FOOD AND DRUG ADMINISTRATION

INSTITUTE FOR SAFE MEDICATION PRACTICES

AND

U.S. PHARMACOPEIA

PUBLIC WORKSHOP

IMPROVING PATIENT SAFETY BY ENHANCING THE CONTAINER LABELING FOR PARENTAL INFUSION DRUG PRODUCTS

Thursday, January 11, 2007

The workshop came to order at 8:00 a.m. in the Lister Hill Auditorium of the National Library of Medicine, Building 38A of the National Institutes of Health Main Campus, Bethesda, MD. Dr. Gerald Dal Pan, director of the Office of Surveillance and Epidemiology, presiding.

PRESENT:

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A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:05 a.m.

DR. DAL PAN: My name is Gerald Dal Pan. I'd like to welcome you today. I'm the Director of FDA's Office of Surveillance and Epidemiology within the Center for Drug Evaluation and Research. And within our office we have a Division of Medication Errors which concerns itself largely with the identification and prevention of medication errors. And we're pleased to welcome you today to this one-day public workshop cosponsored by the FDA, the U.S. Pharmacopeia and the Institute for Safe Medication Practices on the topic of How to Improve the Labels on Intravenous Drug Products to Minimize Medication Errors. So today we have a unique opportunity to hear from all the different stakeholders to get a better understanding of the medication error issues they face and the challenges they have in making changes to improve patient safety.

We'll hear today from the FDA and from the USP which are the two groups that set forth the requirements for labeling, and we'll also hear from the Institute for Safe Medication Practices, healthcare practitioners, manufacturers and the public. Today's meeting is very timely in that it

follows the July 2006 Institute of Medicine report on minimizing medication errors which recommended, amongst other things, that FDA work with other stakeholders to improve product labeling. This meeting though will not cover all aspects of product labeling, but will instead focus on improving the labeling for small-volume and large-volume parenteral infusion products. And we'll take the information we gain from today's workshop into consideration when we get involved in future decision-making on labeling requirements or other regulations concerning these products.

We'll begin the workshop with two overview presentations, one on the scope of medication errors that are seen with these products and the other will give us a historical perspective on the topic we're addressing today. Then we'll begin with Session 1 which includes presentations and a panel discussion on container label information requirements. After the lunch break we'll continue with presentations and a panel discussion on how to minimize confusion among product labels. During both the morning and afternoon panel discussions we encourage audience participation so please use the microphones if you

have any questions for the panelists or if you want to make any other comments. Our final session which will be immediately following the afternoon break will be a one-hour open public session where we will hear from those who signed up to speak through the Federal Register notice. Let me add here that we have a very packed agenda today. We have lots of speakers, and we are aiming to finish on time. So I'll ask each of the session chairs to ensure that your session and the speakers within it keep to the schedule we've outlined. So by the end of this meeting we hope to have a better understanding of the experience and perspective of each of the stakeholder groups as well as ideas and recommendations on how to improve the labels on intravenous drug products to minimize medication errors. So we have a full program and let's get started.

Our first speaker today is Dr. Michael Cohen who is President of the Institute of Safe Medication Practices, a non-profit organization devoted entirely to medication error prevention and safe medication use. Dr. Cohen's presentation will be on the scope of medication errors. So Dr. Cohen?

DR. COHEN: Thank you. Well, good

morning everybody. Thank you, Dr. Dal Pan. Let's see, my slides. This will take me a second here. Do not start the countdown until my first slide is - we only have, you know, everybody's squeezing in their 15 minutes or whatever. There we go. Okay. Well first of all, I'm probably one of the few people in the room that goes back to the days when we were making our own IV solutions, believe it or not, and sterilizing them. When I first started in hospital pharmacy that was still going on in some hospitals around the country. And through the years certainly a lot of improvements have been made. I think personally one of the most important areas of all has been the adoption nationwide and really internationally of pre-mixed solutions of drugs in large-volume parenteral containers, or containers from 25ml on up, especially those that contain high-alert drugs, ones that we previously mixed and unfortunately sometimes caused some very, very serious medication errors. I think the labeling in general has improved as well, but certainly there is still room for improvement.

And just in the way of background, I just wanted to tell you at least from my memory of kind of how we got together to have this meeting.

We actually had several incidents that involved inadvertent direct injection of sterile water for injection. And these were accidentally given because they were mixed up with other containers or in some cases sterile water was actually used intravenously in patients where it was intended actually to be used for - a different solution was supposed to be used for plasmapheresis. But unfortunately the way that the drug information appeared, it looked like sterile water for injection could be given and it was actually used in the pharmacy to compound some of these solutions in error and unfortunately patients died. There were several fatalities that occurred. And so we had heard of this happening in the past where sterile water was confused with other products. As a matter of fact, at one time one of the manufacturers actually used the abbreviation "DW" on their label for distilled water and it was mistaken as 5 percent dextrose water and was actually accidentally infused. At any rate, in looking at the containers it certainly looked like there was room for improvement as far as the warning systems and you can certainly see how people could possibly confuse this and how the warnings were rather weak on the

container. I know some of the manufacturers actually, in response to a series of these incidents that happened - it was about six or seven years ago - did in fact change their labeling. But anyway - and improved their warning.

In the discussions that we had with some of the companies, we had people visit us from **B**axter and also Hospira. I guess it was Abbott at the time. And we also interacted with B. Braun. It just seemed like everyone in the industry was interested in taking a look at the parenteral bag labeling, the infusion bag labeling, the infusion bottle labeling, and we recognized, for example, there was a lot of rather unnecessary information on some of the labeling that was basically covered up anyway with pharmacy labels and just all thought it would be a good idea. So we began to interact with FDA, with Carol Holquist's group at the Division of Medication Error Technical Support, and Mary Gross was there at the time, and the idea came forth about having a public meeting which is what brought us here.

So what I wanted to do in the time that I have is kind of go over - now, I was asked to talk about the scope of medication errors, and I'll kind

of touch on that, but it's a little difficult to do because even one incident that's serious could take quite a bit of time to actually describe. So what I tried to do was I went back into the medication error reports, the newsletter articles that we've done at ISMP and kind of tried to pull out the major areas that I think need improvement with parenteral labeling. So we'll go over that and I'll talk about some recommendations along the way. Dr. Dal Pan mentioned the Preventing Medication Errors Report which was published this past July, and right there in Recommendation Number 4 there's a license for us to even have this meeting, the beginning of perhaps guidance statements from the Food and Drug Administration to help internally and also with the industry to improve this labeling. And so this is kind of a first step in maybe even addressing this particular recommendation is getting all of us together in one room and starting to hash out some of these problems.

I think the first issue is the kind of label clutter that we see. I can tell you both as a practitioner for 28 years and also interacting with nurses, pharmacists and physicians around the country that really you can pretty much bet that

people are not reading the text on the IV bags. And it's often, as I mentioned a little bit earlier, covered up. We have bar codes on these bags now. They're not as readable as they should be. We're certainly hearing that, or getting that kind of feedback from organizations that have adopted bar code systems. And one of the main reasons even for pulling this together as I said was to examine this, do we need this type of text which really doesn't advise you of potentially harmful situations that could be better presented with a larger warning, for example, in some situations. So we'll examine some of those as we go along. So that would be one objective, to take a look at the readability of these labels. And even the positioning of the concentration information. There's a lot of inconsistency here. Sometimes you'll see the dosing above the name of the solution, sometimes you'll see it below, sometimes you'll see a concentration expressed, sometimes you'll see milligrams or milliequivalents expressed for the same product by another manufacturer. And this is something that actually I believe leads to medication errors when nurses are confused, when they see a product that they're not used to for example expressed in one way

and then other products in other ways. And I'll show you some good examples of that.

Tim Vanderveen from ALARIS has been good enough to share this slide with several of us. You're probably going to see a couple of others using this slide today as well, and I know we have people here that are front line practitioners that'll probably even expand on this. And this is the actual, how these solutions are actually used. And sometimes in critical care you have a number of these solutions that are actually hanging facing you, not facing you, some with pharmacy labels, some not with pharmacy labels, some piggyback containers, some base solutions, et cetera. And obviously it becomes very, very difficult for nurses and those at the bedside, others at the bedside to even not make mistakes.

One area I think that we need to look at is expression of concentration and strength. So here's a good example of this inconsistency that I was just talking about. On the left you have a product where the milligrams is the expression used for nitroglycerin and 5 percent dextrose. Then in parentheses you may be able to see at the bottom here it listed as 400 micrograms per milliliter.

This is the exact same solution, yet this manufacturer expresses it as micrograms per milliliter and then in parentheses 100 milligram per container. These have both been around for many years and I think we first pointed this out you know in our journal articles maybe about 20 years ago. But it's still the case today as far as I know, and I still think there's a real good possibility of confusion. I think you can see how easy it would be to confuse these. And there are other strengths as well of these solutions, other concentrations of the pre-mixed and so that is a particular problem. And I think it needs some consistency. So that would be one area I think we need to focus on today.

Another is the location of the concentration and strength. You can see the problem here. On the right you have a 70 percent dextrose solution. On the left you have a 10 percent dextrose solution and depending on the background and how the folds of the bag are, it's very easy to see how confusion could occur between the concentrations. Now, this slide was taken some time ago. I don't know of any regulations that would change this or any specific guidance that would change this. However, some of the manufacturers

have addressed this on their own, and I think you'll see some really good designs that would prevent this type of mix-up, but we have had to deal with this situation in the past.

Another, on the right 40 milligrams per milliliter for the magnesium sulfate bag on the left and 10 milligrams per milliliter for the magnesium sulfate bag on the right. Good background on the label, but again you know depending on how this bag is held in the pharmacy that might be missed. This is a product that I actually picked up from a very, very serious error that occurred outside the United States, and I think you can easily see the problem here as well with the D-5 versus D-50, just that slight turn in the label. So one of the things I think we could do a better job of is the positioning of the actual concentration for these high-concentration products. And not that - I'll show you this one. Not that this is adequate, but I've found this in my slides. On the left is a 50 percent dextrose and you can see that the 50 percent designation is in both corners of the upper part of the label there. And I think that's the kind of thing that's helpful, although I don't think the text here, the font size, is large enough. I think

we could do a better job with that. And it also appears when you turn the bottle upside down. I think you know there's - it would be a good safe labeling practice to do this with the high concentration dextrose products and perhaps some other products to reduce confusion with similar-looking products.

Again, with some inconsistencies, and some of this might involve USP. 0.3 percent potassium chloride. I've never once in my entire career seen anyone order 0.30 percent potassium chloride. They've always ordered it in millimole or milliequivalents. And so you kind of wonder why do we need that type of expression of the concentration at all. And one of the problems is that could very possibly be confused with a concentration of another drug. As an example and not necessarily with potassium chloride, but as an example we've had mix-ups between 3 percent sodium chloride, a hypertonic solution, and 5 percent dextrose and 0.3 percent.

The strength here above the drug name. We love the idea of the use of tall man letterings, or mixed case lettering as some refer to it. And this was designed in this particular case to reduce confusion with another product that's frequently

mixed up, dobutamine, so we really appreciate this representation. However, I do have two comments about the use of tall man letterings. One is, again, there is a real inconsistency. Quite a few years ago we asked the FDA's Division of Generic Drugs to come up with a list of drugs. We recommended some, they added some of their own. And came up with not really standards, but recommendations for the industry on how to express drug names using tall man lettering. And this was done for about, I think it was about 17 or 18 generic name pairs. However, since then quite a few of the companies have gone and on their own taken non-proprietary names and then used certain letter characters within that name on their own in an inconsistent way. One manufacturer doesn't necessarily do it the same as another. And there seems to be no - it's very haphazard. There seems to be no standard, and I think that's very important that even with the IV container label that we all do this the same way and that it goes through some approval process or a standards agency so that we all do these in the right way. I think sometimes I've actually seen these used in such a way that they actually look like brand names, the mixed-case

labeling, and it's kind of you know not exactly what USAN and USP intended with their non-proprietary names being used almost like a brand name. So I think that's very important.

I also want to point out here that with most product labeling you would see the name of the drug, the brand name sometimes and then the generic name in parentheses underneath and then it's followed by the strength. Here we have just the opposite with the strength on top. I think people's eyes focus on the drug name and it's not so difficult when you have similar-looking bags like this to mix up the strengths because they're not necessarily seen so easily, especially when people are so used to with other types of labeling seeing the strengths below the drug name. I'm sure there'll be some disagreement with that.

One thing I think that we need to state is that highly stylized labeling for the IV containers with you know a specific type of corporate dress can be very, very - can be a very unsafe practice. This is no longer the case, but at one time there were these rocket stripes which I think contributed not necessarily in this case because we have red labeling, but what you would see

depending on how the bottles were turned, you would see the rocket stripe and not the drug name and that led to some mix-ups.

The expression of the drug name. One of the manufacturers has gone to vertical labeling for several of their products. Others have not. I'm not sure that we wanted to see this type of inconsistency, but it's another area that we might want to focus on. With package design I think we've made some real mistakes out there. I think we do need to take into consideration human factors, that people don't always do what they're supposed to do. In this particular case heparin is in an upper bag and just an infusion solution in the lower bag, yet the effluent can easily be attached to an IV set and administered to the patient and given without fracturing the separation here and thus the heparin actually remains in the bag. We had quite a few reports like that and unfortunately you know some of the patients got just pure water and not the drug when they needed it for you know patients with pulmonary embolism or deep vein thrombosis. This bag was around quite a few years and then it had - when the company came up with a way to stabilize the solutions of heparin and dextrose the bag was no

longer used, but there are other products that still use that separation, and we still sometimes have situations where only the plain solution is given and not the drug.

This also has been a longstanding problem where we're requiring nurses to pull the plug out of the vial which is inside the bag. There's a process for that. And then shake it up, dilute the drug, and consistently studies have shown in the area of 1 to 3 percent of these are not actually reaching the patient where the nurses actually forget to actually mix the drug. And again, the solution can come out the port at the bottom and patients can miss antibiotics that way. So we need to take these into consideration in designing these products. On the other hand I have to say that this type of product, and there's others like it, they're very worthwhile obviously. They've enabled us to have pre-mixed solutions in some situations where they wouldn't have been able to do that otherwise.

I think we also need to look at some of the carton labeling. This has been a real bone of contention with practitioners around the country, especially those in the pharmacy. The code numbers

are much larger than the drug name, and sometimes the lot numbers as you can see, and this is obviously a situation where you know the intention is the people in materials management that need to choose these solutions will probably go more by these code numbers than the drug name. Unfortunately it makes the boxes look alike and occasionally it leads to a number of medication errors, even more than just one product being misused. So that's something else I think we have to take into consideration.

We have the problem with look-alike containers. That's another area. This is a pre-mixed drug, Ciprofloxacin, that was confused with dopamine. It's through the medication errors reporting program we learned of that. Sterile water with potassium chloride. I think you can see you know it would be great if everybody did what they were supposed to do and read labels, but unfortunately we sometimes set them up to make these mistakes by the appearance of these containers. And again, I think we could use some of the space in the label on the right to improve the warning system and come up with a standard warning that everyone could use. We've even had mix-ups between the cold

storage solution that's used for organ transplant or the organ preservation and intravenous solutions. We've had respiratory therapy drugs mixed up with intravenous drugs.

This is a good example of something that could be done to help differentiate product. I think they do a good job with this. This also, the triangle, the octagon for differentiating the high-concentration dextrose. I think that's very useful. And then of course we had a public meeting right in this room in 2004 on the use of color and there's an awful lot to be learned. You can just type in "color coding" on fda.gov's website and all the papers that were presented that day, all the opinions that were expressed, but I haven't seen anything come back from FDA so far as to how they're addressing that particular issue. I don't know if anything is forthcoming or not, but I think a lot of learning occurred that day, and I hope something good comes from it. But basically most of us agree that the use of color coding was not something that would be considered a safe practice. Most of us believe that you could apply color to help to differentiate products. We talked about the different uses of color that day. And I think that

does in fact also apply to IV containers. And so here's a manufacturer that had both a conventional concentration and a double strength and they used colors to differentiate this. I think this is an appropriate use of color and very, very helpful in preventing mix-ups with these products.

Label reminders and warnings. These are three versions of sterile water. The one on the left - I'm sorry, the one on the top right, you can see where it says "Warning: Hypotonic and hemolytic. Do not inject until made approximately isotonic by addition of appropriate." I think it should say right on the front label panel, right underneath the drug name, "Warning: Do not give intravenously without further," well I don't know the exact wording that I would use. Without making it isotonic or something. But there should be a much stronger warning on this because it will kill people if it is done. I know one of the companies in particular has done something with this and that's very helpful. Except I'm not sure about the color because you know everything is red here, and I'm not sure how well our eye takes in the warning. But I think it's certainly much better, and I think it would be even larger if we didn't have to worry

about the text below that block.

Then the typography is another area. I think you know it's pretty clear what these solutions are, but if you really look carefully they're not the same. This is 0.2 percent, and this is 0.45 percent. That is mixed all the time. Now is it a critical error? Probably not for the vast majority of patients, but it would still certainly be considered a medication error and it is sodium, so for some patients that are sodium-restricted, that might in fact even play a role. I think we could do a better job with the labeling. And again, the inconsistency of having the milliequivalents above the drug name.

Good example of product differentiation. I touched on this a little earlier. And then bar coding. High alert medications. I wonder if the time should come when we actually have some type of a symbol to identify what drugs are high alert. So that might be something that could be useful.

I want to point out that we have had some experience knowing that in a patient room at the bedside products may in fact not even be facing the practitioner and that we also have look-alike containers. There are a very limited number of

colors that can be used on these containers. We see black, blue, we see red. The manufacturers have to prove that it's safe to use these because the inks can migrate into the solution possibly so there's some work that has to be done to use a new color. But in any case, you see the lidocaine here, the way that it's labeled. We had a number of mix-ups between this drug, not this manufacturer's drug, but just lidocaine in general, and other products. Some of these were fatalities. And one of the manufacturers, this is a Hospira product right now, did something that I think is extremely useful and perhaps is something that should be done for that small cadre of drugs that we indicate are high alert, those that are much more likely to injure a patient if they're misused. I know there's some added expense to do something like this, but I just think it's a terrific idea because no matter how that bag is hung you can tell that there's lidocaine in it. Some of them have placed it on the over-wrap, but of course the bags are removed from the over-wrap and then you lose that safety feature once the products are hung.

There's still confusion about where the labels go. I'd love to have some decision-making on

that, the pharmacy labels. So right now they're covering the text that you see there, but there are some pharmacists that put it on the front label panel and some that put it on the back of the bag. We tend to push the idea of putting it on the front label panel immediately below where the drug and the solution are actually listed. That way you would see both pieces of information. Others like to put it on the back or even do two-sided labeling, but in this case the company has done the two-sided labeling for us, and I think that's very, very useful. So the drug always appears no matter how it's hung.

And on the slides, and these will be publicly available, is our list of high alert drugs that we've updated this once through a survey process, a nationwide survey. We intend to continue. In fact, this year we have a whole series of articles planned in our newsletters on high alert drugs. And we plan to re-survey the country - we haven't done this since 2003 - to learn whether or not there are other drugs that people consider to be high alert.

One other thing I think that we have to build into the improvements that we'd like to see is

the idea of companies having a proper response when a medication error is reported. That's a whole other area, but when Diane Cousins and I get letters like this from the manufacturer and that's basically their response. They never tell the practitioners or us for that matter what they really intend to do internally to address a serious problem that's been reported. That's disconcerting to us ,and it's frustrating to the practitioners who want to report to our program. They feel that nothing is being done. And so we'd like all of the folks in industry to recognize that a proper response would be -- not just thank you for telling us, we've entered it into our database, we'll continue to monitor it, but we're working on a solution and you know we'll get back to you. And then incorporate you know an appropriate procedure to actually do that.

We think you should have appropriate staff to whom the error should be reported. There should be specific contact number for reporting errors. Training and understanding of staff and system-based causes of medication errors. The appropriate response that I just talked about. And then adding medication safety information to the labeling. I would love to see that from FDA, some

requirement where you have drugs like some of the ones that I've been talking about that have constantly been involved with serious errors. Why not have a medication error statement in the labeling that would carry into the different drug information texts and databases so that people would be able to see this information and know immediately there's a specific problem that needs to be addressed. I think that would help to prevent medication errors.

And then finally the whole idea of failure analysis. We won't go into that right now. I'm sure others will talk about it as well. But I think really it's incumbent upon you not just to have your internal staff look at a label or a package or a new product or consider what it might be confused with. I think the best way to do that is take it outside of your organization and have expert panels, practitioners that can actually place this in the environment in which the product will be used and then go through a standard process. You might learn a tremendous amount of information that not only will help you as a company to not have to change products down the road, but also I think will be very important to help all of our patients

prevent serious errors. Thank you.

(Applause)

DR. DAL PAN: Okay, well, thanks a lot, Dr. Cohen, for that presentation. Our next speaker is Ms. Diane Cousins who is the Vice President of the Department of Healthcare Quality and Information within the Standards Division of the U.S. Pharmacopeia. And she'll give us a historical perspective on labeling for parenteral infusion drug products.

MS. COUSINS: Good morning and thank you, Gerald. I'm not sure what it says in your career when you're invited to do a historical perspective on something, but I have to admit it's the first time I've been asked to do this. But you know when USP was invited to cosponsor this meeting we really jumped at the chance to call attention to this subject once again. And I say once again because for USP in a sense this is a back-to-the-future and I think the presentation today will show you why that's the case.

