.

Conclusion

This survey was not intended to produce a winner or a loser. It was designed to provide data toward the assumptions, the objectives and the specific approach of the USP proposal for ferrule and cap overseas labeling. The collective responses demonstrate that the USP proposal does not appear to address the variability in users, contexts and needs that exists with respect to drug vial ferrule and cap overseas labeling. The data also suggest that a more detailed and sophisticated approach might be needed; one that perhaps holds the same objective of making the most critical cautionary warnings stand out amongst other less-critical messages, but uses different tactics in doing so.

Finally, it should be noted that any particular respondent's disposition toward the USP proposal depended on their assumptions underlying, or definition of, the terms "restricted" and "cautionary" as applied to ferrule and cap overseas labeling. Some respondents explicitly stated difficulty in providing a disposition due to the ambiguity of these terms. Those who adopted a specific definition often were not in agreement.

Executive Summary – Human Factors Study

What Did We Do?

CAPS, the Consortium for the Advancement of Patient Safety, contracted with Interface Analysis Associates (IAA) to conduct an empirical human factors study of the effects of drug vial ferrule and cap over seal labeling in the context of the recent proposal to limit such labeling, proposed by the United States Pharmacopeia (USP).

The main objective of this study was to identify if the presence or absence of information on the drug vial cap affects the performance, behavior and subjective ratings of health care providers in drug selection and identification tasks. To achieve this objective, IAA conducted an empirical human factors study involving a variety of health care practitioners (HCPs) (nurses, physicians, pharmacists, pharma techs, medical assistants), all of whom normally handle drug vials and are responsible for cross-checking drugs against prescriptions and patient drug delivery orders.

The study consisted of 20 participants (8 males and 12 females) who were placed into one of two groups. Fifteen participants (Group 1) were not instructed about the cap labels or asked to explicitly use them. Five participants (Group 2) were explicitly instructed (briefly trained) to use the cap labels and to cross-check all vial labels with the cap labels before finalizing their selection of drugs for a given task.

Each participant performed a set of tasks centered on selecting the correct drug for a given prescription amongst a large set of drug vials. A total of eight drug selection tasks were used, each presented twice to each participant; once where the correct drug vial(s) had cap labels and once where the correct drug vials had no cap labels. This also included two drug storage sorting tasks, in which they were asked to organize/sort drugs by their cold storage requirements.

What Did We Find?

Based on the performance data and post-interaction interviews we can conclude the following:

1. HCPs are generally not used to viewing cap labels. Even in the presence of cap labels, many ignore them or do not see them and utilize the vial label solely. Further, they are often trained to check only the vial label.
2. Participants of all health care types made many errors, with or without cap labels. Some of their errors would have disastrous consequences (e.g., selecting 100U potency instead of 10U). They exhibit common failures of memory, perception and attention. This demonstrates how difficult it is for humans to distinguish between drug vials that are very similar, even when explicitly tasked to do so in a study. Also, regardless of their failure rates, they are consistently overconfident that they obtained the correct drug vial. This finding actually supports the potential value for cap labels. If key attributes can be reinforced on the ferrule/cap, and HCPs were trained to cross-check via the cap label, we may see a reduction in medication errors.
3. Related to point 1 above, some participants indicate they did not notice the many cap labels during the study, demonstrating how experience influences perception. Others indicated they did notice (and use) the cap labels. It varied from person to person (in the untrained group).
4. When the cap labels were noticed and used, performance was better (the correct drug vial obtained) and faster, and ratings were more positive.
5. When HCPs were trained to cross-check the vial label with the cap label, there was an increased benefit to drug selection accuracy and time.
6. Post-study interviews made it clear that reducing the incidence of cap labels would further reduce the likelihood of HCPs noticing ANY label that does exist (as per the USP proposal). The lack of prevalence for cap labels that exists today results in shaping pre-attentive perceptions that are stronger than the perception of information at the time of the task. In other words, when HCPs are not used to seeing or using cap labels (which would be even more rare under the USP proposal), they literally do not see (perceive) labels when they do exist. They are blinded to their presence.

7. At the end of the session we presented each participant with three approaches to the future of ferrule/cap labeling:

Option 1: *any drug could have a label or not, and of any color/design (as is the case today).*

Option 2: *only volatile drugs that could cause life-threatening harm would have cap labels and all other cap messages would be prohibited (USP proposal).*

Option 3: *volatile drugs that could cause life-threatening harm would be uniquely coded in a special cap color (e.g., red) and perhaps with a special icon, but other drugs can still have cap label, just not in the designated life-threatening color/design. (Tony's proposal based on human factors principles).*

- a. ALL BUT ONE participant selected **Option 3 (HF Principle) as the best.**
 - b. Most indicate **Option 2 (USP) as the worst**, followed by Option 1.
8. Most participants viewed removing the messages on caps as harmful (no participant stated it would be beneficial) and likely to increase medication errors.
 9. Finally, most of the participants indicated that cap labeling could be useful and improve patient safety if they were both more common and HCPs were explicitly trained to make use of them.