What I'll do for you this morning is just briefly to describe the work of two committees that were formed in the early `90s to examine medication errors with injections that were

beginning to become public. I'll tell you a bit about what those committees did, their recommendations for changes in the labels and labeling of injectables and how we USP and FDA moved to implement those changes.

If you are not familiar with USP we are the product non-profit organization that sets standards for drug products in the United States. We do this through authority created for us in the Food, Drug and Cosmetic Act such that the standards we set are enforceable by the Food and Drug Administration. USP also operates a couple reporting programs for many years and two of those currently are focused on medication errors. This gives USP the chance to hear from front line practitioners in the design of its standards to address errors that may be occurring to prevent their recurrence for the future.

In the early `90s fatal medication errors began to make the press and perhaps more frequently than ever before, and the public began to demand attention to this matter. And these are errors I know many of you are very familiar with, some of them unfortunately still occurring such as the administration of undiluted potassium chloride

injection, the administration of intrathecal vincristine and the administration of cancer drugs like cisplatin and methotrexate that were being administered as a single dose or regimen and not over time as it was intended. And so there was attention in particular to some fatal events that occurred in Washington State. And because of those events there was a bill introduced in the legislation that would require the color-coding of all ampules, vials and pre-filled syringes by pharmacological class prior to their sale in Washington State.

Well, as you can imagine there was quite a stir about this, not only by the pharmaceutical industry, but by healthcare practitioners alike. And there was in fact a compromise struck with the representative who had introduced that. In fact, the industry had pointed out to that representative that the ultimate responsibility for labeling design rested with the FDA and with USP and so Representative Grace Cole had agreed at that time to table the bill if realistic guidelines could be submitted to FDA and USP by a practitioner industry task force that would study the issue of errors with small-volume parenterals at that time, the focus of

this particular issue. The task force in fact was organized by the PMA, which was the Pharmaceutical Manufacturers Association, which of course now is the Pharmaceutical Research and Manufacturers Association or PhRMA. And FDA and USP engaged with this committee because they were also - we were also currently studying revisions to existing labeling laws and requirements that would address errors with injections. And in fact this committee included 17 individuals from eight national organizations, practitioners, and 70 industry representatives.

At about the same time the Home and Hospital Parenterals Subcommittee of the USP's Drug Standards Division had concern about rising injuries being reported from the accidental misuse of injectables. And the committee had identified overcrowded labels as one possible cause and of course this overcrowding becomes more of an issue in emergent situations. And this is where we started to see errors occurring as well. And although certain of these product labeling issues could have been addressed by changes to the USP-NF, there were other requirements that were federally mandated and needed revising or deletion of federal laws or regulation. And as it turned out as these two

committees were moving in parallel it was the report of the PMA committee that would also provide support for many of the changes that came out of the joint USP and FDA committee.

The recommendations that were common to both reports are listed here. And the PMA committee had decided that all injectable labels certainly must be read, but also that they must be legible and they immediately eliminated color from their discussions and said only that color should be used as an enhancement in product labels. But beyond that the two reports were very similar, and I'll lay these out for you in a side-by-side comparison.

First on the issue of size of information on the label. The FDA and USP committee had recommended that the drug name and strength should be the most prominent information on a product label. PMA committee agreed, but they added that the drug name in that case could be either the proprietary name or the established name that would be most prominent. And so the "either" there gave the industry the ability to choose between one or the other, not necessarily both.

Also regarding size of information on the label, this particular recommendation addressed

the relative sizes of information. The recommendation asked manufacturers to voluntarily select a type size for company-related information that would not upstage the name and the strength of the drug. Now there's little difference really in these recommendations except that the PMA encouraged discretion - I thought those were interesting words - in the size of company information on the label.

Now most information that was recommended for elimination was probably information that could be listed in the package inserts. So it's not that it would not be available, but it would be available elsewhere than on the immediate label of the container. It was felt that this elimination of the information from the label itself would not in any way compromise patient safety and so the items that were recommended for deletion to the right side of the slide are the words "sterile," "non-pyrogenic," "pyrogen-free," the controlled substance warning, the legend warning, the "Caution: Federal law prohibits ..." warning, and non-specific dosing information which was always on labels, "For usual dosage, see accompanying package insert." Well obviously that was not critical. The FDA and USP committee did add information and that's to the

left. Information that could be deleted might include container descriptions, storage requirements and the controlled substances designations. Now, the two items in black actually reflect FDA's formal response to the panel's recommendation when it was published for public comment and the FDA supported keeping storage instructions on the label so that healthcare practitioners wouldn't get familiar with not seeing it on the label because the majority of products that they would handle would not require storage statements then. So their fear was that when a storage statement did occur, it would not be seen or it would be easily overlooked by the practitioner. The FDA also formally opposed the removal of the schedule for controlled substances on the label because they believed it would cause confusion since many of the products that bear that designation could be stored or handled differently depending on their schedule. For example, Schedule II narcotics versus other drugs held under lock and key.

In the third area of the recommendations regarding abbreviations, the FDA and USP committee recommended that drug titles should not begin with the chemical symbol such as the Na for sodium, K for

potassium, that if injection is part of the established name then it should appear in full. However, on very small, and they actually use those words, very small labels it may appear as an abbreviation of INJ. So there's no solid recommendation about the size that would move it to that use of the abbreviation.

The PMA committee agreed with the joint committee except that it supported USP-type abbreviations like hydrochloride, HCL for hydrochloride, it supported the word "injection" to be used with the trade name as well as with the established name, and it also addressed punctuation marks, that punctuation marks like a period should not be used on the label and that the designation of USP should not be used where space is critical. And of course without that designation if there is a USP monograph the drug is still required to meet the USP standards or to state how it does not if it is not a USP standard. So there's an implication even though USP isn't on the label that it does meet the USP standards.

The final area, the area of the term "single-use" and "multi-use" was really the area that was most contentious. And while the FDA-USP

committee made several recommendations, there were some additions by the PMA committee and then there were several responses by the FDA either in agreement or in disagreement and I'll go through those as well. The items that were recommended of course by the committee were the preference to use "single-use" and "multiple-use" rather than "single-dose" and "multiple-dose" because there were products that had more than a single dose in a container and yet were intended for a single use. The expression of strength would be one where the total strength per total volume would be included on the label. Where the strength of certain drugs was expressed in percentages or in milliequivalents, that committee felt that that was acceptable. And they also recognized that there could be products that were available in dry powdered form where only the total strength of the dry powder and not the reconstituted product should be on the label.

And the PMA committee added a few to that. First, that the total strength per total volume where the total volume was 1 ml would eliminate the use of the 1 and that the only numerals would be used in immediately preceding the ml. That the statement of total volume that

appeared anywhere else on the label could be eliminated and that the total strength, total volume as well as the strength per milliliter which happens to be a USP requirement as well should be in close proximity to one another so there was no misunderstanding of what was in the container.

Now the FDA responses here were a little bit more substantive. They disagreed with the single-use, single-dose - the use of "single-use" instead of "single-dose." They had a comment that the "single-use" would imply that there's no preservative in the product and unless reserved only for use with products not containing preservatives the FDA would not support it. Regarding single-dose less than 2ml, the FDA was comfortable with total strength per total volume. And where the size of the container would exceed 2mg, you see two expressions of the strength here that would be acceptable to the FDA. So you see the total mg per total mls, the milligrams per ml, and then total milliliters in the container. Regarding the multiple-dose products, the expression of the total content was of concern to the FDA because they felt that such a large number that would be routinely visible on the label could become so familiar to

someone that they might expect that this was an acceptable dose for the product, and that they might then administer that level of a dose which was a multiple-dose container and that would cause errors. FDA did agree with the expression of the strength on dry powders to reflect the pre-reconstitution strength.

Now where are we today on these issues? Well, we thought that this was sort of an important recount to give you because we thought it was important for you to see that standards and regulations actually were changed where they needed to be, particularly regarding the legend for example. That there were voluntary changes that were proposed like the proportionate size of the company information to the drug name and strength, but because they were voluntary they inconsistently appeared on product labels. You'll also hear about some changes in USP standards and requirements that are currently in process, and I might add to the end of that finally after all these years. And I would expect that today we'll have some refreshing new ideas that we'll think of that can address the problems that we're seeing today. And the only thing that I would say in closing that I would hope

that what we do identify today doesn't take another 15 years for us to address as some of these have taken for us today. Thank you.

(Applause)

DR. VAIDA: Thank you, Diane. I'm Alan Vaida, Executive Vice President of the Institute for Safe Medication Practices, and I'm going to be moderating the rest of this morning's session. We heard from Dr. Cohen about the scope of the problems and Ms. Cousins talking a little bit about the historical perspective and for the rest of this morning what we're going to hear is from representatives from the United States Pharmacopeia and the FDA talking about some of the requirements for labeling for large- and small-volume parenterals. Then we're going to have an opportunity to hear from two of the manufacturers on some of the challenges that they're facing with some of the labeling requirements and also trying to meet some of the safety requirements that their customers would like for them to meet. We're going to have a break in between and then we're going to end the session this morning with an opportunity for you to ask some questions of all this morning's speakers.

So our first speaker is Dr. James Kelly

from the United States Pharmacopeia. Dr. Kelly is Scientist, Department of Healthcare Quality and Information Standards Division. He currently works with the Compounding Pharmacy Expert Committee and formally with the Parenteral Products Industrial Expert Committee. He's the liaison for USP on that committee. So Dr. Kelly?

DR. KELLY: Thank you. Good morning everyone. I'm going to in a way continue a presentation that Diane Cousins had started. She had shown you the background of what was going on as part of a committee's trying to establish standards. And what I have done with the Parenteral Products Industrial Committee is go ahead and incorporate standards that are now coming around to help us with these problems.

My objectives of this presentation would be mainly to give a background of the USP requirements for labeling on parenterals. The requirements will be mentioned in General Chapter Number 1, which is Injections, and new requirements for General Chapter 1 Injections will be talked about. The USP Compendia is recognized in the Food, Drug and Cosmetic Act of 1938 and is FDA-enforceable. The Compendia contains general

chapters, general notices and monographs. And I might mention that if the general chapters and general notices generally take precedent unless the monograph has a different labeling procedure. Then the monograph would take precedent.

And I just wanted to define how the USP defines the small-volume parenterals and the large-volume parenterals. Small-volume parenteral is any injection that is packaged in containers labeled as containing 100 milliliters or less, whereas the large-volume parenterals is a single-dose injection that is intended for IV use but packaged in containers labeled as containing more than 100ml. One of the requirements for labeling from General Chapter Number 1 for Injections is that in liquid preparations, the label should include the name of preparation, percent or amount of drug in a specified volume, ingredients added to adjust pH or make the solution isotonic are declared by name with a statement of their effect. Number 2, in dry preparations to which a diluent is to be added prior to use, the label should include the amount of active ingredient, the route of administration, the expiration date, name and place of business of manufacturer, packer, or distributor, and also an

identifying lot number. In addition to these, it would also have to have the composition of recommended diluents and we could have names only if the formula is present in the monograph. Amount of diluent to be used should also be on the label so that we know the final concentration and the final volume, a brief description of the physical appearance of the constituted solution, directions for proper storage and an expiration date that will give the time period the constituted solution will be of a certain potency and strength.

The USP medication error reporting programs, and there are basically two of them, gave rise to causing changes in the requirements, mainly because of all the reporting we got from different areas where they would talk about medication errors. Potassium chloride for injection concentrate has been mentioned previously. There is a section in General Chapter 1, Injections, that lists the following text. And it essentially is saying that only a black closure system on the vial can be used on these products and it's prohibited except for the potassium chloride for injection concentrate. This goes back to color-coding. Color-coding is not very popular these days and I think Mike Cohen mentioned

that earlier. It's not the best way of all times because manufacturers tend to change colors and that can cause confusion and errors.

Printing on Ferrules and Cap Overseals is a section that came about, and it was originally in Pharmacopeia Forum back in 2003. And we have only cautionary statements to be printed on the ferrules and cap overseals of vials. And the cautionary statement is basically one to prevent any life-threatening condition if the injectable drug is used inappropriately. And I give example of "Warning: Paralyzing Agent." Now, this is mandatory on all these paralyzing agents that are manufactured by industry. The committee had to come about with a notice of postponement, and the reason for the postponement was because there was a new revision that had extended the official date or effective date of this section. And it went from October of 2005 to February of 2009.

Finally, this is the last - this is the final version we have that which I just mentioned we have a revised version mainly from comments in industry and the committee's decisions. It was voted on by Safe Medication Use Committee, Nomenclature Committee, and Parenteral Products

Industrial Committee. Now the first part is similar to the last version with the exception that we say on the top circle surface. The reason for this is that a lot of companies will clutter the top of the - of either cap overseal or ferrule with a lot of information, logos, any other kind of information there, and it will just prevent, if there is a cautionary statement put anywhere else on the cap or ferrule, it'll detract from that cautionary statement. And it goes on, the other one had gone on, with the exception that the last, Number 3, identifying numbers or letters such as code numbers, lot numbers, et cetera, can appear on the side - they call it the skirt surface of the ferrule - on vials containing injectable products. This was brought about by industry to make quality assurance better and make sure that there is no mix-up in any vials. And we do have them all with either identification or some kind of lot number to be placed on the sides so that it eliminates any kind of problem in quality control.

And the second section, any anti-counterfeiting scheme must not detract from or interfere with cautionary statements. As you know, there's been a lot of discussion and controversy

today about counterfeiting of drugs and how to prevent counterfeiting. We have had groups in different industry talk to us and say, well, if we put a lot of information on there, won't that prevent counterfeiting. Yes, it could in some instances, but however we want to make the condition that if you have an anti-counterfeiting scheme such as RFID or any kind of bar code, it must not detract from or interfere with the cautionary statement.

The current requirements for labeling of strength and total volume for single- and multiple-dose injections is basically to have the amount or percentage of the drug stated in the specific volume such as this example I give here for diazepam. Now, there's a new requirement that will be going into Chapter 1 for Injections, and this one also will become official in February 1, 2009. What I mean "official," it will be going in official text, but it will become effective, it will become implemented at this date.

For single-dose, multiple-dose strength per total volume should be the primary expression followed by strength per milliliter enclosed in parentheses. And containers less than 1ml with strength per fraction of a ml should be the only

expression of strength. The following format is acceptable for contents greater than 1ml, total strength, total volume 500mg per 10 ml and followed by 50mg per ml, or if any other instance where you may have a biological product it would be total strength and total volume such as 25,000 units per 5ml and the strength would be of course as follows. The following format will be acceptable for content less than 1ml. You can have 12.5mg for 0.625ml as an example. And there are four exceptions to expressing strength per total volume. The first one is primary expression of drug content per container would not be any practical - would not suit a practical purpose in preventing errors if you had a vial of insulin. The use of lidocaine or other similar products ordered as - usually ordered and administered by percent. So that would be applicable and acceptable. And if you have a local anesthetic, say in combination with epinephrine expressed as a ratio 1 to 100,000, in such cases total strength should be used as 1 percent, parentheses, 100mg per 10ml. And in the following one it would be dry solids which need to be reconstituted should follow the same format with the exception that only total strength of the drug would

be listed. I'd like to thank you very much for this presentation.

(Applause)

DR. VAIDA: Thank you. Our next speaker is - let me just get this set up here for one minute. It's Dr. Eric Duffy from the FDA who's going to be speaking about FDA requirements for large- and small-volume parenterals. Dr. Duffy is Director, Division of Post-Marketing Drug Evaluation, Office of New Drug Quality Assessment, Center for Drug Evaluation and Research, as we all know as CDER, at the FDA. He's been there for over 16 years and he now has oversight for changes to manufacture and controls for all marketed drugs. Dr. Duffy?

DR. DUFFY: Thank you. Well, good morning everyone. Can you hear me? All right. I'm actually very fortunate to follow the presentation from the USP representative because many of the requirements for parenteral products, infusion products, come from the USP General Chapter Number 1. I will review the requirements and as I say, most - as you'll see, most of the requirements do indeed evolve from the USP. However, there are some regulatory requirements which I will briefly review

and they're derived from sections of the Federal Register - Code of Federal Regulations rather, principally 21 CFR Part 201. There are also additional requirements in the Food, Drug and Cosmetic Act.

Let me start by just commenting on what the minimum requirements really are. I think as the discussion proceeds here today we'll probably come back to the same type of comment frequently and that has to do with clutter. Oftentimes really difficulty in knowing what the product is and how it's to be used is obscured by a lot of information. Useful information, yes, but oftentimes it's more information than is really needed. So the regulations provide for minimum requirements, those bare bones statements that are required on the label. And I'll review them for you here.

The first requirement, and this is for - it's really primarily intended for presentations that are very small, very small ampules or vials, and it's principally for SVPs. The proprietary name is required. The trade name is oftentimes used, but the proprietary name is indeed required and its prominence needs to be - relative to the trade name needs to be such that it is at least half the size

in terms of typeface. The established name needs to be expressed according to a certain pattern, and I'll review that in a moment. The lot number needs to be there for tracking purposes and for adverse event reporting. The name of the manufacturer or the re-packer and/or distributor is indeed required and a few other assorted requirements which I'll review in a moment.

In terms of nomenclature, there are indeed conventions. And here I'm going into the USP. I won't go into tremendous detail because we just had a very fine presentation on this, but the classes of drugs are expressed in specific ways. There's drug name and injection, a for-injection, something to be reconstituted, then there are different types of products such as emulsions, suspensions and injectable suspensions. These are all prepared in different ways and clearly instructions for preparation are necessary. Additional USP requirements would include the name of the preparation. And the next requirement is oftentimes confusing. It's how to express the concentration or the amount of drug present. It should be expressed in terms of percent content in a specified volume. Whether that's total volume or

some unit volume is oftentimes a matter for debate. It's not entirely clear in my opinion in the USP Part 1.

The total amount of active ingredient for a dry preparation should be expressed. The route of administration, whether it be IV, SC or whatever should be expressed. A storage statement should be included and the expiration dating as well. Again, the name of the manufacturer and a lot number. Now, when you have a very small label, not all of this can go on the label so sometimes a matter of debate and it's a matter of opinion as to what is the bare bones essential requirement. What is a small label is also something that is oftentimes not entirely clear.

The label statement should designate the volume, for an LVP the concentration of each ingredient. For example, many products come in varying concentrations. I'm giving here an example of dextrose. It should be expressed in terms of its percent. Sodium chloride as well is another one commonly used.

There are some specific types of products for which there need to be some warnings, essentially. Irrigation solutions should be clearly

labeled as not to be used for infusion. That is oftentimes a source of a problem. For safe use of a product, an injectable product, one needs to inspect it prior to use for particulate, discoloration or whatever problems might be evident just on visual appearance. So the label should not obscure the product. One needs to be able to look at it, put it up to the light or whatever. So the label should be placed so that there is sufficient clear vision of the solution that the vial contains.

Another case where some essentially warnings need to be present would be for a pharmacy bulk pack. It needs to be clearly stated that it is indeed a pharmacy bulk pack for multiple - for pharmacy compounding in a typical pharmacy admixture program. Pharmacy bulk packs are indeed intended to be penetrated only once, and I believe that's a potential source of error. An expiration - a use period should also be expressed in the label. That's typically four hours. And pharmacy bulk packs are intended to be limited only to injections or for injections and injectable emulsions. As I say, it needs to be clearly indicated that a pharmacy bulk pack is really only for admixture programs, so a label statement such as "Pharmacy

bulk package. Not for direct infusion," should be very prominently expressed on the label. The intended admixture preparation procedures should be clearly expressed. Now, obviously a lot of this information is not going to be able to go on an immediate or carton container, but this would be on an insert label. And again, the expiry, the use period should be clearly expressed.

There are some special cases for particular types of products for safe use. One example is for total parenteral nutrition products there are concerns about leechable aluminum or aluminum present in excipients. And so we have a regulation that requires that the aluminum content be expressed. And that can be found in the CFR Part 201.323. And the label - and this pertains to large-volume, small-volume and pharmacy bulk packs of TPN products. And there should be a clear expression of the aluminum content such as "Contains no more than a certain number of micrograms per liter of aluminum." This regulation, by the way, was a long time in coming.

Another special case for safety reasons is the labeling for sulfites. Certain people have allergic reactions to sulfites although there's some

debate as to the prevalence of sulfite allergy. It depends on who you talk to about this. I've heard some people say that there are only anecdotal reports numbering less than what you can count on one hand, and others say it's far more prevalent. However, just to be cautious there is a requirement at least that it be labeled whether it contains sulfites or not, and it need not necessarily appear on the immediate container or carton label.

There are some additional regulations for labeling which I've listed here and the first citation I have here, the CFR Part 201.15 states that the prominence of important components of a label are required. And this of course is always a very subjective sort of discussion one enters into, what's prominent. What should be more prominent than this? Are there other components of a label that draw one's attention from the statements that need to be most prominent? Are there fanciful logos or artwork that detract from one's ability to pick up on the most important components of a label? Oftentimes an interesting discussion that we have at FDA with the industry as they're proposing various types of labels.

Another requirement is for where the

expiry appears, and that should be in a place where it's, again, easily found, prominent. Oftentimes this is a subject of debate. The identity of the product needs to be clear. That's pretty much obvious. The established name is required. And as was mentioned previously there needs to be clear indication when it's a controlled substance.

So essentially this is what we have for the bare bones requirements, much of it referring to the USP. But when it comes to establishing and approving a label, it's oftentimes subjective and we enter into conversation with our partners in industry to arrive at what we consider to be an appropriate label for safe use of the product. And for marketed products, which is what I'm responsible for, oftentimes companies go through a program to review their product line to see whether or not they feel that the product maintains its labeling in a way that continues to provide for safe use. And we encourage manufacturers to review on a periodic basis their entire product line to see whether or not they feel that the product maintains labeling which continues to provide for safe use. And we would encourage people to come to us and enter into a conversation about potential revisions or changes

to labeling to improve and continue to provide for safe use of their products.

So that's all I had. As I say, I'm fortunate to have followed the USP presentation because we do refer in large part to the USP requirements. So that's all I had and I'm looking forward to a good conversation throughout the day to see if we can come up with proposals and suggestions for how we can best continue to improve product labeling to ensure safe use. I wanted to make reference to one of my colleagues, a pharmacist Dr. David Lewis who assisted in preparation of this presentation. Thank you.

(Applause)

DR. VAIDA: Thank you, Dr. Duffy. Our next speaker is Vicki Drews. And Vicki is Associate Director, Global Regulatory Affairs for Baxter International. She has 18 years pharmaceutical industry experience and her primary role is in drug products packaged in flexible plastic containers. Vicki is going to focus on some of the challenges for small-volume parenterals faced by industry.

MS. DREWS: Can you see me? It's a common problem that I have. Well, while this is getting set up, I just wanted to thank the

coordinating committee for this meeting, for giving me personally as well as Baxter an opportunity to share our experiences and thoughts around small-volume parenteral labeling. But I also wanted to thank everybody in the audience for taking time out of what I know are busy schedules these days. And I also wanted to in particular thank a few of my colleagues, some of whom are here in the audience today, for providing me with valuable information and most valuable graphical information for sharing with you today.

So with that I am going to be speaking about labeling challenges for small-volume parenterals. And I did make a few notes so pardon my shuffling of paper here, but I want to make sure that I get you the right information. A quick snapshot of the next 20 minutes. I'm going to focus in on the scope of my discussion a little bit just to make sure that you have a clear perspective on the information that I'm sharing, and then we'll jump right into the challenges. We'll talk a little bit about the current state of Baxter's labeling. We'll talk a little bit about the solutions that Baxter has implemented historically over the years and discuss a little bit about the barriers that

we've seen in implementing those solutions as well as barriers to making those solutions effective. And then I'm going to give you some of my thoughts on what would be logical next steps.

So as my introduction explained, with insignificant exception the experience that I've had in the pharmaceutical industry has been limited to solutions in flexible plastic containers, both SVP as well as LVP. So what I'm going to be talking about today are flexible plastic containers with solution volumes from 25ml to 100ml. And I will be focusing primarily on the labeling on the immediate container although to a lesser extent I will bring up some factors of secondary packaging labeling, in particular the labeling on the over-wraps of our containers. And at Baxter, over-wraps take the form of either a transparent high-density polyethylene over-wrap or an opaque foil over-wrap. And it's important to note that these over-wraps are removed prior to use so their value as far as differentiating products is somewhat limited. That being said with regard to narrowing the scope I just want to make note that a lot of the challenges that I'm going to be talking about today apply equally to other types of small-volume parenterals, vials,

ampules, syringes, some to a greater extent, some to a lesser extent, but I think that a lot of the challenges are shared across the product line in general.

I want to talk a little bit about Baxter's SVP product portfolio. It kind of falls into two big buckets: diluents, which are the 5 percent dextrose solutions, normal, half-normal saline solutions, and then there's a bucket of pre-mixed drugs in many, many different therapeutic areas. And I wanted to give you this information for a couple of reasons. Number one, because I wanted to point out that for instance in the case of penicillins or cephalosporins, product mix-ups in this category could have significant health consequences if these products are administered to the wrong patient. And similarly, products in our critical care family such as our highly concentrated potassium chloride products could have significant health consequences if the right patient gets the wrong dose. So the challenges that we've heard this morning about or the problems that we've had in the area of medication errors are certainly relevant to this category of products.

So what are the challenges that we see?

Well, most obviously there are challenges in space. And complicating those challenges we certainly have the required content which Dr. Kelly and Dr. Duffy so nicely went over in great detail before I got here. But the content really in my opinion falls into two different categories. We've got required content that is driven by regulatory requirements as we heard this morning, but we've also got required content that falls into a category called legal sensitivities. These are statements that companies are reluctant to really take off of their labeling because of liability concerns. And some of these statements are rooted in history. And I think that it does us justice to take a look at these statements as we move forward to see do these statements really have value as far as the safe use of the product is concerned today.

The second category of content that I want to speak to a little bit is the consistency of content. I think as a company Baxter believes that having consistency in your labeling is really value-added, that you know we're using the same statements to describe the same things, we're putting those statements in the same places on the label, but we find this to be a challenging job because when we

submit labels for review to FDA there's an element of reviewer preference and a lot of these comments are very valid comments, and we make those changes, and we would hope that we could make those changes across all of our products, but in the end we inevitably - it inevitably leads to inconsistency in our and I don't want to say content, but the presentation of the information.

Another one of the significant challenges I think that we have for SVP and this probably applies to LVPs as well is in the area of color. There was a little bit of discussion, actually there was a lot of discussion this morning about color-coding and the values, but I wanted to talk a little bit about some of the limitations we see. Number one, I think that there really is a finite number of colors that we can use on our bag. And even though a printer might tell you there are 500 or 5,000 different Pantone colors, the difference between a lot of those colors are really not very noticeable. And second to that, some colors are just better than others for printing on a flexible plastic container. I think that we need to be looking at the contrast nature of the inks to really determine whether these are suitable and

effective for differentiation.

And also along the lines of color we've got the cost impact. For every color that you put on a bag there is a separate print plate that needs to be developed and manufactured. And although these print plates aren't made of gold, they are used in substantial quantities in the manufacturing environment. So there is a cost of equipment there and there's also an added step to the manufacturing process when we add color, and this is additional colors to the labeling. So not only does it add cost in terms of equipment, it also adds cost in terms of time. Another element of cost, and this was alluded to earlier this morning is the qualification of the inks. As was mentioned, these inks when they're applied to the immediate container do have the potential to migrate into solutions so there is a very robust qualification activity that's associated with that, with getting these inks into production including biological testing, chemical testing and then most often there is a regulatory approval process that's associated with that. So all of this put together you know what we found is that these challenges have limited our ability to really make timely changes to labeling.

So just to kind of give you a graphic in terms of space constraints, you'll see these are the plastic containers. And I don't have a pointer, I apologize. But there's a 25ml, 50ml, 100ml bag. All of the bags are the same width. They range - they're 3 and a half inches wide and the length varies from 4 and a quarter inches on the small bag to about 6 inches on the large bag. Oh, thank you. Ask and you shall receive. If I can figure out how to work it. Okay, well I'll figure it out when I need it. Apparently I'm just not pointing it in the right place. Okay. Can you see it? Oh, I see it's very faint there. Okay. It'll do. But what I did want to mention here thought that although the overall size of the container is quite constrained, the actual printable area of the container is substantially reduced. And this is due to manufacturing considerations, the seal area, et cetera, as well as the area that is reserved for the bar code. And I - this is probably - oh there. This area here really is the area that is reserved for the bar code. And these are not exact dimensions. I put them together myself.

With regard to labeling content, I'm not going to belabor this. I think that Dr. Kelly and

Dr. Duffy did a great job this morning. We've got that regulatory-driven piece, but what I do want to mention here, and I think Dr. Duffy was the one who alluded to it, is that not only do we have the space constraint on the container, but we have this fairly large quantity of information that we are required to put on the container. And in the end we still have to have labeling that's sufficient to allow for the clinician to visually inspect the solution. So it does present problems as you might imagine. And then again as I mentioned before, there are statements that we've been adding which are not really driven by regulation and standards, but are really by reviewer preference and again these are value-added statements and we tend to drive them into as many labels as we can because we do believe they're value-added. The last bucket which I talked about earlier is this bucket of liability-driven statements.

So at Baxter today what we've found that we have is really a state of induced similarity. And the similarity is between different doses of the same drug as well as between different drugs. And in the end - and the similarity really is an end result of the space constraints, the consistency

that we try to drive into our labeling and the color limitations that we have from a qualification perspective. And all of this really does impact consumer and patient safety.

So here, since a picture is worth a thousand words, is a graphical representation of two different doses of our highly concentrated potassium chloride product. And as you can see they look very much the same. This one is actually two different drugs. So despite the difference in names, the difference in quantity, dosing you know because of the font size that we're dealing with here and the limited space that we have available, the similarity in the colors, the two products do bear a resemblance. And it's worthwhile noting here, there it is, that this area on the left of all of this text, on both of these labels is the area that's reserved for the bar code.

So what has Baxter done in the past to try to address some of these challenges to enhance the safety of our labeling? Obviously our goals were to differentiate between different doses of the same drug as well as between different drugs, paying particular attention to those drugs that are used in the same therapeutic area. So we have gone into

using color differentiation as well as graphics to help enhance the difference between the products. And this has been used both on our over-wraps and most notably the foil over-wraps as well as on the immediate container. And I say on the foil over-wraps. The foil over-wraps are very nice for us because they have much larger printable space and we have a lot more flexibility in terms of colors to put on those over-wraps because the foil itself acts as a barrier to the inks permeating into the solution. So we do have a lot more flexibility and the timeframe to getting the ink to qualification status is much less.

And Baxter also has had some limited experience with standards. So I'll call them quasi-standards and I'll talk a little bit more about those later. So here's an example of some color differentiation and graphical differentiation that we've attempted on our foil over-wrap. In this case this is a fluconazole solution. But you'll see the color reversal is pretty obvious. And then in the right-hand side of the title block there's a graphic, the two circles for the 200ml code, four circles for the 400ml code. But again, it's important to note that these over-wraps as I

mentioned before are removed prior to use and therefore probably in most instances never make it to the patient bedside.

I think we saw this earlier today, but although these are technically LVPs, I think it's a great example of the use of color as well as graphics to differentiate between products. And I think it was Dr. Collin who showed a very similar graphic here, the difference between dobutamine and dopamine. Another example, color and graphics on the container. Again we're looking at fluconazole where we've taken the graphics that we used on the over-pouch and incorporated them into the label. So we've got the 2 for the 200, the 4 for the 400. And here it's even more noticeable, the space on the left-hand side of both labels that is consumed by the bar code.

So now I'll take you through some of the experiences that we've had with labeling standards. And again, these are real limited standards so I don't even know if "standard" is the right word. But we have two experiences, one outside of the U.S. and in the LVP market, and that's in Canada. And this standard was developed in part based on feedback and discussions that we'd had with Dr.

Cohen and others from ISMP. And the concept of this standard was really the prominence of key product information and the consistent location of that information so that you really have a know-where-to-look type of label. The second experience that we've had is with our heavy dextrose solutions. And I think somebody actually flashed a picture of this earlier this morning as well. These heavy dextrose solutions are used in the pharmacy for compounding total parenteral nutrition solutions. And in this case it was a cooperative effort across manufacturers of these particular products with input from HIMA and FDA. And it involved enhanced graphics as well as the prominence of key product information. We also standardized color for these particular solutions across industry and there was an effort to eliminate text as well as to standardize what text we determined to be critical to the product.

So here is a graphic showing the Canadian LVP standard, a standard label on the right, the old label on the left. And you can see that the three pieces of key product information, the drug, the diluent and the dose are very prominently displayed in a kind of a matrix or

quadrant format in the middle of the label. And this is a picture of the heavy dextrose labels. So you can see that the concentrations, which were the factor in a lot of the medication errors are prominently displayed both by increasing font size as well as graphical representation, and the pharmacy bulk package warning prominently displayed as well on the center of the label.

So what have we seen at Baxter as far as barriers to effective solutions? As I mentioned before, the limitations of the over-wraps. Although it's very tempting to do some differentiating using over-wraps, we do recognize that the effect of differentiation is limited here. Manufacturer variability. You know, I think this one is key. You know, if Baxter decides they're going to label their dextrose products in blue and Hospira decides that they're going to do theirs in red, the effect of the differentiation is lost. So we really need as industry and as regulators and patient advocate groups, we really need to drive consistency in standards into this area.

There's also human factors that we need to consider. And you know what we've found over time is that although some of the enhancements that

we've made to our products are really good and really effective, coming out of the gate there is an acclimatization to it. Customers get used to it and over time we see the ramp of product mix-ups kind of coming back to that previous state. Other factors include color-blindness, directly related to any decisions there might be around color-coding, language barriers that we're seeing in the hospital and other clinical environments as well as the unfamiliarity with scientific abbreviations. And this is particularly relevant for products that are used in multiple care environments, in acute care as well as in home care environments where the skill level of the end user may vary. And then you know certainly another barrier from an industry perspective is the cost of making changes. And it's not that we don't want to expend the dollars to make our labeling more effective, we just want to make sure that the solutions that we're implementing are the right solutions so that we're not facing the same problem two years down the road.

And I wanted to talk a little bit about SVPs in particular because that is the focus of this presentation and I did show you a lot of LVP shots. What we found is that these historical standards,

in particular the Canadian standard, really looks like an acceptable solution for LVPs. We've tried to apply it to our SVP products, and we find that the space challenges that I mentioned earlier really do inhibit our ability to apply this standard as it is today. The bar code space infringement is a significant factor as well as the quantity of the required text that we talked about earlier. So just to kind of again put you into perspective, I want to remind you that although the challenges that I was talking about really came from my experience with flexible SVP products, I do think that the challenges that I talked about do have relevance and applicability to other SVPs, in particular the space constraints which are probably more notable on other SVP products and content requirements apply across the board as well.

I also wanted to just talk briefly to the diluent SVPs because they do present a very unique challenge. Unlike the pre-mixed drug products which are single-dose pre-mixed products that are ready to administer, the diluent SVPs are used primarily for admixture. So the bar coding and other product labeling that's on that bag as it's printed at the manufacturer is not representative of

the admix solution as it gets to the patient.

So what do I think should be the ideal state today? Well, I think we need to foster bar code technology. I think it was a good thing. I think it has a long ways to go. You know, manufacturers are there with regard to getting the bar codes on the bag, but I think there's some quality issues. I think somebody alluded to that earlier this morning with regard to the scanning, and I think that there are probably still instances where hospitals don't have the suitable equipment for scanning all types of bar codes that are printed on the parenteral products. And I think that we need to take a look at our labels. We need to implement labels that are based on practitioner input, that are focused on patient safety, but that are also realistic and feasible for industry to implement. Personally I think we need to rely less on aesthetic and variable differentiations such as color and graphics, and rely more on the prominence of the key product information. I think we really need to force a good, a true knowledge of the product before it's being used. And last but certainly not least I think that we need to standardize these things across the products, across

all product lines, LVPs, SVPs, vials, ampules, syringes as well as across the industry. So I think this kind of boils down to developing some sort of labeling standard.

So what do I see as being the next steps? As far as the standard is concerned what do I see I guess as being the key elements of the standard? First of all, I think it needs to be regulatory in nature. I think that's very important. I think it obviously needs to be focused on patient safety. I think it should be developed by a multi-organizational task force and certainly representatives from the very people who are here today. And I think that we do need, as I mentioned before, to minimize the impact of human factors. Reduced reliance on color and non-value added text and increased focus on key product information. And from an industry perspective it needs to be robust and enduring to the extent possible so that we can minimize the cost of reactive changes to customer feedback moving forward.

So how do we remove some of the barriers that we see with regard to the standards itself or some of the product information such as bar codes that we do see as good differentiating elements?

Well, for manufacturing and for healthcare providers I think that we really need to give serious thought to investing in new bar coding technology, to reduce space requirements - and this doesn't have to be limited I suppose to bar coding technology. I mean, any kind of auto-identification technology. And there has to be an investment in the suitable bar code scanning equipment or systems so that the end user is getting the full benefit of those bar codes for maximum patient safety. And then for everyone I think that we really need to move in the direction of developing a regulatory standard. I think we need to drive consistency across all parenteral products. We need to reconsider the required elements for immediate containers for SVPs in particular, and I think this can be done by prioritizing information for smaller containers that have space limitations and provide flexibility to alternatively include product information on secondary packaging or package inserts.

So in wrapping things up you know what kind of benefits could we expect to see from a standard of this sort? Obviously we would be maximizing patient safety, but I think in addition to that we would realize benefits in the area of

efficiency. I think it would reduce the time for labeling development, and I don't know if Dr. Duffy would agree, but I think it may even reduce the regulatory review time. If there's a standard out there, we develop the label to meet the standard. If it meets the standard, I would think the label would be approvable. And certainly there are you know there is going to be unique situations where certain products are going to require different warning statements, et cetera, but I think that this would be a good goal. I think that we would also see reduced cost. The reduced cost in product development that gets directly to labeling development, reduced cost in the product lifecycle because we as industry would probably have a minimized instance of reactive changes to address customer feedback, and I would hope, although this certainly isn't my area of expertise, that by having labeling standards that meet everyone's requirements that it would streamline pharmacy operations and it would hopefully reduce the incidence of product mix-ups thereby reducing the cost of patient care. So that's all I had. Thank you.

(Applause)

DR. VAIDA: Thank you very much. We are

a little bit ahead of schedule so why don't we take a break, but try to reconvene back here at about 10 after 10:00, and that way there's a cafeteria downstairs. Those of you, that way you have a chance to even finish a coffee or that because they don't want food or beverage back in the room. But we'll take a short break now and then convene back here about 10 after 10:00. Thank you.

(Whereupon, the foregoing matter went off the record at 9:50 a.m. and went back on the record at 10:14 a.m.)

DR. VAIDA: All right. We'll get started back. And our next presenters are from Hospira. We have Dr. Mary Baker who's Senior Medical Manager, Global Medical Affairs and Dr. Tom Willer who's also with Hospira and is Global Regulatory Affairs Director. Dr. Willer previously worked with Abbott Laboratories as Regulatory Affairs and Dr. Baker's responsibilities include directing clinical programs in parenteral nutrition, labeling and promotional review, drug compatibility, large- and small-volume injectables and medication error reduction. Their focus is going to be on challenges with large-volume parenterals.

DR. BAKER: Thank you, Allen. Can

everybody hear me? Great. Okay. Again, I'm Mary Baker from Hospira. I'm in Global Medical Affairs. I work very closely with our regulatory group and Tom Willer, also our graphics group and our label control group. We've got hundreds I'll just say of large-volume parenterals and in terms of labeling changes when you include our large- and small-volume parenterals you're talking several thousand labeling changes every year. I'm going to give the basic overview of the challenges we face and then Tom will give more of a case study presentation. For those not familiar with Hospira we're a global specialty pharmaceutical and medication delivery company. If you want to find us we're about 30 miles north of Chicago in Lake Forest, Illinois.

Jim Kelly also previously mentioned the definition of large-volume parenterals as found in USP General Chapter 1. And the challenges we face at Hospira are certainly found in these main categories, but are not limited to these categories. First of all, the limited amount of colors which Vicki previously mentioned, and I'll go a little bit more into that. Limited space. Even when you're dealing with something greater than 100ml, there's still a lot of information. Mike showed a slide of

a large-volume parenteral with a lot of information on there and that was a liter container. Printing technologies and government regulations.

As far as limited label space goes we deal with LVP plastics with basically two different types of material, polyvinyl chloride or PVC is the most common. It's been around probably since about `71 and polyolefin is a relatively newer material that we work with. Printing technologies, however, really haven't changed all that much. Hot-stamping is the most common. It's where you take a metal plate, a hot metal plate, and you apply it to an ink ribbon. And that's pretty much what most LVP labeling uses. Thermal transfer, a little bit newer process, but that results in slower line speeds, it's difficult to use with continuous motion and you have size limitations. You need certain amounts of space around the printing.

Here's an example of a hot stamp. Typically made of titanium or steel. It's a proven technology, again the current printing standard. Tons of validation work, years of validation work to rely on. And it's pretty durable. However, you have a limited ability to minimize the font size. Take a look at that LVP that Mike showed and it

would be really nice to minimize some of those letters in order to more prominently display the name of the drug, but with the printing technology the more you minimize the font, the greater chance that the letters will run into each other. Hot-stamping is a direction-dependent process and the colors are limited. In terms of qualifications, basically the inks that have been qualified are blue, black and red with white with the thermal transfer. Optimally you use two colors per label. That's for setting up the processes. You do need open space between the color blocks, at least a quarter inch because the plates vibrate.

And there are challenges with label content changes. Anytime we change a hot stamp plate it's time-intensive, labor-intensive, somebody's got to do it, and it's expensive. Now, a plate runs anywhere from $800 to $1,200 per plate and a line may take up to 16 plates. So that can, when you have hundreds of LVPs, that can get into quite an expensive process.

In terms of color-coding, both Tom Willer and I spoke at the FDA meeting in March of 2005 where Hospira took a position against color-coding. The reason we did this was that there are a

lack of colors. A Pantone chart looks very nice, but subtle shades of green, subtle shades of blue, you can't pick them up. And again, you have to qualify each color for the immediate container. Color-blindness in certain practitioners. Hospitals have irregular lighting. It's not all what you see on TV. You have very nice lighting except when you go into a patient room it's dark, you don't want to wake up the patient so you have limited lighting. And we firmly believe that the drug name and the strength is the primary identifier. Government regulations which Vicki also mentioned. There are evolving standards for drug labeling, one being the prominence of the national drug code, bar code placement, putting a unique bar code on over-wraps and radio-frequency identification. We are missing a slide. Okay.

Hospira has an active label enhancement group that meets on a monthly basis. We have practitioners from medical, regulatory, graphics, label control and we review either entire product lines or we review classes of drugs or in many cases complaints that have come in from the outside. And each item is reviewed no matter if it comes from the customer or if it's an internal process and we do

make changes in our labeling. Now what I think some practitioners don't realize is that the time it takes to make the changes, that even if we do make a change, that the labeling has to be changed and then to get it into the manufacturing process, if a product is not made frequently, if it's made only once or twice a year the changes won't be seen immediately. And Hospira believes that this is not just a Hospira issue. And it was said very well in the ISMP newsletter that fixing blame on FDA, the pharmaceutical industry and medical device companies isn't the answer. We all need to join in a concerted effort to get all key stakeholders to work together. And I'm going to turn the presentation over to Tom to talk about some case studies that we've had at Hospira and some recommendations.

DR. WILLER: Thanks Mary. Labeling has come a long way over the years and in this slide you'll notice a variety of methods used to assist reading the labeling such as different colors, graphics, font size and even white space. We've tried to do a whole different variety of things to differentiate the products. There's a tremendous advancement since the early 1980s when I worked at Beecham Labs where we had simply two colors for our

labels. All human products were in blue ink and all vet products were in green ink. Medical practitioners actually had to read every label. That's sort of a new concept today seemingly.

What I'd like to show here is examples of labeling on the primary container. You kind of see the way we've tried to differentiate them. Notice the differentiating conventions on the strength. We've used some vertical bars and the differentiating the vertical bars depending on the individual concentrations. See the extra-large font for part of the drug name, namely dopamine. This is called tall man lettering as Mike pointed out and we use this for drug names that might be confused with similar names, such as dobutamine.

And again, as Mary and Mike and others have pointed out, we do have a little bit more ability for foil over-wraps because they have more printable space than we have on the flexible containers. As Mary pointed out, flexible containers generally are printed online from plastic containers that were actually buying the - I'll call it virgin flexible material is actually folded, sealed and printed online. So we don't print anything ahead of time. It's all done in one

continuous operation, therefore making changes rather a big activity. Again, notice the consistency of labeling information that you see on these compared to - to support the inside container. And as Mike pointed out, we tried to put the flip side of important information, any information for our products when we can. But as he also pointed out, this is a significant additional expense. It basically doubles the cost of labeling. The goal of course for labeling is communication and the clearest possible way to do this is to try to support patient safety. This may be done via human-readable printing or via machine-readable bar codes. We've look at that also.

Now, this is interesting to Mary and I because we work a lot with trying to improve our labels. And in the 1990s we worked a lot with Jerry Phillips at FDA to try to come up with a system to review similar-sounding or similar-looking labeling. Here's an example of a frequent conundrum for a drug company labeling department trying to create new labels. There are more than one drug that starts out with the letter `H' of course. In this case, drugs are used in the same area of the hospital. Differentiating the labeling is crucial.

So here are examples of labeling strategy to differentiate heparin. And you can see the different ways we've tried to do it.

I heard a proposal this morning that said there ought to be a standardized presentation of labeling information. What a great idea, but not a simple one to implement. For these three products, we've tried to put the key information in different locations so that it does look different. But be very careful if we try to move forward with a standardized approach to labeling, like we always want the concentration to be at the beginning of the drug name or at the end of the drug name. Great idea. It's going to lead to them all looking the same. And again, we're trying to use, one of the other speakers, Mr. Duffy or someone else was talking about human factors. That's very important in label development.

So here's our strategies for labeling and differentiating heparin. Note the information in red and the information in black. As Mary pointed out, we have a limited number of colors that we can use and we have a quarter inch space between the colors. So if we went to more colors or we went to red/black/red, we'd still need another quarter

inch of lost space. Note that the key portion of the product name was shortened to highlight its key position while the complete name is lower in the label. This greatly helps communicate the product name and the concentrations to the user. So it serves no purpose to just have this full name on here and possibly just delete this information. And so we've tried again to highlight the critical and important pieces of information, namely the two USP units or the 25 USP units, one for - two USP units for arterial line, 25,000 for pulmonary embolism.

Here, please note the use of large font and the effort to highlight the difference between the product names with the goal of helping to prevent similar product names being mixed up again in a busy hospital setting. Hextend uses the exaggerate `X.' It looks sort of ridiculous, but it sticks in your mind, and that's the whole purpose of labeling differentiation. And after you kind of look at it awhile it seems kind of cool, so I really admire the people that came up with this idea. Also note the different placement of the 6 percent before Hetastarch.

Under label enhancement, as Mary pointed out, Hospira takes our labeling responsibility very

seriously. In the early 1990s we created a label enhancement committee that meets monthly to review the selected labeling. We examined two similar pieces of labeling and see if there might be areas for improvement. As noted in this slide, there usually are things that can be done with white space, font differentiation, word and concentration sequence, graphics, tall man lettering that I previously mentioned. You can kind of see them all here and how they do look quite different.

Is there anything that could be deleted from the primary container? And we believe yes. All information on the primary container is repeated from the foil over-wrap, from the product insert and from many companies' websites and by the end of 2006 we're told that all electronic copy of labeling, the insert, will be on the National Library of Medicine's website DailyMed. So there's multiple places to get the full labeling information in addition to the limited space on a product label. Could the primary labeling be streamlined to reduce redundant information and thereby freeing space for a larger print? We believe yes and we're going to present some ideas here.

So again, for tall man lettering it

leaps out at you the differences between the two and that's the whole point here. Tall man lettering provides clear differentiation between somewhat similar names. And as one of the speakers pointed out, if there is a growing or a list from the FDA of preferred conventions for tall man lettering or for future products, that's a great idea. And if we move forward on expanding that name, someone should take the lead, possibly OGD and look at the drugs that are coming off of patent for the next five years rather than looking at the past. There's a great rush right now for new generics to enter the marketplace and it's important that we think about this proactively. And again, labeling review time at OGD sometimes takes awhile as they go back to see what's on a branded product. It's after the fact that OGD attempts to standardize some of this labeling into the 21st century kind of concepts of label improvement and this takes time and redundant effort, I think.

So here's how we currently label some of the products. Notice the huge amount of real estate that's devoted to the "each 100ml contains" statement in which every ingredient is normally written out in full. Is this needed? Is this

statement needed here or could scientific notation be used, for example? Make it a little easier to see. As noted in the previous slide, this is repeated from the over-wrap in the package insert as well as readily being available online. We have the capacity to print lowercase letters if we could increase the font. One of our problems with printing on plastic online is the plastic is flexible and it stretches when it's hit with the heat imprinted printing process. So because of the font sizes, if we go to uppercase/lowercase, the lowercase letters are smaller. And for us, I know it sounds ridiculous, but the lowest we can print with clarity is 7pt font and that's not a font that I think the medical community would like us to be printing at, yet we're constrained by the huge amount of information. It's a bit difficult to read.

However, there are other options. Let's look at the same three labels after being revised. Now, we've added white space. Looks very different. And we've added paragraph breaks. And again, look how different this one is from the preceding one. We used scientific notation. We've uppercase/lowercased the label. We've bolded the

caution. Mike had mentioned that earlier as a great idea and we put in larger font sizes. And this is the case where we really didn't remove anything, we just used scientific notation. So it's a spectacular improvement I believe.

We're excited to be here and to be able to present some ideas for discussion. We enthusiastically support re-evaluation of product labeling to help enhance patient safety and help reduce medication errors in part potentially due to labeling. We encourage any efforts for the same standards to be applied in all FDA review divisions in the development and review of drug labeling.

Now, in industry we're encouraged frequently to think out of the box. And so we thought about possibly putting in a smiley face for pediatric dosing, or possibly this is labeling that is for the future. However, in more seriousness, in summary, we're in an exciting time of examining the criteria for evaluating what is a good LVP label. We support any strategy to review aspects of what should be the mandatory information on an LVP label and what can remain only in the package insert. We support considering the removal of some redundant information that is in the LVP over-wrap and the

primary container. The fewer words that are on the LVP container label, the larger we can make the remaining critical verbiage to identify the drug name, concentration and warning information. Dr. Mary Baker and I look forward to the outcome of the important meeting we're having today in evaluating drug names for similarities as well as overall evaluations of important labeling content. Thank you.

(Applause)

DR. VAIDA: Thank you very much. If we could - you could stay if you want. And if I could have the speakers from this morning's programs come up and take a seat. And in your program with the agenda in that that you received this morning there's also a set of questions that we had hoped to answer throughout the day today both with the morning session and the afternoon session, some of these discussion questions, and I actually have them up on the screen here. There are microphones at your places and if what you could do is raise your hand if you have a question and then I will point to you and hopefully be able to get this right. And there's a button on the microphone so make sure that you put the microphone on and then when you're done

with the question to shut it off. And if you want, you could direct them to individual panel members. So do we have any questions to start with from the audience? Anyone have anything? Yes.

AUDIENCE MEMBER: I have a question for the FDA. Does the FDA require all these products to be reviewed prior to marketing, and if so do you require submission of the final color printed label for evaluation before you give market authorization?

DR. DUFFY: Well, the answer to the first part is that yes we do review. We need to review and approve the label prior to marketing. And that's a process where the company would provide copies of proposed labeling, and this can be provided in mockup. It need not absolutely be provided, the final printed label be provided, but that's clearly more helpful. But we do need to see at least a mockup in full color in full size for our evaluation. And it's a matter of, in the course of, I don't know how many people are familiar with the approval process, but at the end of a review cycle the entire label is essentially negotiated. And the focus is primarily upon the insert label, the indications and the warnings and all those - all the other aspects of the drug that were developed during

the clinical trials. But another key component would be the immediate container label, the carton and any other related labeling that goes with the product itself.

Now at FDA the insert label is primarily the responsibility of the clinical division and the product itself, the immediate container carton, et cetera, that part of the labeling is the responsibility of the chemistry manufacturing controls group. And we work in collaboration with the medication errors division, the safety group and a full evaluation is made both from a clinical - the immediate container label is a collaborative effort, review of the immediate container label is a collaborative effort with the clinical, the safety and the manufacturing people.

DR. VAIDA: Thank you. Yes?

AUDIENCE MEMBER: My question is also to the FDA. My question has to do with generic labeling. When we submit labeling as part of our submission with the generic labeling, we will try to remove some of the redundant text that's on our smaller labels and put it on a container label and it is quite a few times met with resistance by the labeling reviewers that they would like that on

there because it's on the innovator's labeling. Will this initiative then be able to allow us to do that, or will we have to wait until the innovator's labeling has made all of these changes before the generic will be able to make these changes?

DR. DUFFY: Generic labeling is supposed to be the same as the innovator except where there are specific obvious differences that need to be made - changes that need to be made. For example, the manufacturer, the name of the manufacturer. But the labeling does need to be the same as the innovator. Some minor variation in appearance is acceptable, but the content needs to be the same.

AUDIENCE MEMBER: The content is the same in essence because our labels are just - our container label may be smaller so we cannot fit the entire storage statement on the container label, or we may not be able to fit "each ml contains." So it will be on the carton label as allowed in the CFR, yet as I said, it has been met with resistance from the OGD, the labeling reviewers stating that because the innovator has it that we also need it. I'm just - that's where I'm asking that question towards. Will that then change with this initiative?

DR. DUFFY: I don't know the answer to

that. But the basic principle is that the generic product should follow what is on the innovator's label. Now if there are space limitations, that's clearly an issue that needs to be discussed. Simply provide adequate rationale for the changes that you've made and presumably it would be - if it's reasonable it would be accepted.

AUDIENCE MEMBER: Hi. I have a question again for the FDA following to that question. It's like if a product that is generic now and they discover, like Mike Cohen reported in his report, many medication errors based on a generic name, and if they want to follow it, would you accept it even though it wasn't what they call in the innovator original labeling packaging? I hope I make myself clear. We have a lot of medication errors that we reported in a lot of drugs like has been mentioned is going generic. I had asked the generic company about something. They said oh, we can't do it, it goes back to the innovator. They have to do it. So in terms of patient safety, if they, how you say, approach you saying, okay, we're not following the innovator, we're changing the labeling concept with a high alert drug or whatever it is, would you allow that through because you know many multiple reports

being given, like ISMP, USP, that are a joint collaborative effort. Would you expedite that or you would send it back to the innovator waiting for them to correct it? That's my question.

DR. DUFFY: I mentioned that the generic label can be different in certain ways from the innovator and one of the ways, one of the justifications for having differences is safety. What the process would be at the agency would be that we would discuss the change and the rationale for it and we would permit a change and the agency, if the agency felt that this was a safety issue we have procedures for going back to the innovator and raising the topic and seeking to make changes if they're appropriate there as well. The matter of timing, I'm a little uncertain whether the generic would be permitted to change before agreement was reached with the innovator, but if we find that there's a safety issue in the labeling we would certainly address it for all manufacturers.

AUDIENCE MEMBER: Okay, thank you. That was my concern.

DR. VAIDA: Mike, did you want to?

DR. COHEN: Just a little bit of follow-up. This really is a serious problem because we do

recognize problems out there, we hear from the field and we do report them. We try to communicate them. And we recognize that there really is a need for change and it can go on literally for years before that change is eventually implemented. I'm really concerned about this inconsistency and you know not to put FDA on the spot, but the enormous amount of time it's taking for example to get guidance to the industry and to their own people within FDA. And this is what's causing some of the inconsistency and it's terrible. I mean, we have calls from companies for example, they'll ask us because we can freely discuss things with them obviously, and they'll ask us for you know how do you think FDA will react to this or react to that. We'll give feedback to the company based on what we've been told by people within FDA and then they'll actually make a change and then submit it you know with a new product for example and it'll get rejected by another person within FDA. So that's a very serious issue I think and it's really affecting patient safety and I really think we have to do a much better job. We've been told for example guidance statements are coming out now for the labeling and the packaging since the 1990s. I heard Jerry Phillips talk about that in

1998 or 1999. For example, the way some of the label expression of the concentration and how much, for example, you know should a vial of 10ml express the entire amount in the container primarily and then per milliliter. Where should it appear, should it be within the same rectangle so you can see both pieces of information or should it be per milliliter and then the volume elsewhere. There's no guidance out there and everybody does their own thing and the nurses get confused. They see it one time in one way and they see it another time in another way and it causes very, very serious errors. Fatal events. And for this to go on since 1999 and probably even before that is just, it's terrible. You can't have that continue. And I'm sorry to have to put it that way or you know, but really it's a serious issue and we've got to get something done with these guidance statements to move things forward. I don't know what's holding it up.

DR. VAIDA: Anyone else? A question up here?

AUDIENCE MEMBER: A number of the speakers have talked about how do you reduce label clutter and I think one of the speakers mentioned that one possible way is using scientific notation,

but are there other thoughts as to how one can reduce label clutter since that seems to be a recurring theme?

DR. VAIDA: Anyone want to start with that?

MS. DREWS: Well, I think probably one of the most obvious ways to reduce label clutter is to take a critical look at the clutter and to determine what really is critical product information that needs to be put on that label. I don't know that I personally am fully in agreement with scientific notation and this is just an anecdotal story that I'll tell you, but we've actually had customers that have called us up and said can you tell me what NaCl means? So you know I don't think that we should assume that everybody that is looking at these products are skilled clinical practitioners. I think there are you know we really need to look at the flow of the product in the clinical environment to ensure that the people that are actually placing the product in the inventories are able to understand the labels. And that gets to the human factors I think that I might have mentioned related to understanding scientific abbreviations as well as language.

DR. DUFFY: Well, I think one way that this could be addressed would be through label comprehension studies. Developing different appearing labels that highlight certain aspects of the label, include or delete others and see whether or not people actually in a kind of almost clinical setting would be able to comprehend the label. I think the human factors is a very important aspect to label development, there's no question about that, and the comprehension studies I think are key.

DR. VAIDA: Any other comments from the panel?

AUDIENCE MEMBER: Kind of tagging onto that last comment and this question's addressed to the panel in general. To what extent are human factors engineers or other experts in that field or in the fields of human cognitive science involved in evaluating or assisting in the design of these labels? For any of you.

DR. WILLER: I'm with Hospira and most of our products are generics so we run into the issues raised before. If the innovator's got it, we've got to have it. If the innovator's got all the clutter as we talked about here then we've got to have the same amount of clutter. Again, we're

very, very constrained by the labeling space issue and is all that information needed for today. Does the practitioner - does the nurse administering the product read the "each ml contains." I don't know. Perhaps it's more important for the pharmacist who selects the medication, but at the administration end of it is all that information beneficial? And again, your idea of a cognitive study might be useful.

DR. VAIDA: Any other?

AUDIENCE MEMBER: Actually, the person before me just had my question, but I don't think I got an answer that I understood so I'm going to just restate it one more time. And that is from an industry standpoint, if you could just comment to the quantity of human factors engineers or cognitive psychologists that are actually present in your companies that look at the labels are able to look at usability studies when these labelings come out. If you could comment to that.

MS. DREWS: I'll give it a shot. I don't know. Like Hospira, a lot of the products that I get involved in are generic products, so we are - the only labeling design that we really have, the only labeling design process is literally a copy

from the innovator label onto our current container. That is not to say, however, that when new products are in development that there are not, and maybe there's some other folks in the audience that could speak to this a little bit better. You know, when we do have novel products that we're developing new labels for, I believe that we would involve a human factors analysis in that and that would be part of our clinical appropriateness type of activities before the product were approved for launch.

DR. COHEN: I'd like to comment as well. Part of the problem I guess is that there really isn't a heck of a lot of research as far as you know what makes for a good label, what should be positioned in certain locations, how large should it be. You know, some of the things we've heard about putting the strength before the product name versus after, below, above. If we had enough room I think on the label we probably could end a lot of these problems by making the numbers large enough, et cetera. But when I say not enough research, even the use of tall man letters. There's only one study that we even know of that actually shows at least some benefit to that. Most of the practitioners, their gut feel is it's really helpful, but there's

not a lot of research even with trademark and medication errors or non-proprietary name and medication errors to the extent where it's very difficult to get people to make the changes that we think are necessary. So that's one thing.

I think what a lot of the companies have done which I think is a great idea, especially in the area of trademarks, is involve practitioner panels to look with a critical eye at the product name or in this case it could be the packaging and the labeling. The Institute of Medicine Committee on Preventing Medication Errors which I served on made that recommendation that you know companies should involve practitioners, that there should be an analysis of the labeling, the packaging, the drug names with feedback. So that's at least somewhat helpful. It allows them to position the product in the area that they use it. But I think we do need more research and probably the human factors folks could help in that area.

DR. DUFFY: No, I think that these comments are good, that the human factors studies really would be beneficial. I don't think there's any question about that. But in my experience the primary focus is on the trade name and look-alike

sound-alike kinds of studies, whether or not it's easily remembered, you know. That's the focus. It's from a commercial perspective primarily, rather than emphasis on safety.

DR. COHEN: Yes, we've seen hardly anything with a requirement for labeling and packaging. I think almost all of the companies now, if they're coming out with a new product before they you know determine with finality what that trademark is going to be, that's so important to them that they will in fact test that out in the field. They have a lot of practitioners involved. There's several groups that do that. And it's very helpful I think. But that has not crossed over to the labeling and packaging for the most part. It should be there. I know it adds some expense but it can save a lot of grief and obviously a lot of patient harm if it's done. So I think that's something that we'd like to see a requirement. That was mentioned in the IOM report.

DR. VAIDA: Yes.

AUDIENCE MEMBER: I'd like to follow up one more question on that comment. When one talks about you know getting input from the practitioners on the label, which particular practitioner are you

looking at? For example, are you looking at the end user who's at the bedside, perhaps the nurse, or are you looking at you know the pharmacist or the person ordering the drug because obviously there's package inserts, there's the cartons which are present initially, but by the time you get to the bedside. So when you're designing the label on this final container who are you designing it for?

DR. COHEN: You would be looking primarily at the end user. That is, the nurse-patient interface, the doctor-patient, the pharmacist-patient interface. But it's not just there. It could also be in the pharmacy. I mean, you'd want a wide array. And a lot of it is product-dependent too. Where it's going to be used. You might - if it's going to be used in the operating room obviously you'd want to involve anesthesiologists, nurse anesthetists, et cetera. So when these studies are designed, for example for trademarks, that is all taken into account. And they go right for the people that are going to be working with these products. That's a big part of it. They actually have a standard process. I kind of outlined it on one of the slides. We didn't have time to go over it, but you know who will prescribe

it. How does it even get into inventory. Who will prescribe it, how is it processed in the pharmacy, who will mix it, and it goes on and on all the way up to the point where it's actually given to the patient. All those individuals can be involved with the packaging and labeling study.

AUDIENCE MEMBER: I'm sorry, I just wanted to respond to your comments, Mike. I really appreciate hearing that the end users need to be involved in the evaluation of these products. I was an IV pharmacist for 20 years and an end user and experienced you know some of the challenges that we've talked about.

Once more to kind of turn back to the human factors issue, there's a lot of science - you're right, there's not a lot of research about how labels might best be presented or formatted, but there is a good bit of science and research about how human beings process information. And I think that there's an untapped resource in that field for applying those principles here, it just hasn't been done yet. So I'd just like to offer the comment that perhaps companies could look a little bit more closely at employing the expertise of these people to help us with these problems.

DR. COHEN: By the way, can I just finish off? Thank you, that's an important comment to make, but I want to finish up with something I said earlier that just popped into my head. In the area of trademark review, there's at least some idea of how to do that. There's no official guidance at this point I guess, but it has been mentioned in some statements that have come out of FDA. But that's something that FDA could lay out you know. How should this analysis be done, the failure analysis. How should it be done, who should be involved. There could be some guidance for that as well and I think that would be important to have.

DR. VAIDA: Yes?

AUDIENCE MEMBER: We heard three presentations about what's currently required, either from USP or FDA about what labeling is required at the current time. What I didn't hear was why. I mean, we've identified at least indirectly a great deal of the labeling which may or may not have any value to the practitioner at the bedside. So why is it there?

DR. VAIDA: Maybe Diane or Jim?

MS. COUSINS: I can give you a historical perspective only so far back.

DR. VAIDA: A good question to basically go through with the process. We heard some of the synergy here with the USP and the FDA. Do you want to?

DR. DUFFY: Well, I'm not sure how to respond to that. Things do evolve and one - you know, there's a - when you conceptually think about having a label, what you start out with is trying to be complete. And so I think the human tendency is to say well, if you want to express what the product is you should list what is in it. So for example some of the electrolyte solutions or total parenteral nutrition products, vitamin solutions, many, many components present. And so conceptually you think well, you want to say what it is, the identity as I had mentioned. There is a regulation requiring that identity be expressed. So the tendency would be to say all right, all the components need to be there. Therefore, that LVP you figure oh it's pretty good size, it's big, may as well go ahead and use that territory and fill it up, when I'm not sure whether or not the practitioner really needs to - first of all, is anyone going to read it? And secondly, is it really necessary for safe administration of the product?

This is debatable I think and frankly we'd like to hear comments from people about you know practitioners, people from industry, what their feelings are in terms of what is really necessary on a label. I had mentioned in my presentation that there are some minimum requirements in the case where there isn't much territory on the label. Now, how about a label where it's larger where you could for example have much more than that expressed? Is it really necessary? This is something that can be discussed.

Now, in terms of the review at FDA, one primary concern is safety in review of a label. And so if an argument can be made by the manufacturer possibly based upon a human factors study or something of that nature, that's something that we would certainly want to hear about and you could develop a rationale which we certainly, if it were persuasive I would think we would agree with it. If the clutter could be reduced and therefore prevent medication errors, I think that could be a very persuasive argument.

MS. COUSINS: I think I'm over the shock. I think I'd like to say just generally speaking, and it kind of keys off your word

"evolving." When USP standards are created, they are reflective of the best thinking at that time by the expert committees that create those proposals. But those proposals also go out for public comment. And as you saw with the joint committee from the early `90s, there are comments that come back that may require the proposal to be modified in a way that sometimes it compromises you know the opinions of all the parties that be. I think the most important part about that process though is that it is a continuous revision process. So where we are today does not have to be where we are tomorrow or a year from now. And so the purpose of my presentation earlier was to let you know that there are things that can change, even things as drastic is changing the regulations as they did in the early `90s that can accommodate the best thinking of the time today. So I would encourage you to keep that in mind as we move forward. Really, what we decide on as standards at some point in time may no longer be the best thing to be doing. But we need to hear from you.

DR. WILLER: One of the problems with drug safety and patient safety as we think of better ways to have labeling. An example would be,

"Warning: Contains sulfites." Great idea. So the agency said put it on there. It's rare to never agency has put this on but takes something else. So when we put the new "Warning: Contains sulfites" on there we've got to reduce the size of everything else on the label. So have we accomplished the goal of that important new information? I can only think of one instance and maybe other experts would remember more of FDA ever allowing us to remove something. That was the warning federal prescription law. And here again it was almost a perfect move by the agency, or at least by the law-writers, the people who wrote the law, which was they wanted the Rx-only put on there. What's the importance of the word "only"? It's either an Rx drug or it's not. I'm not aware of the same Rx drug being OTC and Rx at the same time with the same name. So again, we've got to put on that extra wasted space for O-N-L-Y. It's a small thing, but all these things add up in the very, very restricted space that we have.

And you know we try to do the best we can. We hear competence and complaints as I do from my relatives about labeling being too small. I'm as irritated as anybody that we're going to 8pt type or

something. It's hard for us to print that and so we would like to have it larger for the patient safety issues, but we're sort of constrained.

DR. VAIDA: Yes?

AUDIENCE MEMBER: Just wanted to give a little bit of an opinion to the person who asked the question about where did these regulations come from. And certainly I don't work for USP or FDA, but I believe it's rooted in public policy from when the FDA was not the FDA as we know it today, but was sort of an infant group as a part of the Department of Agriculture. And I think that this all developed as a part of that and has become what it is today. I think Tom that you make an excellent point with labeling that when we do have to add something that the agency wants us to add, they seldom ask us to take anything off. And you do end up with a lot of label clutter. And I really like the presentations this morning and Mike, I see what you mean about label clutter. We all have that and I thought that Tom had a very good label that he put up that used the chemical symbols and had the white spacing and everything. But one concern that I have about taking a lot of information off of the labels is what Vicki brought up, the legal sensitivities.

Because the package insert seldom follows this product to the bedside or to the end user and so you have to rely on that label that's on the actual product, the unit of use. And I sometimes have a little bit of a worry if we take a lot of information off, are we then going to move ourselves into a failure-to-warn situation where the users will say, well if I had had this information on the label, I would not have made that mistake. So I just wanted to, always being the conservative in the group, card-carrying conservative, I just wanted to bring that up that yes I think that we can make changes and good changes to the labeling, but at the same time we have to look at these other considerations about that the package insert doesn't follow - the box doesn't follow along and you end up with this product with a label that needs to have all of that information on it.

DR. COHEN: Keep in mind too, you know we're in the age now of you know machine-readable code, RFID, things like that that you know perhaps can bring that information right to the bedside. For example when the nurse scans the bar code or you know reads that RFID chip that might be embedded in the product they could get that warning information

very easily. So we have to think about the future too.

AUDIENCE MEMBER: No, I agree absolutely and Tom also made a good point that labels are available on the internet. You know, you can get this information all the time. But in the actual hospital setting where - and they may be in an emergency situation and people are extremely busy and running around and grabbing a product, they don't have time to go to the internet to look up to get information on that product. And I think that you know you really have to have a certain amount of information on that label.

DR. BAKER: But some of the information though doesn't really contribute. You know, "Usual dosage: see insert," doesn't tell you much other than to look for the package insert and you're hanging the bag and it's like well now what. So I don't think that that's really providing information. And also, can we condense some of the verbiage. "Use aseptic technique, consult with pharmacist if available" takes up a heck of a lot of space.

AUDIENCE MEMBER: No, I absolutely agree. All I'm saying is that if we do start to

remove information from the labels, we have to take everything into consideration and especially the reviewer differences at FDA and real problems. We do have real problems in terms of doing a generic label and having to be similar to the innovator. And we at B Braun have tried to add geriatric information and pediatric information to package inserts for some of our products and have been told that we cannot put that in there because the innovator doesn't have that information in their package insert. So you know there are constraints that we have to live with and it would be nice if we could put those things into a generic package insert. But again, the agency is constrained as well because they have to live with the same regulations we do.

DR. VAIDA: Up here first. We'll come back and then I think Jerry has a question.

AUDIENCE MEMBER: It's exciting that we're looking at standardizing labels and I think Dr. Cohen mentioned about machine-readable code. My concern is that when you look at bar code technology, there really isn't a standard format and there are so many different ways that manufacturers either put information or don't put information that

I think if we're going to try to gain real estate and share information there has to be standardization in the type of information that can be machine-read so it can aid either at a bedside scan or in a pharmacy scan or even if a material handling scan. So just I think it's absolutely critical notwithstanding the labeling that has to go and be printed on the bag is that the bar coding format is standardized so we're all using the same format so it has the same amount or the same type of critical information that can be shared by all users.

DR. VAIDA: Okay.

AUDIENCE MEMBER: I want to offer my apologies. I wasn't meaning to attack. The lady below expressed me much more eloquently than I do. My concern was that in this discussion that we in fact take a look at what we do now and ask ourselves why we do it because it may be there's a good reason. And in our haste to clean up the labeling I did not want to throw out the baby with the bathwater.

DR. VAIDA: Very good comment. Jerry?

MR. PHILLIPS: I think we can find the origins of FDA's labeling regulations in the Food,

Drug and Cosmetic Act when it was originally done. There are labeling regulations that were put in the Act itself or in revisions to the Act. And then FDA then implements those through the Code of Federal Regulations through rulemaking that elaborate more on the intent of what Congress put in the Food, Drug and Cosmetic Act. Just to change the "Caution: federal law" statement required a change in the Food, Drug and Cosmetic Act itself and then a change in the Code of Federal Regulations. So that is quite an intensive process to go through from the agency's perspective and Congress. Thank you.

DR. VAIDA: Yes, sir.

AUDIENCE MEMBER: Yes, I had a very similar thought as a couple of things that have been expressed. We sort of have an 800-pound gorilla in the room here to a certain extent. I think several of the presentations have made it quite clear that space is the issue. And a lot of the priorities and values of different kinds of information. For instance, we have discussion about complex studies of human factors analysis. Well, if some of the fine print, some of them even inactive ingredient statements, et cetera, could go away or be dealt with in a prompt fashion, so many of these other

issues become so much easier. But we have the momentum problem because we sort of have a disconnect between the safety issues that should be a primary public health issue being expressed here by all sides, and yet you have an act from Congress and a whole set of regulations and the timing mismatch between the level of concern and the cycle time to get any of that changed. I mean, we recognize that FDA, you know what would you do, say take your existing regulations and tell the FDA reviewers to exercise a lot more discretion? I wouldn't do that if I was an FDA reviewer or somebody you know finalizing the labeling.

So how do we get a mechanism maybe similar to this but more focused, getting to higher levels of the agency or the USP or both. Because the transmission of transmitting all this good energy to the road and getting somewhere as Dr. Cohen said just doesn't seem to be there. A line takes 10 years to get authorized to change. So there's a mechanistic problem in the industry-government interface here in getting these things on a higher priority, having I don't know a blue ribbon committee or something that could get whatever's necessary in the Act and the regulations on a much

faster turnaround time. The generic companies. It's very impressive how few options they have. You know? I've dealt with generics as well as brand products and there's just no latitude with a generic reviewer. They are constrained to say basically you have to have the same. Until the innovator does their thing there's nothing I can do for you and you can't do any of that innovative stuff. So there is a disconnect between public you know health priorities and the mechanisms of these changes. And something on an organizational level needs to be done better I think to get a higher priority for the issues.

DR. VAIDA: Tim?

AUDIENCE MEMBER: The thought occurred to me that we've talked a lot about size and size constraints. And if you think about say a syringe that's used to add to an IV and how little information is required on that, but that same IV has a whole bunch. Is it because you have the size so you can, or if you don't have the size you don't have to? I mean, it kind of seems like if you think about just a tablet or a capsule in a unit-dose package has virtually no information, but all of a sudden IVs have a ton of information. And I'd ask

any of the nurses who are in here, have you ever read that bag of dopamine besides the - and in fact, a comment about that and it relates to human factors. Most of the nurses select dopamine as 400 and 250 or 800 and 250. They don't - and those aren't even connected, but yet that's the way that at least with smart pumps all of the libraries are set up as far as I know. But it seems to me that we have a real double standard and I don't know how we get by with it with the same medication that might either be an oral or an injectable, or an injectable and an IV. What's the difference? I mean, why do we have to have all that information on one and not on the other?

DR. VAIDA: What - and that, actually I was going to have - we've heard a lot about the real estate from both of the industry speakers, that there's very little real estate. We hear a lot about what is really needed on there. And actually as a question, there was some changes made. Diane, when you gave a historical perspective there were some changes made on that labeling. What do we have to do to basically take a look at that information that's needed on there? What is the process? And I would imagine it's beginning with USP. And does it

actually have to go all the way back as Jerry said? It doesn't sound like there was actually, it went to Congress or anything else at that time to make some changes. What would you see as an outcome of looking at some of that information? Even not taking into account how the drug appears or how the concentration appears which I think we all hear there needs to be guidance. There needs to be some guidance. But how would that process start? And would that be going back to USP?

MS. COUSINS: I think the first thing that needs to happen is there needs to be agreement on the issues. You know, when we talked about clutter and someone asked the question, I mean there were different perspectives on what's clutter. So I think the first thing is we have to define the problem and we have to agree to what the issues are. Then I think we have to look at where, you know the requirements, the laws, the standards interface with what we think is the best thinking of this time for what ought to be and evaluate what could be done to address those things. There are many places USP doesn't have standards and we could create them and that's very easy to do. I say very easy, but certainly easier than sometimes revising. You might

think it would be just the opposite, but sometimes that's not the case. So I think that we just have to proceed in a methodical way, and this is certainly a great first step, to start to gather the parties, identify the issues, look within the context that we are operating in and then determine where we need to be. Where's the best thinking at this time and how do we get there? Because if we talk about the constraints we're going to be constrained. If we think without constraint, we'll have a better idea of the ideal. And I think we have to think like that. It's true it's difficult to change laws, but I've never seen a better fan for a fire than an IOM report. So this is gives us certainly at USP a lot better way to move forward in these areas than ever before.

DR. VAIDA: Any comment? Yes?

AUDIENCE MEMBER: I'm also speaking from a generic perspective, so the Office of Generic Drug Labeling Review keeps getting asked questions, but Mr. Duffy I do have a question for you. Some of the things I've experienced, I have gotten a deficiency from the agency asking me to use tall man letters only to have it rescinded a month later asking me not to use tall man letters, although another

generic company is on the market with tall man letters. I also have gotten - everything I sent in I put total strength per total volume and I've had label reviewers tell me not to. I've also, everything that I sent in begins "Usual dosage: see package insert" but as a generic I constantly get comments back telling me that I must put exactly what's on the innovator. For example, "See accompanying insert for dosage administration." Even though I try my best to constantly reserve real estate, my question is what sort of training goes into label review? That might be a really big, wide question, but is there any kind of subjective training that goes into OGD label review where - because I argue these and I'm not usually successful.

DR. VAIDA: Carol?

MS. HOLQUIST: I can help Eric try and answer that. I actually used to be a labeling reviewer in the Office of Generic Drugs. So how do you get training in there? You learn the regulations. And you learn the regulations. The regulations say you have to have a usual dosage statement. But what also binds generics, as we heard before, is they have to be the same as the

innovator. I'm kind of surprised that you would get some feedback on changing your usual dosage statement to me because it seems like what was on there was okay. Jerry can probably speak better to why maybe they would require something like that, but I can speak to the epi. I think what you're referring to with the tall man lettering is actually - and this is something I wanted to get feedback from the panel as well on - is that you know now everybody's saying tall man lettering, yes, it's the next best thing. You know, it's going to create - it's going to minimize all these errors, especially with established name confusion. But what I think I'm also afraid of is that if we overuse it, we're going to dilute the effect. And in the case where you go a rescinded letter I believe is when a company wanted to highlight epi on the label and it was not a product that contained epinephrin. And we thought, at least I know from a safety perspective we thought highlighting was, I think, I believe it was Epirubicin was putting epi as highlighting epi so that it wouldn't get confused with other rubicin products. And we thought from a safety perspective that that really wasn't the best use of tall man lettering, that there could be other ways that we

could differentiate that product so that it wouldn't get confused with other rubicin products. So I think that's a question I have too.

I might not have answered all of your questions about labeling reviews, but the label reviewers, they do go, you know, they get trained hands-on by other labeling reviewers who have been there from you know time on. There's team leaders. But they have to follow whatever the innovator has. So if the innovator has something on there, they're going to ask you to put it on there. There have been times when there has been an error that we have asked the innovator to change it based on the error. It may not be to remove some sort of statement on the label, but it might be to actually change the trade dress of that particular product because the error may be related to the fact that the vials all look alike. So there are ways that you can minimize your errors from a generic perspective, it just really depends on what the issue is. It's not that they can't do anything at all.

AUDIENCE MEMBER: May I also ask is there an upcoming list? I believe Mr. Willer referred to this also. The tall man lettering list that is on the FDA website is quite dated. I can't

even remember the date, but I know it's been several years. And as Mr. Willer alluded, there's a lot of products coming off patent very soon that tall man lettering would be very good for and an updated list would help in some of these issues. But some of the label reviewers will allow me to put "See package insert" and some will not. So it's very inconsistent on the label review.

MS. HOLQUIST: Yes and I think if you have problems with the inconsistency, I think you really need to bring that to the attention of the Director for the Office of Generic Drugs because if there is, you know, you're hearing from one group in OGD that it's okay, but you're hearing from another group in OGD it's not, they can get together. You know, if they're made aware of it they can get together as a group and say this is what we're going to come up with and they have a standard. It's a small you know amount of people. That wouldn't be a difficult process.

With respect to the list of tall man lettering, basically the list that's only up there is the list that we knew of that we actually asked people to change which was the list that came from ISMP. What we're finding is that a lot of

manufacturers are doing tall man lettering on their own and slipping these things in in what we call annual reports which because they consider it as a minor and editorial change, where to me I don't think tall man lettering is a minor and editorial change. For the example of the Epirubicin. And I think that was a case that brought it to our attention and so now our group, because we're so concerned about this, is trying to take control of it and we're trying to work with not only OGD but new drugs too, if anybody comes in with that request or they see something like that in an annual report that they at least you know ask us about it because they think it's a good idea. And I recognize that things are going to be coming off patent, but it gets back to the point do we want to highlight every generic product with tall man lettering. I mean, do people think that's a good idea, or do we think it may minimize the effect.

DR. COHEN: Well first of all, I agree with a lot of your comments. And I do have a problem with everybody using tall man letters helter-skelter for unknown reasons in some cases. And I mentioned before, I've actually seen a couple of cases now where the tall man letters that were

emphasized actually made it look like it was a brand name. And obviously the whole idea of USAN and your non-proprietary name development is you know, it's opposed to doing something like that.

But it isn't even just the pharmaceutical product labeling that's using tall man. Infusion pumps, smart pumps now have the drug libraries and they're using it. The pharmacists are using it individually in their hospitals and there's inconsistency there, the way that it's done. The letters that are emphasized are not always the same even between two companies. I've seen that happen already.

So again, you know a lot of this is leadership. It's somebody's got to take charge here. Even in the last conversation that we had about you know where do we start, what Alan was talking about. Somebody's got to embrace this and say you know here's how we get this going. Here's who the players are. Let's bring these people together and you know maybe work on individual problems one at a time. I don't know but one of them is certainly going to be tall man letters because that - the growth has just been unbelievable since the 15 or 20, whatever it was, were approved

by FDA. And I absolutely do not agree that with some of the ones that are being used, no question about it. Like epi would not be a good idea, definitely not. So somebody's got to be.

DR. VAIDA: Comment by the panel? With that we'll take one more question.

AUDIENCE MEMBER: I have a question. Are we also looking at the way these products are being used? You know years ago - I speak to my mother who's been in the nursing profession for 40 years. You used to go to nurses training and you used to - you picked up the bag, you read it, you hung the bag, you read it, you spiked the bag, you read it, and that was part of their training. And I find now that with every, you know with all the cutbacks in every part of our society, that a lot of these nursing training stuff that seems so important at the time have slipped away and there needs to be also some accountability in the training in the healthcare profession as well. I have seen complaints come where the bags are clearly two different - you can't - they are so far different from each other, but we still get a complaint of a medical error in a hospital and it turns out to be it's because they're in the storage room where the

letter, you know the one product starts with "O" and the other one starts with a "P" and in the alphabet that's how they're stored, and they were hung that way. And I think there needs to be more emphasis and regulations also in that part of the industry as well. I think cutbacks hurt everybody and you just, you know you have to read the label.

And I think we can do a lot of things here, but I think we need to work within the hospital setting. You know, years ago you would hang three bags. Now, you saw a picture there. There's 20 bags being hung. How can any individual keep track of that? And are we doing anything, looking at some of the things we could do in the hospital or pharmacy setting?

DR. VAIDA: Was there one more question here? In the middle? Did you have a question before I end?

AUDIENCE MEMBER: For just a second, perhaps to change the focus. Several of the speakers - I'm speaking here as a practitioner. Several of the speakers have mentioned cost, the cost of changing fonts, of several colors. Can you just give us an order of magnitude? What are we talking about here in terms of the label cost? How

big a fraction of the cost of the product is that?

MS. OLINGER: I can address that a little bit I think. I don't think it's as much the cost of printing the label once you get going, but it's to change an ink like they said previously, you have to validate that. You have to do leechables, extractables, everything that goes with that so that the cost of validating and qualifying a new ink can be in the hundreds of thousands of dollars. And changing the label for, as Mary said, if you've got a couple thousand drug products and in our case we extrude the film, do the whole process right on the manufacturing line. To make changes to that sometimes requires re-tooling a manufacturing line and shutting that line down totally so that you're not doing any production at all on it. And these are not high-margin products. You know, that if you have to shut down you lose a lot of money. So it becomes an extremely expensive proposition for a company to make massive changes. So I hope I addressed that.

DR. VAIDA: Okay. Before we break for lunch here I - we still have our afternoon that we're going to hear from another manufacturer and also some practitioners and then we're going to have

time for some public comments. And hopefully we will have some closer conclusion at the end of the day. It does sound like there are a couple of issues. One is the actual safe labeling of the medication, the way concentrations are which we heard from people, even controversy on tall man lettering, but there also is this issue on real estate that does sound like when I hear about even if you're adding something, not taking something away. In my prior background as a hospital pharmacist, if we would add drugs to formulary, we would always be asking what are we going to take off of formulary so we're not just continually building the formulary. But it does seem like there are those couple issues here. One is addressing that safety of the naming of the drug or how that font appears and that, but also is there some other issue on just talking about what is the other needed information on there on the label.

So with that we're going to break for lunch. There's a cafeteria downstairs. There's also some other, if you're familiar with the campus I guess there's some other eating places along the campus here. And we're going to reconvene here at 12:45. So we'll reconvene here at 12:45. Thank

you.

(Whereupon, the foregoing matter went off the record at 11:32 a.m. and went back on the record at 12:51 p.m.)

MS. BECKER: Thank you all for returning from lunch. I hope you enjoyed that little respite and are ready to dig right in to the next session where we're going to change our that a little bit here and listen to the practitioner perspective on labeling. And our first speaker is Debora Simmons. Debora is the Associate Director and Investigator for the Institute of Healthcare Excellence at the University of Texas MD Anderson Cancer Center and is a member of the United States Pharmacopeia Safe Medication Use Expert Committee where I've had the pleasure of working with Debora for a couple of years now. Debora is a founding advisor and board member of Citizens Advocating Patient Safety, a partnering safety coalition of consumers that helps healthcare advance a safety culture through alliances with the national and international healthcare communities. Debora is program manager for the University of Texas's Close Call Reporting System which has 10 reporting hospitals and over 10,000 close calls in its database. Debora is the

program manager for the Healthcare Alliance Safety Partnership, the first non-punitive error reporting program in the country. This partnership with the State of Texas Board of Nurse Examiners and 10 participating hospitals allows nurses to report errors without fear of reprisal by the regulatory agency. Debora sits on several state and national level committees influencing safety concerns and regulatory issues. She's a clinical nurse specialist in critical and acute care and also teaches clinical nursing. Debora is a member of Sigma Theta Tau, is a Virginia Henderson Fellow and is the recipient of the 2006 Research Leadership Award from the Texas Nurses Association. Debora?

MS. SIMMONS: Well, thank you for having me here with you today. Can you hear me okay in the back? I always make sure with these things. I'm always I'm only hearing myself and you're all out there going huh? What's she talking about? Thank you so much for having me here today. You're some of my favorite people because of the work you do and so hopefully I'll be able to add a little bit to this presentation quickly as I go through and kind of keep to our timeline today and give you kind of the perspective of these nurses that we keep talking

about that are the ones there that are picking out these IV bags and getting confused about the labels. And I can kind of give you the perspective from the nurses' eyes.

I'm going to just briefly go through - when I was trying to think of what would be interesting for you to hear about, I came up with kind of four big buckets of areas that might be of interest to you. I'm going to try not to quote a lot of research to you because I think this group has seen the research that's out there. I can show you some of the gaps. I'd like to share with you some perceptions of information that nurses have, kind of give you a challenge around that, talk to you about the limitations of nurses and the work environment and the task load as well.

First of all, perceptions of information. What's the on the label for parenteral containers. I challenge you to go to a clinical area and walk around, kind of do a randomized trial here, random meaning walk the halls, and just ask the nurses that you see what's on the parenteral containers. Because the first thing they're going to ask you is what all is a parenteral container because nurses don't think that way. They think

about what they need in their workplace to get their work done. And I want you to keep thinking about that as I go through this because I will tell you, if you put a bunch of nurses on an island and did Survivor with them, at the end of the show you'd have a well woman clinic and you'd have - everybody would be inoculated and everybody would be in great health and their cholesterol would be down because they are very task-oriented. That's what we do. We come into a situation and we make things work. And so the way that they think about things is what do I need to do in order to fulfill this for my patient. And that's going to be their motivation. That in itself is a wonderful thing. That in itself is a bad thing because they will do what they need to do to get that work done.

So on your illegal - because we're not going to get consents here - walkthrough to talk to nurses, ask them what's on the parenteral container, get those answers back, and I'll tell you this is what I got. What I got was they need to know what the amount is, how much is in there. They need to know if there's a drug in there or not. They need to know concentration. A couple of them said expiration date and they need to know the route,

what it's for, and that's it. So I was really kind of pleased to hear you talk this morning because this is what I keep hearing from you over and over again and I'm kind of surprised at the consensus that I'm getting out of this group. Is that there is a finite group of very important facts that we need to know on these containers. The rest of it, I was asked at lunch if a nurse ever reads those. Upon occasion we do. We do when you've got a patient that's got something exceptional, when you've got a different drug that you're not used to. Other than that, that information is not something they usually use. So when you see something like this where you've got 10 milliequivalents of potassium in one bag and 20 in the other, and they're in the same bin in the same drawer on the bottom so you have to stoop over and look at it, it's very easy to see how these look very similar. And if you just miss that one number, then you're going to pick up the wrong bag in this situation. The implications for this, I think time and time again I can say this, and I think you've already said it to me is that nurses need only the essential information for the task at hand. And if you consider that they are the highest population you

are going to be dealing with in administering these IV fluids, I think that's a call to action there to simplify the information. If it's not, then perhaps I can show you a few more things that are going on in nursing that will change your mind.

One of the things you might ask as you walk the halls is where are the nurses because right now in the United States there's an 8.5 percent shortage in nursing. And I'm not going to spend a lot of time on that. It's multi-factorial why this has happened. It's got to do with Baby Boomers. It's got to do with opportunities for other say careers where you don't have to stay up nights and weekends and work all the holidays. It's got lots to do with what's going on with the industry. But the fact is right now there's at least an 8.5 vacancy rate. And some of our smaller hospitals where we do consulting in smaller towns where there's critical access hospitals in Texas, they will tell you if one of their nurses goes down, that's it, the hospital about closes because they may have only five or six nurses in a small town. So we've got a great shortage here both in our metropolitan areas and in our urban areas too. And the Health Resources and Services Administration

projects that the nursing shortage should grow by about 1 million nurses by the year 2020. I don't see that having any relief so far and in the meantime you might be thinking about this, that the average age of a nurse is about 46.8 years of age. I don't know where they got the 0.8 thing. But anyway, what you have before you now is a little greater than average older nurse here giving you this lecture. And the study that Buerhaus actually put out gave us some more interesting news in that the growth in nursing, the nurses that are coming back into nursing are over 50 years old. So I would say that now we've got kind of a middle-aged nursing population here that we're dealing with.

Well, there's some bad news about that. And that is of that growth factor, I find over age 45 - I don't know if you've noticed this, but we all tend to get a little bit farsighted. And so the small print is difficult, impacting nearly everyone. And they say by you know 55 it's 100 percent of the population is affected. Letters start to look fuzzy. In my own case I noticed I started wearing these all the time, in the clinical area, much to my chagrin I just had to take them to the grocery store because I couldn't figure out what was on the box in

the grocery store. And we start trying to compensate for that. But we have not compensated for that in the workplace of nurses at all. We have not put better lighting in. Reading is extremely difficult in low-light situations. I now have these high-intensity lights over my desk, I have it over my reading chair and we have done nothing about that in the nursing workforce.

In fact, this actually is like the rest of my slides, we just went walking with our camera one day through some of our consulting hospitals and this is a neonatal intensive care unit. Now, do you see a problem with this picture? This is actually during the day. This is a low-light stimulation environment. And when I asked well what do you do if you need to prepare medication, what they told me is we go here under the lamp. Well, you and I know that you can't always go under the lamp. When you're in a high-intensity situation where you have to respond to patients' needs, got a lot of things going on, that's just not going to happen.

The other problem that we have with vision, and this is across the board too but especially is kind of influenced in age is that maturity decreases our ability to discriminate

cluttered situations. So if you've got your little greater than average nurse here walking around teaching clinical nursing students and we've got a patient going by with this IV pole that's got multiple bags up there, what do you think the chances are I'm going to be able to read all those labels? Pretty poor. And if you know human nature and the way that we work and the way cognitively we put things together, you start realizing how these things begin to happen. Because we similarity-match and we go with what's familiar with us and we make those assumptions, not consciously by the way folks. This is all unconscious. This all goes back to the human factors and usability facts that we need to deal with in clinical situations.

So this is the slide that Mike Cohen used earlier that I also will take license with. Because if you think about the yellow labels here on these IVs and across the board, differentiating between each one of those much less unraveling the spaghetti of tubing is going to be a challenge. This is not the nurse's only patient either. You know, this is one patient, maybe one of two, in an intensive care situation one of three or four. But when you start adding those numbers together, this

task becomes even more daunting.

This is an ECMO unit. This is actually an IC unit with an ECMO patient running. As you can tell again we've got much visual display here, a clutter of information that's being presented to you at one time. Now, this is flat information in the work environment. I'm not even talking about trying to go back and find the finite details and minutiae that make taking care of this patient safe that comes out of the package inserts where the font, as you have aptly pointed out is very small. We're trying to get all of that information down there. And besides that, for package inserts, do we really know how to present that information so the most important information is presented in a way that it comes out to the practitioner? I am recalling something that Mike Cohen would speak to much more succinctly about the Denver nurse case where they were looking for the route of administration for that drug, and they were looking in the package insert and they did not find it. Now, on one hand you may have someone that tells you well, you know, they just weren't vigilant enough, they just didn't look enough. But over and over and over again when we've done error analysis we've seen careful,

thoughtful practitioners trying to find information and they do not find it. We've simply got to learn how to present this information in a better way so people can discern between the pertinent points.

So here's the other good news about the work environment in nursing if I haven't cheered you up so far, and that is new products are added daily. If you're a new nurse on the unit and you're just working in that unit in a usual fashion, what you feel like is that you're in the middle of tidal waves of information. You get new products in constantly and despite the best efforts of the pharmacy and everyone else to in-service to bring the information to bear, you're just not going to get it. It's going to come to you and you're going to open a patient's drawer for medications and pull out something you are not familiar with. What we know now by human factors analysis and cognitive analysis of some of these errors is that people at that time go with what they know. The human brain works in a pretty predictable fashion in that we look for things that are common to us, that feel comfortable to us and we put those two facts together. We kind of work like a Windows file system in that we start seeing something unusual in

the environment and trying to make it fit like something else. So if you wonder why some of these new products come out and they make spectacular and horrible errors with it, start looking for something that looks like that. And if you can gain the trust of the clinician well enough, they will tell you well it looked like this so it must have been that. And that in itself is something very important for us to learn in this industry is that that's the way our minds work and that's what we will do when presented with unique problems.

The labels vary. Our hospital is on a purchasing group and so I know because we're a state institution, we try to be fiscally responsible and good stewards of the money that we are entrusted with, we try and make the best purchasing decisions we can. And when I talk to the purchasing department what they tell me is well you know, we've got a price break on this and if we go with this then we can save this much money for the hospital. And you know in these days and times it's a really hard sell for me to go back to the financial officer and say we need to change our purchasing practices because if you really look at the margins that we're dealing with now in the industry it's very, very

important for us to have that financial outlook so that we keep our industry going and we keep the patients coming through. So we get labels, we get different products from different manufacturers all the time. And for the nurse at bedside that feels like random acts of violence I think sometimes. They're going about their day and all of a sudden they're presented with something they've never seen before and they have to problem-solve right then and there on how to deal with it.

There's a lack of consistency. I think you have proven that to the point where I really don't even need to speak to it much this morning. As I watched your slides go by, I see a lot of efforts in trying to change these labels for the font, for the background and for the color. And I will tell you right now it's a mishmash out there. It's just a roll of the dice what you're going to get at bedside and then you're going to have to deal with it. The other problem with that though is this. Remember I talked about the fact that we similarity-match. We do that so unconsciously in normal human operations - and this is even past nursing, pharmacists do it, that's the way our brains work - so that we are going to go with what's

in our data file here and we're going to match to what we saw before. So now if we've got a little bit of a change in that we zero in on the tall letters and the tall letters are a little off. Now you've got them hanging the wrong bag.

Low or no light. Have you ever walked through the units at night? It's completely dark in there. We're trying to get the patients their rest and you know, some of the errors that we've looked at through our system in the last couple of years have been in the middle of the night, especially pediatric units where they just got a baby to sleep and they're trying to keep the baby asleep, trying to give everybody their rest and they take a little bit of a shortcut and kind of work with it in the no-light environment. And there's incentives for that isn't there? No one wants to wake up the patient and wake up the baby. Nobody wants to wake up the parent. So you take that little bit of an edge there and now you've got an error going through. All of these kind of are contributory factors. Can you put your finger on just one and say well that was it? Probably not. What you look at is with all of this in the milieu you're going to get these kind of errors. Constant distractions.

I'll talk a little bit more about that in a minute.

The other piece I wanted to bring to you and kind of talk to you about is the emphasis on task completion in nursing. That again and again with the nursing shortage and the different shortages that we have faced and kind of the re-engineering that healthcare does over and over again. I don't know how many of you are in hospital systems, but you've probably gone through a couple of consultants in the last years I would imagine. I was in one hospital. We went through three in four years. We were all like bomb-struck you know at that point because we had people coming and saying well you know if you do a time study it should only take this much time so change this process, so change that process. And the real emphasis then becomes how do you get these things done. Get these things done. And remember what I said about nurses' orientation being I'm going to get this work done in this period of time. When you add to that that their incentives are on task completion, on getting it done in a certain time period, then we've got another recipe for disaster because as our human nature takes over, we start trying to get those tasks done. And so we start dropping off these

other things that we know are safe practices as we go along.

What you'll find sometimes when you look at error reports is you see failure to follow policy and procedure. I don't know if you've ever run across that before, but that seems to be the causative factor that somebody will stick that on there. Well, the real problem with this error is they didn't follow policy and procedure. And my second challenge for you today is to go look at your policies and procedures and kind of look through the time period that it takes to complete that task and then multiply it by the number of patients and then multiply it by the number of drugs and now multiply it and then add in all the distractions that we have in all the other tasks. And what we've done is set up some pretty unrealistic expectations in a lot of areas by doing that. And I'll confess to you today I've written a lot of those policies and procedures. They were eloquent. I think I was the only one that read the full thing. They were very long. But did I actually see if someone could operationalize that in clinical practice? I don't think we've done that. So it's time for us to kind of get away from this idea about not following policy and procedure.

And when we have a tendency to go there, we need to ask ourselves what was the situation at the time, what was the number of tasks that person had to complete and what was their motivation for not following policy and procedure.

The other piece that follows into this is again going back to human factors and looking at cognitive analysis of some of the situations you realize that we look but fail to see many times. We will look at something, fail to see it, or we will see what we want to see. And we've demonstrated that over and over again. The more familiar the color, the shape and the type, the more likely we are to similarity-match. And this is grounded in the human factors science, it's been around in other industries. Other industries deal with this. We have not approached this in healthcare and certainly not worked with it with labeling. We definitely need more attention to this area. So we do get things like 20mEq looking like 10mEq and during all of this we've got distractions going on.

And here's the one little piece of literature I'll bring to you. Tess Pape did a study on innovative approaches to reducing nurses' distractions. And what she actually did was she

took this bright orange stuff like they put on the people that are working on roads and put these big orange aprons on nurses that said "Leave me alone, I'm giving medication," and actually put them out in the units. And what she found was it worked for just a few days and then everyone was immune to it and started distracting them again. That tells me a couple of things. One of the things it tells me is the tasks are so pressing that they are moving past those thing and so we really need to spend some time looking at where are nurses giving medications. The other thing that's kind of interesting if you've seen the medication carts that roll around the halls, we put nurses in the middle of a hallway to prepare medications, one of the high-risk and demanding tasks that they have with critical thinking skills and we wonder why they make mistakes while they've got everything else going around them and all this noise, call bells, everything else going on. USP again from the database has shown time and time again that many of the errors, three-quarters of the errors in this particular study were influenced by distractions. This one, distractions and workload cited as contributing factors.

I would say we have definitely proven

there's distractions, but in the meantime what we've done, this is the industry's answer to that, is we have bagged them and tagged them and now we're tracing them through the hospital. We've put tracer tags on the nurses so we can track them on these little GPS maps and then we've got little communication devices, either walkie-talkies or we've got telephones. Now the telephones are particularly nice for us because you can give that phone number to the family of your pediatric patient so while you're in the hallway preparing your medications you can have the family also calling you. One particular response to that in 2002 I think you might find interesting is that on Labor Day a group of nurses put a box in the middle of the unit and put all their tracer tags in the box and then the box disappeared because they felt like it was an invasion of their privacy because they'd actually been tracking their break time and seeing how many minutes they were spending in the break room. So obviously this is not an answer is to go ahead and put tracer tags on them. We've got to go a step past that and actually look at the cognitive and physical workload of nurses and make changes in the environment so that they are able to complete

these tasks safely. I especially liked their statement was that they had a concern because increasing corporate industry's effort routinize and speed up the complex work done was in a time of chronic under-staffing. And we all know that patients are not getting less complex that they're dealing with.

Just a word on computerized systems real quick. There's challenges to cognitive performance. Perrault and others in the aviation industry talked about the way that people "trust the computer." We have found over and over again in our work that people trust automatic dispensing machines. When you go in there and you put it in the computer that you want heparin, out comes that drawer, you believe that you got what you programmed in. But we also know that humans are the ones stocking those drawers. And so what we see is people taking out 10,000 units of heparin and giving it instead of 1,000 units and coming up with horrible results. Over and over again. So automation on one hand is good. On the other hand it is not and will lead us down another path. Also, we say that we need to do this because they won't apply the five rights. The next time someone says "five rights" you can tell

them that you know there's plenty of evidence out there now that that was absolutely the wrong type message to teach nurses because you can be right on all five of those and still make a medication error that's dire for your patient. It's an unrealistic requirement for the workload that we've got now and absolutely for the information load we've got now on their medications it's not reasonable.

This is just an example we got out of the close call system. I wanted to show you two labels that got confused. This actually came out of an automated dispensing machine. They were getting ready to do a procedure where they passed a probe with a patient hoping they got lidocaine out and when they opened the bottle luckily lindane shampoo has a rather distinctive smell and so they recognized what they had and were able to stop it. So even with a color differentiation it came out of an automated machine and they trusted it.

Stocking in drawers in these automated machines again is a problem. I was talking to some of you at lunch and asking why do these things need to be opaque. I understand that some of that's cost but I'll tell you, when you dump all of these in a low drawer because these things are heavy and they

want to keep them in the bigger drawers, the deeper drawers, it is really difficult to look down there and to be able to differentiate because of lighting and looking through that wrapper at that point. The other thing is some of these dispensing machines, you know if you're asking someone to reach over their head in order to identify something chances are they're not going to. And the medication load. Three to four patients is our load at Anderson and we've got one of the best patient loads I think in our medical center. Each one has an average of about 20 medications. So it's 80 chances per shift, 80 simple chances, this doesn't even count everything else that's going on, to make an error.

I couldn't help but look in our close call database to see what we had gotten as far as close calls. Now we collect information from front line providers about when they have near misses, when they actually almost make an error and it's anonymous. We came up with of the 7,300-some medication errors that are reported in that database a pretty significant, 633 were attributed to labeling and packaging errors, problems with the labeling and packaging. Which I find some consolation in because I think what it says to us is

that they're actually to take a minute and think about the label that they were looking at and say yes, that was a contributing factor, that was a problem and perhaps labeling/packaging would be something I could change to make it better.

Implications for research. I think I could preach to the choir now which is my favorite thing to do and say that we need applied research. We've already gone through the demographics of this. We've gone through the occurrence rates of this. I think all of us agree, the public agrees that there are medication errors and there are problems with it. All of you agree that there's a problem with the amount of information that's presented there and we have quite frankly moved like a herd of turtles through peanut butter on this issue. It amazes me the lack of agility in healthcare for responding to these type of problems. You know, that we have discussed this over and over again and we can't come to a solution. It's kind of a little embarrassing at times that we are not able to be agile enough and to take a lead and take a stance and move forward on this so we can actually make a difference. Because all this time I've been talking they've been out there pulling these medications and giving these to

patients. You know, time is ticking as we go along.

We need more applied research about the work environment of nurses. Luckily an IOM report came out supporting that. I highly recommend it, Transforming the Work Environment of Nurses, an excellent, excellent report on keeping patients safe. We need to look at physical and visual limitations and actually make some changes in the workload accordingly to that and step bravely out there and look at cognitive load. What is the amount of information, how are we teaching critical thinking skills, how are we supporting critical thinking skills? Because as the shortage moves further, we are not going to be supporting it more. We're actually going to be finding more and more shortcuts as we go along through this process.

So kind of my conclusion of all this is that we can't change cognitive functioning. This is going to be the human condition. We can't perfect human performance and reversing aging is pretty futile. The time and gravity thing, I don't think we're going to make much of a dent in it. But the best reduction strategy is actually anticipate these errors which I think we've already proven we need to and design systems to prevent them. So I would hope

that some of you would walk away from this saying that you could do applied research or if you actually did make an intervention in the clinical area and then measured those results so the industry will follow. At this point that's what's needed and I think it's what's going to move us forward. James Resen says that you can't change the human condition, but you can change the condition in which they work. And I will tell you, there's not very many nurses here today, but that the nurses that are out there I'm sure would support that as well. Thank you so much.

(Applause)

MS. BECKER: Thank you, Debora. Now you know why I like working with her so much. Our next speaker will give us the pharmacy perspective. Timothy Lesar, Dr. Lesar, is the Director of Pharmacy and Patient Care Services Director for Diagnostic and Therapeutic Services at the Albany Medical Center in Albany, New York. He has served on the faculty of the University of Minnesota and the University of Illinois at Chicago. Dr. Lesar's research and practice has focused on understanding and improving the medication use process with a focus on medication errors and deficiencies. He has

participated in numerous patient safety initiatives and collaboratives. He is a member of the Joint Commission's Medication Safety Advisory Group and the FDA Drug Safety and Risk Management Advisory Committee. He's a recipient of the ASHP Award for Achievement in the Practice of Pharmacy and Health Systems in 1991 and 1998 and the ISMP Chair's Award in 2000. Dr. Lesar has more than 90 publications in the medical literature. He received his BS in Pharmacy from the University of Wisconsin-Madison and a Doctor of Pharmacy degree from the University of Minnesota. He completed an ASHP residency in hospital pharmacy practice at Bassett Healthcare in Cooperstown, New York, and a fellowship in pharmacokinetics at the University of Minnesota. We welcome Dr. Lesar.

DR. LESAR: Good afternoon. I'd like to thank ISMP and FDA for inviting me today. It's an honor and a pleasure and it's nice to see some folks that I haven't seen for awhile. I'm going to be presenting from the pharmacy perspective here and I'll - a little bit difficult to see that, right? But when I thought about what to present I thought I'd present again what our world is like and how these things interact with our world.

You know from an introductory standpoint, just to say that when I look at our day-to-day functions, improving the design of parenteral fluid both large-volume, small-volume parenterals as well as the labels the pharmacy places on products really are needed to reduce risk. They produce risk, they can help reduce the risk. And also, everybody understands that in the pharmacy world and elsewhere in healthcare we're trying to reduce the number of things that we have to actually prepare. That is, we have to change the way it comes from the manufacturer. And I think this is something you're going to see more in the future, but it will never be eliminated. We'll always have 500g neonates and 400lb athletes in our hospitals. So while we can move toward more pre-made materials which will make labeling by the manufacturer more critical, we'll also have that we change those products and we add additional labels to products that the manufacturer makes. And certainly we're seeing a growing number of products and often very complex products with complex dosing structures on a frequent basis that enter into our system.

But we do think there's been substantial improvement in labeling over the years, but we still

I think our day-to-day experience, the things I see, the things that my staff brings to me and says oh, look what we did, the risk management reports that I read, our quality reviews all demonstrate that we still have a lot of risk and a lot of errors that are occurring. So clearly further efforts and I think this is a great first step. I think Mike's point about somebody's just got to take charge of this, take hand on this and move this forward is really required so that we can take care of our patients in a more safe manner. And I think one of these things - and this process is really going to require some very robust risk assessment that looks at the context, looks at exactly what's happening and understand that things are different in different parts of the organization. The pharmacy, if we have to prepare something the label means a little bit something different than if it's pulled off the shelf by a nurse. So every place that you see these things being used, the context is extremely important and so you're going to get a lot of people saying this is most important on the label and you might say this is most important. It really depends on what the context of that label is. And so it will be a difficult process, but I think it's

doable.

And so key point. This has to be - whatever we do, whatever you do, whatever decision is made, this has to be done in terms of the context in which the products are being used, both in the person who's using it. A great discussion of what the nurses are thinking when they're using it. I'll try to provide you some information on what the pharmacist is thinking and what environment they're in. And also that - understand that healthcare is highly dynamic. Just because they do it one way in one institution or on one floor of the institution does not mean that it's not done differently in the same institution down the hall or by a different individual. Very dynamic, very different and each situation creates its own sets of risk.

And so when evaluating potential problems, I think it's important that everybody understands what the flow of a product is through a healthcare system. And this is a slide that I've used in the past to try to explain to people who don't work in healthcare system why something that looks perfectly clear, perfectly safe isn't once we start using it. And the point is that once you introduce anything into the healthcare system,

whether it's a new product, a new drug, even a new process, there are many, many factors that it interacts with that were not thought of, not predictable in how they interact. So anytime you input anything into the healthcare system we're going to create errors and it will be - they'll be very understandable in hindsight, but not predictable in foresight.

And I think it's important that you understand what the flow cycle looks like in most parenteral products. And if you look at, you know one of the things is we do when we decide we're going to buy these products. Sometimes the formulary committee decides you're going to buy something that's going to decide that we'd have a product in the organization used depending on what the needs or types of patients you have. There's contracting, as was already mentioned. We're primarily a Baxter hospital. We primarily have Baxter products. Some hospitals might have Braun, some might have Hospira. Depends on contracting. What happens if there's a shortage? What happens if there's a recall? All of a sudden we have different products. But there's a decision made. These things are purchased and they're really - they're

purchased and they're received into the organization, usually into a storeroom. We happen to have our own storeroom. But also central supply distributes most of the large-volume parenterals. Even the potassium-containing large-volume parenterals go to the floor. They don't go through the pharmacy. All right? So there are two different ways some agents are actually distributed. We get them, they sit in our storeroom. Pharmacy needs them. They come up to the pharmacy and they are placed on different storage areas in the pharmacy. Depends on where we're going to need them. These are always done by clerks, techs, never done by pharmacists. Mike showed you some of the boxes that look the same. So we've actually had situations where we bought through purchasing got the wrong ampicillin, multi-dose 10g vial that looked like a 1g by another company. We never had the 10g before. And believe it or not it went through this whole system, made the whole cycle because somebody made a mistake in purchasing.

So anywhere along this process you can see errors that get into the system. But once this gets somewhere down in the pharmacy, and I'll show you what that looks like. And then out of that

stock, the working stock, a technician or a pharmacist selects that product. They may label it, they may prepare a drug dose with it and then we send it. We distribute it. And this may be - we may distribute it as a unit dose in a cassette. We may send it to the refrigerator on the unit. We may place it in a automated dispensing machine. And believe it or not, we do think about what that product looks like. Those automatic dispensing machines you saw what was called a matrix drawer. That's a drawer that's open and you can select different products. We have almost eliminated those from our organization because people were picking the wrong things out of that matrix drawer or got the wrong one, put it back in the wrong matrix. So our drawers don't allow that. They light up or only one of those boxes open at a time. Or we've taken that type of thing off the floor so nurses don't have the opportunity to make that error. So you can make a lot of decisions in here about trying to reduce that risk.

So they move up, off and on, then they get closer to the patient. Now they're on the floor somewhere for the nurses to give. But remember, our goal here is to provide to the nurses a low number

of things to select from, and those things that they can select from that are accurately labeled and easily identifiable and limited. So they don't have to do a lot of selection and make those errors. And then of course the nurses are going to give that drug. And also in here it's not just nurses. If you go to the operating room it's the anesthesiologist, the OR nurses, sometimes OR techs. It's the profusionists, it's the dialysis techs in the dialysis unit. Go to the cath lab it might be the - they'd have cath lab assistants now who do these things. Who's ever doing these things, these again differ wherever you go in the organization. So what's critical to them varies and what environment they're in in terms of their selection of the product varies quite a bit.

If they're not administered or if they're overstocked or whatever, things are then returned to the pharmacy. Guess what? They've got to be identified and placed back into the stock again. So actually you can see where things have to be identified numerous times. So every place you see a spy glass we've got to identify these products. Sort of all around the system, multiple places to identify.

Now, welcome to our IV room. We are a 630-bed hospital. We have a large 50-bed neonate intensive care unit, Level IV. So we have 500g neonates. We have multiple, multiple intensive care units, pediatric, adult, intense, medical, cardiac, neurology. And so we have just about everything. We have transplant patients. We run the whole gamut. So we see, we have to provide through our central pharmacy we provide drugs to all of those patients. So our IV room is large. We dispense about 1,200 a day that we actually prepare and label, IVs that are prepared. And these are just some of the places. Look, here's multiple drawers like this containing over-bagged IVs, shelves, refrigerators, and so that's what it looks like. Very, very hectic. Make a lot of things that are needed immediately and multiple people working.

And so I was just going to go through and hit many of the items that were already talked about but from our perspective. One of the things that was discussed were over-wraps. In a pharmacy department, much of what we select has an over-wrap on it. Over-wraps are critical in terms of our ability to identify there what we see. When we select an agent, we're selecting for the most part

something already with an over-wrap. So this is what they look like. This is a pretty clear picture of what over-wraps look like when we select a product. How many people would think this is clear? These are two different drugs. So these type of over-wraps, they should be eliminated. Go to the foil ones.

Here's a foil wrap. Look at the difference. This is - I squeezed down so the moisture inside the over-wrap makes this more visible. But you can see the difference. Here's over-wrap paper nicely - you can actually read that. This really is unacceptable. Over-wraps are terrible. So here you go, they clearly obscure the label. And by the way, in the pharmacy they stay on until use. We don't have a lot of these products in our Pixis machines, in our base cabinets, but you can see if this was in one of those matrix drawers on the floors how easy it would be for that to be - for someone to make a mistake, to simply put it back in the wrong slot and easy to make an error. They're very difficult to read. You really have to take the example of the poor lighting. They're almost - they're very, very difficult to see. So over-wraps should be easy to read. Just over-wraps,

and we have shelves full of them, drawers full of drugs in over-wraps that are similar to that.

The refrigerators are very similar. Refrigerators will contain drugs that are either not stable at room temperature or drugs that we have prepared, ready for use. So this is one of our refrigerators. Here's another one of our refrigerators, some syringes. Here's the small-volume, some are large-volume parenterals. The yellow labels are patient labels that have been added over the top of the manufacturer label. So refrigerators are always in short supply. They take up a lot of space. We could not squeeze another one into our IV room. And this is also true if you go out to the floors. We take these products and we place products like this, we take those to the floors and put them in the refrigerators on the floor every day. And some of those floors, some of those refrigerators are essentially - in the intensive care units look like this. And the nurse is going to go in there and select the right drug. Somebody selects it, puts the wrong one, puts it in the wrong bin, all of a sudden you have trouble identifying that drug. So environment and context are extremely important in terms of looking at how

these things interact. So to say, to hold a product in your hand and say gee, and hold two of them say yes, these look pretty different. You can see you start placing them in a context like this, things don't look so different anymore. So the printed products are never handled in isolation. They're always bunched together. They're always kept in close proximity, okay?

So there you go. That's just a drawer. I opened up a drawer in our IV room. You tell me if I placed a similar red and black-labeled product in that drawer that I could tell the difference. So when a tech goes to get that, we don't go just get one of these usually. We have over 550 patients in our hospital at any one time. When a tech goes in there batching things, they go in say I need 15 of these. They take 15 of them out. Do you think they look at every single one? Or even if they looked at every one, do you think they would recognize the difference if there was one wrong one there? No, they wouldn't. So you can see where the over-bag and the similarity now create a tremendous risk for error. And remember, this is what - somebody took this out of a box that Mike showed you, put them into the drawer, one of our techs or clerks did

that, and now this is how they sit. And if they were to grab 15 but only use 12, somebody had to put them correctly back into the drawer.

And this is just a good example of a shelf, kind of like you saw before with large-volume parenterals. Here's foil-wrapped one. Here's over-bagged one. Here's another foil. So it's very easy to see how things get placed on the wrong shelf or selected from the wrong shelf. So the other thing in this room, I didn't show any people, but believe me there's people. There's maybe eight or ten people in this room at any one time, pharmacists and techs, clerks moving the materials. So this is a high volume of work, lots of things that have to be done right away. There's a huge supply chain function. That is, it's a materials management function. We are trying to maintain a limited number of working stock in the right places. But pretty much there's a huge turnover because we have limited space, plus the more - if you don't want to have your inventory so large, that you have problems with expiration dates and things that if you have too many obviously you have an issue with selecting the wrong product. IVs, the huge number of IV products that we go through. Remember, we have a

lot of custom-made products that we have to make because of our population variation. So we have a large number of different products.

Disruptions. Very common, as was stated before. And this is very reliant on human resources. We are a hospital that's about 40 percent into bar code administration. In the pharmacy we use robotics to dispense most of our oral drugs, but we don't use them at all in our IV room. And we also use bar code to load up our Pixis machine. So to check the Pixis material, then to get them into the right drawer in the Pixis machine we also use bar code. But in terms of the IV room, there's not really good products out there for us to use bar coding in the IV preparation part of the pharmacy department. So one of the most critical areas is in IV preparation and we really don't have some of the technology that's going to be really applicable to making doses for neonates. Some of it's becoming available and we'd like to apply it as we go along. But again, it's highly variable and highly dependent on human performance and often once we make a product, it's very - you can't tell. You can tell if you have two tablets in your hand, but you can't tell if you put 1g or 2g of a drug in a

bag anymore because it's a clear solution.

So the other issue. I talked about purchasing. So product lines. Remember, product lines look very similar because it's typically product dress and companies have a typical way they want to make their product look. And so products that come from the same company tend to look the same. Different companies though, I do agree they do look different. However, there are chance look-a-like situations. And so drugs do tend to look different. Here's a Braun bag that we tend to stock. Most of them are Baxter products which look like this. And the contracting pretty much determines that in our organization. However, if there's a shortage, we run out of something, have to borrow it, there's a recall, all those things could require us to produce - to order in other different types of products. And here's an example of product line. Dopamine. There's a tall man, but when I went and said - when I went in to take my pictures, I said okay you know give me dopamine because I was just looking, I was going to take a picture of tall man. So the pharmacist went okay, I'll get them. He went to one drawer, got this. He took about 10 steps and down an aisle and got this one. Took

another 10 steps and got this one. He said oh, we have to separate them because we get these mixed up all the time. All right? So you can see, you know, it seems - they're definitely dopamine, but it's so easy to confuse them because they look so much the same across the product. So people adapt.

Across product lines there's chance look-a-likes. I saw this riconazole over-bag and I think they are very distinguishable. But the problem is in an area, in a place like Albany Medical Center is we maybe purchase something else and if another company decides to have color dress. There's lighting issues, there's color vision issues. There's a chance, just like we know from other types of products that something is going to appear that looks similar or appears similar to somebody as something else that has a distinctive look. So oftentimes a distinctive look is advantageous until something that's made by somebody else totally different also has somewhat distinctive look like that, and people will confuse those things. We clearly see that.

I think Mike showed Brevibloc foil wrap. Another label. Different colors differentiate the two concentrations. This product is actually what

we would consider very good at this point. I'm just waiting for something else to show up that looks like that. Blue line here says injection. Nice big letters. Pre-mixed injection. May start with a `B' who knows. This could easily, given - if something came with the same color, could easily be mixed up even though it's a different drug name because that distinctive color and that distinctive look. Right now it's a great example.

How should you express the drug name? How would we like to see the drug name? This is a bad picture, but this happens to be a Xerox of a bag that was involved with an error in the pharmacy so I thought I would just use it. This is Gentran - Dextran 40. Look at this label. Gentran 40. What's this? 0.9 percent sodium. Look at the size of that. Then down here it says you know it says injection. Then it says Dextran 40 and 0.9 percent sodium chloride. And you can see oftentimes things are picked by our technicians, prepared - the pharmacist checks them. You can see, what is Gentran? Goes back to that. What is Gentran? Well, Gentran is Dextran. The technicians do not know that when we hire them. They have to learn. Many people don't know. It's not a common brand

name that people use. No doctor ever orders Gentran, they order Dextran 40. So again, brand names. This is stressed here. Everything we do in the pharmacy is really based on a generic name. We enter into the pharmacy computer by generic names. Any label we produce has first the generic name. The generic name is the primary identifier. We translate - most of our labels have both a generic and a brand name on, but the first name is always a generic name.

You ask me, the first thing here should be the generic name and in bold, the largest font. Don't tell me what's in it until much smaller if I'm interested. Don't tell me how you buffer it. I'm not really interested in that until I need to specifically look for that information. Okay. But here it's very difficult to tell what is this. Tall man lettering. Another point. Very nice. Here's dobutamine, dopamine. They jump out at you. This line, why is that there? I don't know. That's very interesting. Who decided to put the line there? I wasn't sure when I started looking through these products again, I don't remember ever that being discussed ever in any literature, but very interestingly you know it looks like that's the

whole word. And I'm just waiting for the error, for the techs to think oh this is just the salt or something. Dopamine - and you can see, it looks pretty distinct. So then what I did, I just took the color out. Just an example, here's how it would translate into the IV, the product. This is what it would look like that would come out of our pharmacy system. It would come with this label, patient's name would be here, tells you what the drug is. Here's our bar code so the nurse uses it when she bar codes it, when she gives it. And so it does translate there.

Talk about tall man, you talk about consistency. We're trying to be consistent in our tall man. Tall man in our IV labels, in our automated dispensing machines, in our electronic formulary, in our pharmacy computer system and hopefully it will eventually be our CPOE system, in our medication administration record which is pharmacy-generated, or in our electronic monitor. And so when we started looking at this we had to do exactly that. All of a sudden we noticed that the tall man lettering differed across our system because somebody would look at something for one source and one of our systems - from one of our

systems, but for the IV labels they looked at something else. And this became a real problem. They said well gee, here this manufacturer uses this. And I would look at that. I use - tend to use what's listed in Lexi-Comp which I believe is the same as ISMP because Lexi-Comp is our drug information supplier so they use it, they produce our electronic formulary and they also produce our drug - one of our online drug information systems. So it's there. There's not much I can do to change that. So we try to be consistent from our drug information resource so we try to make our medication administration record, the pharmacy computer and our IV labels all match. But you can see if we've done that and a manufacturer decides to use different tall man lettering, you can see what the problem is. So tall man lettering needs to be standardized and it should be controlled through either a standards within the organization - through the manufacturers or by regulation.

But look what happens when you take the red and the coloring out. You know, all of a sudden while that may stand out at you, I don't know. I would see a tech who sees this all of a sudden. I'm just telling you and a tech grabs it, puts a patient

label on it, prepares it for the pharmacist. The pharmacist doing 24 things went in, they're calling staff in the emergency room and people are screaming at them because we're not getting the drug fast enough. All of a sudden because the tech was able to take this product and they confused it, the pharmacist might not pick up the error. Redundancy is important for that double-checking in our system is important. I'm not so sure sometimes we aren't making our own set of errors.

But you can start to see what some of the differentiation starts to make its own problem. And in terms of us trying to differentiate it in a system that is complex, it starts to become quite problematic. And you see some of the things we try to differentiate in certain systems are problematic. And the other thing - we also mentioned understanding - we often talk about what people would understand and the suggestion that somebody would ask what NaCl is. That doesn't surprise me very much at all. There are a lot of people who work within the drug distribution process who just are not savvy. They don't understand drug names. They don't understand how drugs are named. They don't understand the difference between the drug and

the salt. There's a lot of issues like that that keep coming up. And so you can tell that the people who - and if one person makes an error can then lead somebody else to make an error as well. And so you can see things that make a difference.

So here again, color, talked about color. While it makes a nice difference here it leads to error here. And so I think it's a - use of color has a major problem is that in isolation it looks good. In certain selective areas it looks good, but as the number of items accumulate, the number of things we have, I think color leads to error. Color actually I think has even more of an impact on somebody's recognition of an item than does form. So anything - and there's fewer colors than there are forms, that is, names. So I think color is actually a problem. I think it should be used extremely - in extremely rare cases if at all to help differentiation. Because it's just going to accumulate. When you put it in an environment like this, things start to really look alike. This is a good example where things that are black just look alike. And the names look pretty similar, sodium chloride versus dextrose. This is just a good example of - we send the vials of the drug in with

the bags to be prepared into our clean room to be made. And so often these things are sitting next to each other in another bin. All they do is tumble in, or somebody says oh that one fell out and put it in the wrong bin. All of a sudden somebody who thinks they should be the same thing, they aren't.

So and this is some prepared IV products. I'll talk about - only mention that color, believe it or not in our pediatric system we use color. But and you can see here. Here's our pink, our yellow and our blue. But they don't mean specific products. Yellow - I mean pink, that's for patients who are 0kg to 5kg. We have standardized concentrations for them. Blue is for patients who are 5kg to 20kg and yellow is for anybody over 20kg, including adults. And these are books that tell us how we make each of those specialized products that we make for those patients. The labels are all yellow. We don't differentiate them by color. We don't differentiate the product by color, but we have identified that this type of patient gets this kind of product. And it has a quite different dynamic than picking things by color. We found that actually to be a very effective process. So here's color, two drawers, as I said you can open up.

We've really tried to avoid having two of these products in drawers right close to each other or one on top of each other because you can see two different drugs piled together, there's not much to tell the difference, is there? Especially when you add the over-wrap. So color is bad if you ask me.

What about labeling? What should be on the - what should be the name? Here's magnesium sulfate, foil over-wrap. It says this is - they're very reflective. We have fluorescent lights and lots of them in the IV room because the IV room you want to have a lot of light because you see a lot of words and it's easy to read. But you can see because of the reflectiveness of these products all of a sudden things start to get obscured. And Mike showed you some of the bags, the way they fold. And 1g, this is 1g of magnesium sulfate. It's interesting. Here's 4g and here is the 1g. So they have 1g total and that's how we usually give this drug, but again here's the concentration, 40mg per ml. And over here 10mg per ml. And they do differentiate. Do you know that the 40g bag is 40mg per ml? The 40g bag used in obstetrics. So you can start to see obviously we keep those things way away from these because it's not hard to see how those

things differ. But also you start to see where these things become prominent. We almost never see anybody order magnesium sulfate. They give them 100 cc's of 40mg. That's not how it's ordered. It is ordered as 1g, 2g or 4g. This should be more - in this type of product if you ask a pharmacist, this is the operable 4g in 100 cc's. That's the operable function. It's not 40mg per ml. We would see in a product like this, this should be not - this should be the prominent. This confuses people. We've got another product that's this. So 1g is important. So as I said, context. If you give the whole dose, typically that's how it should be expressed. If you're giving it a drip, typically it's concentration that's important. And this just goes to show you that this becomes what your eye comes to is this 40mg.

What about the operable value? Here's dopamine. Right, we have these different concentrations. And look how we express the concentration, 3200mcg per ml. And that's good because dopamine is dosed usually in mcg per kg per minute. So this is operable. And this is probably okay as an identifier. For these type of drugs it probably does make sense to have both the

concentration - the total dose, total amount contained in bag and the concentration expressed appropriately. But this should be done consistently. I think we're always looking over bags, how much is this. Some of them are in boxes, some of them are over here, some of them are over here. This makes them start to look like - but if there was some way that we could be a sequence, some display makes a difference.

Now what about zeroes? Lots of zeroes. Zeroes confused people. Decimal point errors are not uncommon. Somebody calculates a dose, they make a tenfold error. Just I think, I bet while things are dosed a certain way. Here's 2500mg in 250 ml's. Why did you tell me that? Why wasn't it 2.5g in 250 ml's? And you gave me 10mg per minute of Brevibloc. That, sometimes the boluses are given in milligrams but it might be dosed in milli-mic's per kilogram or milligrams per minute. Just funny how this is expressed. Dopamine again, I hate to pick on any of these, but it's a good example. So dual expression is important, but how it's done I think really needs to be addressed by the human factors people because I'm not sure exactly how it is. I know that we see errors because of this.

Couple of points again, going back to that extra information. Here's that Gentran 40, you know. So why is all this stuff on here? Why do they tell me that there's all this. Look how big this is and then you tell me in pretty big font again down here. I don't know why that's done. That doesn't make any sense. We never read this stuff. We don't really care how it's buffered. I can go to the package insert, I can go online. I think those points are very valid. So all that stuff you think has to be on there, nobody ever reads it. And if we do it's because we have a problem and we need to.

What about the patient labels? Here's a good example. Here's that dopamine bag we would take. We're going to put one of our labels on it. What happened to all that stuff that was on there? It got covered up, right? This is how all of our dopamine bags look. If the nurses take one out of there, in an urgent situation they can't take them out of their - they put a label on it over the same spot. Here's more patient labels. Here's some prepared small-volume. These happen to be chemotherapeutic agents. We put another big label on it. What did it cover up? All that stuff that

was so important. Also, here's a patient label. Interesting how they - now these things come together and we'll talk about human factors. Gentran 40, sodium chloride. The pharmacist enters into the computer the patient was supposed to get 3 percent sodium chloride, 500ml. Technician goes and selects - going looking for this. What do they find? They find sodium chloride, 500 cc's. It's not the right concentration but to them it might be close enough. This goes to the pharmacist. Look at this. What caught their eye here? It wasn't this and it wasn't this. It was sodium chloride. Well gee, not a big surprise is it? So here's a classic example where human errors, you know. This statement, this is what caught their eye. So you can where expression and what's on the label can make a huge difference. Now this is a very nice visual example of an error caused by that.

And the last point to sterile water. Again, sterile water you know our point has always been keep them - just don't let it get out of the box. That is, it goes only one place in our IV room into one drawer and the problem is as I mentioned there's lots of places where things can get diverted. You know, if somebody makes a mistake in

central supply and orders sterile water or something and it ends up on a unit because someone picked up the wrong box because it was labeled poorly as Mike showed, ends up on a rack somewhere. Somebody says, you know somebody's looking for dextrose 5 percent in water and they see water, they pick it up and they give it. So you know, differentiation of that bag. There are certain bags that maybe perhaps we should make them very differentiated with very bold warnings on them. Use some of that real estate to say that. And I think the clear thing though is that they also, no matter what we do with it it has to not be available to be selected from.

And so in the product cycle we have to identify things multiple, multiple times and that humans don't identify things the way we want them to. So the things that we're trying to talk about here and make it our ability to select products in that context really has to consider what that context is like and that is very cluttered, very dynamic with a lot of people making very quick decisions, people trying to work quickly, people again doing the things that they're familiar with. They're going to select the things that they most think match what they're looking for and they're

going to choose it. So there does need to be standardization across the products. There was an effort made with OTCs. I'm not saying that was perfect, but that was done. Some decided that we're going to make OTC labels standardized. Distinguishing features are helpful until something else has similar distinguishing features. We need to minimize the amount of information. I'll reiterate that point. We need to design these things to accept patient labels. We're putting bar codes on things. When we put patient labels on things, that typically means we don't have open stock on the floor for the nurses to select them which is a good thing, but we're going to cover it up with a patient label coming out of the pharmacy. And so we need to understand what also the context of use does to the recognition of the labels that we decide are good. And we also need to make a system that's more responsive to change and I think that's been said as well.

So those are kind of the pharmacy standpoints. There's many other things that can be talked about in very specific circumstances, but I think that those are the high points and I'll stop there and I'll thank you for your kindness.

(Applause)

MS. BECKER: Thank you, Dr. Lesar. We're going to switch hats again and bring back the manufacturers perspective and some initiatives that have been created. Susan Olinger is the Corporate Vice President of Regulatory Affairs for B Braun Medical Incorporated and has served in that capacity since October of 2004. In her role as Corporate VP she oversees the staff responsible for both device and drug regulatory affairs in the United States and Canada as well as interacts with B Braun medical regulatory affairs staff worldwide. Prior to joining B Braun Medical Ms. Olinger was employed as Director of Regulatory Affairs for both Ono Pharma USA Incorporated and Abbott Laboratories Incorporated. She received her BS in Physical and Life Sciences from Wilson College. In addition, she has completed course work for her Master of Science degree in Biomedical Science from Hood College and in Health Law from DePaul University. She is currently pursuing her juris doctorate from Concord University.

MS. OLINGER: Thank you very much. Good afternoon everyone and thanks very much for inviting B Braun to be a part of the meeting today. While

Shawn is putting up the presentation, I've been very interested in the presentations and especially Debora's when she was talking about the visual limitations and the low light conditions in the hospitals and so forth. And I was smiling to myself because I made my husband install a 10-light chandelier in our master bathroom so that I would have more light in there. And for those of you who were brave enough to stay at the Pooks Hill Marriott last night, I was pleased to see that they had done a lot of renovations, but the counters in the bathrooms were so wide that I was virtually crawling up on the counter to get close enough to the mirror without my glasses. So I understand those limitations that people go through.

For those of you who are not familiar with B Braun, and I do pronounce it B Braun partially because that's the way the Germans pronounce it. We are a German company. And also because people tend to not ask if I can get them good prices on toasters and electric shavers. B Braun is actually a very old company, about 169 years old. In Germany the corporate headquarters are B Braun Melsungen AG and if you're in Germany that's B Braun Melsungen AG is the way they say it.

We're headquartered in the United States in Bethlehem and Allentown, Pennsylvania. About 30,000 people worldwide. And we have a product portfolio, and I apologize for my typographical error, of about 4,000 finished goods and about 12,000 finished components.

I will be able to get us back on track I think in terms of time today because a lot of the things that are in my presentation have already been discussed ad infinitum, like lettering and color differentiation and so forth. So I'm not going to spend a lot of time going over that, but I have taken some notes as the presentations have gone through and maybe I can come up with some different things that we could discuss in panel discussion. So I wanted to talk a little bit about - again about lettering, sidebars and the upright and inverted positions, a little bit about color differentiation, watermarks, symbology and bar coding.

So we go back again to the lettering. And this is an example of the tall man lettering. Again this is our duplex line of cephalosporins where we do have tall man lettering, but not on all of our duplex products, not on all the ceph products. One of the reasons for this is because we

have - some of these are ANDA products, some are NDA products. And we talked earlier about there was some difference in the latitude that OGD has with labeling as compared to what the NDA review divisions have. So we have not been allowed to put tall man lettering on all of our cephs, but we do have it on a few and I just wanted to show you these. I do think it's a good thing to have it on this line because we have CefuROXIme, CefaTAXim, CefTRIaxONE, CeFOXItin. These names are very similar I think and I think that the tall man lettering really helps with these particular products. But I also agree that there is a big danger with overexposure in using the tall man lettering. And FDA does have this defined list of products for which you can use that. And the cephalosporins I will tell you are not on that list, but we do have the tall man lettering. It has been approved by the FDA. But I will say that I agree with those of you who have spoken before me that these labels are cluttered.

Symbology. B Braun, Baxter at the time, Abbott now Hospira in a HIMA task force did develop this scheme for labeling. The dextrose, the three different concentrations and you can see the symbols

that have used. I think that that actually looks good on these labels. But again, throughout the presentations I've seen that what I thought looked good on the labels didn't necessarily translate to what looks good the end users. So I think there is a lot of work that we can do in those areas. But I think these are easily identifiable and these types of changes with a symbol like that I believe are relatively easy for us in industry to implement on our labels.

Here are examples of some sidebars that I think add additional differentiation. Makes the name more prominent on the label. It makes it a little more easily identifiable. And as you can see on the heparin we've got some color differentiation as well here. The inverted bar I think adds as well because these labels you can read whether they're hanging on the IV stand or whether they're laying in a drawer or a bin. So I do think that the inverted bar adds a little bit of differentiation to the label.

Colors and symbols again. And with these we've got the concentration in a different color. But I see the point that people have been making today. If you look at this it reads very

differently from here. We've got different units on there. And I do think that standardization of the way we do the units could be something that we could work together with industry, with FDA and with the users in order to develop better labeling in that regard.

This is an example of from B Braun's PAB line where we've used a color differentiation for the metronidazole, the dextrose. What we've got is red for pre-mixed drugs and then black for the drugs that can be mixed. And then for our PIC line for the sterile water, the basic irrigation products and for the urologic irrigation and so forth we've got some color differentiation there as well with the red, yellow and green. But again, the lettering is still all black. And you can see that we've got room here for bar codes on these. So there is not a lot of real estate left on these labels, but I think they don't look quite as cluttered as some of the others.

Watermarks are another thing I think that can distinguish a label. And this is an example of two that we have. And I'm actually very ambivalent about the watermarks. I believe that FDA doesn't care for them too much. I like the way you

can actually see this on the label. I think it stands out a little bit. On the other hand, I think that it really detracts from the text on the label and makes that hard to read.

And bar coding, that was - actually the Coordinating Council for Medication Error and Reporting had recommendations on bar coding, that they should be scannable and human-readable, they should have the NDC number, the lot and batch number and expiration date. They should be down to the unit of use, a standardized location on the label and they also recommended wraparound labels. Well, the final bar code rule went into effect last year. I don't know if all the companies have implemented them yet. I know that some companies, including B Braun, had to ask for an extension in order to implement the bar coding. It was more difficult than expected because of the equipment, getting the equipment working correctly to put the bar codes on the manufacturing line and the fact that we had to shut down our manufacturing lines in order to get the bar coding up and running and to get that implemented. So I don't know if everyone has been able to do that yet. It did pose some difficulties and some logistical problems. It was expensive for

us to implement that. However, our bar codes do conform to these requirements.

Wraparound labels, we're actually looking into that at B Braun because we're looking at a new packaging configuration for some of our products and we are looking at wraparound labels and whether that would be good for this particular product. But again, even bringing a new container to the market, it takes a long time and it takes a lot of money, in the millions of dollars to introduce a new container. The one thing I wanted to talk about as well, the standard location of the bar code label. That again is logistically difficult for a company to do, to standardize that.

So, some obstacles. The bar coding requires that the end user has the equipment to read that and the equipment to read the bar code as we have done that. I think that color differentiation and you've heard a lot of that today from everyone. I think everyone here agrees that color coding and color differentiation is not the final answer. And I've heard a lot about standardizing the labels so that all the manufacturers have a very, very similar label. But then I also saw in the last presentation that all those labels looking the same can lead to

some confusion as well. So I do have a little bit of concern about standardizing those labels so much that you really can't distinguish not only between manufacturers but between product lines and types of products. So I wouldn't want to add too much more confusion there. And the companies will always want to have some differentiation so that you know whose company's label you're dealing with.

Over-wraps, I wanted to talk about that. It wasn't a part of my presentation, but I've heard about over-wraps today as well. We don't put the - we would not put the over-wraps on if we didn't have to because it is an extra cost. It takes more time to do it. We would like to eliminate that, so maybe that is one of the things that we should be working on as a group, industry, FDA and the users so that we can see how we could eliminate over-wraps on these products if we can.

And back to standardization of labeling. Maybe we could standardize more the way we do the concentrations and the strengths and the units on the labels. That may be more helpful than trying to standardize in other ways. And then again, eliminating some of the information that's on the labels, I think those are three things that we

should probably work on as a group to try to do. And although eliminating a lot of the information on the labels could go back to actually amending the Act, the Food, Drug and Cosmetic Act, so all of these changes are not as easy as we may like them to be.

So just in summary the industry response to labeling issues has been bar coding, color differentiation, symbols, watermarks and lettering. But as we said earlier today, we really are required to follow the agency's regulations on labeling and the agency itself is constrained in what they can do with labeling, especially with generic products because the generics have to follow what the innovators do. We think that - I think that color-coding leads to more of a reliance on the color than the text and at the end of the day there's no substitute for reading the labels. Again, I think we should work as a group on minimizing the information on the labels as much as possible, designing based on what the end user wants, and these are points that I took from the last presentation because I think they're very valid. I think they're things that we can work on and that they may give us a good result. And the

last one is room for patient label if the pharmacy has to label and put on there. So that's all I have. Tried to keep it brief. Again, thank you very much.

(Applause)

MS. BECKER: Can I have all of the speakers join us up front? I think the ones even from our first in the morning. They said they wanted you to come up and answer questions if necessary. There should be enough room. It might be tight. I actually have another request. If you have a question, if you could please identify yourselves so we can get that down. That would help. Now that everybody's cozy up here. Questions for our panel? In the back?

MS. MCGAHAN: My name is Chris McGahan. I'm with Abraxis Bioscience. And the question that I have is for the pharmacist and the nurses. Given that there's a lot of extra information on the labels, a lot of our labeling has spaces to put patient information, time that it was opened, patient's name. Is that something that really gets used, or is that just part of the extra junk that should come off?

DR. LESAR: For the most part it's just

extra things. It's either going to get covered up or it's going to be ignored. Even right down to thinks like what's the salt of the drug. Even saying things like injection. You can say why are you telling us injection. To me, most of that stuff is extraneous, not important at all. But to that end user we can always look up in our system when we decide to make something, everything is standardized. We're going to look up what the buffers are, can we make it, what the stability is, that's all going to be built into this process. These are controlled through other mechanisms than somebody holding the bag and reading it. So many of those things are already constrained by organizations such that they become not important because there is not - they're not a variable that is important that has already been constrained by some other system in the organization. So you're not choosing between the fact that that information doesn't provide anything for you to choose among as it were. So it's not really important or that's already been considered.

MS. SIMMONS: Am I getting it straight that you're telling me that on the actual medication, the IV bag you have room for that?

MS. MCGAHAN: No, more like on the PVP bottles and some of our other, like 30ml, 50ml bottles. We'll have on them spaces that'll say the patient's name, it'll say the time that it was opened, it'll say initials of nurse. I don't know that - that's my question is if those type of things are actually being used or if it's just taking up extra room. Because it'll just say date, time, and there's little lines to write this information in. But as I'm seeing, if it's coming from the pharmacy it looks like another label is being put on instead.

MS. SIMMONS: I will tell you that nurses have many, many, many places to document those things. And it's documented on the MARs, depending on what kind of system they have in place, the bar coding and things like that. I would really - I would very much doubt they ever look at that.

And you know in all honesty too, with due respect to the industry and what you're putting on there, we really don't care about what company produces it either. So we really don't care about trademarks and that sort of thing. And for most nurses I think if you do your walkthrough as I suggested they're going to say who is that. Because again what they're looking for is that essential

information. They have to get that particular task done safely.

DR. LESAR: If you look at our IV labels that we place on a bag that we have manipulated it has very little information on it. It has the name of the drug obviously. One of the things is we take that label and put it on the right drug. It has to be there. It might have an expiration date which once it's come out of the over-wrap that dating is placed by us. It's no longer - that bag doesn't know when it was taken out of the over-wrap and when it's been taken out of the refrigerator. So some of those things, the initials typically are the signature of the pharmacist and that's actually pretty much a requirement for us to be able to track who checked that bag. Well you can do that by logs, you know. It's always been a tradition that doesn't leave the pharmacy unless it has that written initial on it. So there are some things on there that that's not particularly what I would call extraneous information. But we've often been asked by nursing interestingly enough to add all kinds of things to these labels. And we've actually been the ones that are saying you know does this drug need, double-check is this a high-alert drug. That often

has to do with safety as well. And actually we've been sort of against that because we think it just clutters the label and obfuscates some of the other important information. So to your point is I think we try to reduce that. In some cases you know that's not quite possible, but we work pretty hard to keep that information pretty small. But some of it you just have to have.

DR. COHEN: I just want to remind people too that most of our healthcare organizations I guess outside of ambulatory care are accredited in some way and there are accreditation requirements. So in the past few years much more emphasis has been placed on having pharmacists prepare a lot of these doses. So before where some of the drugs that you might be talking about had to be labeled by nurses up on the nursing units, that's actually done now in the pharmacy. So it wouldn't be a bad idea to have somebody in your company kind of stay in touch with the various accreditation requirements. For example, in the operating room environment there were some new requirements through National Patient Safety Goals for labeling of products. And that's actually created somewhat of an industry in some ways for some companies.

DR. LESAR: I just might also add that there's tremendous limitations to the pharmacy system labels that I think could be a whole other discussion about - our ability to create labels that differ. We struggled, we had to talk people into allowing us to do tall man lettering onto our IV labels for instance. So I think there's some limitations there in terms of what our abilities are as well.

MS. BECKER: Thank you. Yes?

AUDIENCE MEMBER: Dr. Lesar, you mentioned the potential opportunity to put dosing units on the IVs. And while I would agree with that, I think we have to be really careful. We measured the variability in a hundred hospitals in their drug libraries and their smart pumps and we found as many as 11 different dosing units for one drug. And so I think the amount of variability that actually is in practice, whether the drug is being dosed as milligrams or micrograms, whether it's dosed as grams or milligrams. Magnesium was our all-time winner with 11 dosing units. So putting dosing units on there and the concentrations, it's a double-edged sword I think. Something we need to be really careful. Obviously it's not good practice to

have so much variation, but it's just that's the way it's developed and we were surprised. We're now looking at 250 hospitals and we're finding even more variability than we found in the original hundred. So the concentrations are less variable even though that's what JCAHO has focused on, but the dosing units - and then when you throw in bolus doses which are almost, they're always different units than what you have for continuous infusions. It makes it even more complicated.

MS. BECKER: Yes?

MR. BRUGER: Andy Bruggar, Baxter. I was interested in the pharmacy labels that are applied to the containers. Are there standards as far as the size of those labels or the content of the information that goes on those labels?

DR. LESAR: I don't believe there's any standards. I mean, it sort of depends on who's your vendor, what kind of printers you use, obviously your software. There are typically what we would call what would be the standard: date of preparation, the patient's name, drug, concentration, total amount. There are some actually lists of what has to be on the label. You know, JCHO actually defines what the minimum

labeling needs to be and so some of that is actually defined through JCHO. And you know typically it varies from hospital to hospital, but the standard elements are going to be there.

DR. COHEN: I just want to say that we've actually been working with some of the computer system vendors and we've actually started a process to help somebody come up with official standards. We've actually been interacting with practitioners in these companies and have put together some standard label formats. And there are some constraints like you know not enough space in certain fields you know to do what we would like. It's not the easiest thing in the world to do, but there are two label formats that we have been working on. One is already finalized. Another one is in process and we're close to it and we can provide more information about that. Or maybe Allen, are you - Allen Vaida, are you familiar with where we are with that at this point? Stewart's project? Oh, okay.

DR. VAIDA: Yes, I think what we were saying as Mike was saying too, we're working with some of the vendors with that but I'm not familiar with anything else.

DR. COHEN: Okay.

DR. LESAR: I will say how hungry we are for that type of information that the minute we saw that it was printed off my computer, given to my computer guy and said we need to match these standards. So I think that those are the type of things that as practitioners that we are looking for. So I mean the importance of that, we know it's a problem and we wanted to have the minds come together about what this should be.

DR. COHEN: That's exactly what's happening. You know, one particular computer system vendor has many different hospitals and they're all telling them to do something different and they would like to have a standard way to please all their customers. So that's why we've been interacting with them to do that.

MS. BECKER: Okay. Question in the back?

AUDIENCE MEMBER: Yes, I have a comment related to the same thing with the labels and it's related to placement and to bar coding. You know, the manufacturers are doing one thing with respect to where they put the bar code on there as well as where they put the labels. And the pharmacies and

the hospitals, I'm with a pharmacy outsourcer and we do the same thing with respect to trying to put bar codes and label placement where we want to put it. And if you look at, I'll give you an example on the LVPs. I mean there's hundreds of millions of LVPs sold with saline, dextrose, lactated ringers, et cetera, and pharmacies are adding drugs to what percent of them? Let's say 30 - 40 percent, 50 percent. And they're putting their own label on top of the manufacturer's IVs. Well here's a problem I can absolutely tell you I've been in a lot of hospitals and I watch to see where that pharmacy label gets placed with a drug in it over top of a manufacturer's IV bag of a plain saline or a plain LR, something like that. And just like I saw up on Dr. Lesar's label, got a great label but you didn't cover up the sodium chloride up at the top and you know whether that's routinely the way you do it or whether that's just the way one technician did it, it now says sodium chloride, the underlying label from the IV manufacturer, and now it's got the drug with sodium chloride underneath on the pharmacy label.

Well, one of the other issues that it raises is sort of a race for the middle of the bag

by the bar coding because as we all know these curvatures are not always you know read. You put a bar code on the outside of an IV bag, it doesn't get read very well. I as a pharmacy outsourcer have been asked when I put my label on it with a bar code can I cover up the manufacturer's bar code label from the Baxters or the Hospiras of the world. Can I cover that up because now the nurses don't know which bar code to read. So I'm throwing out a lot of different things that probably could be commented on by any of the panel members, but one thing I observe is if we're looking at taking some of that large language off of an LVP that's in the center that may not add a whole lot of utility, maybe we could lower the base IV labeling into the middle of the bag, keep the big bold letters of saline and lactated ringers, et cetera, so when that pharmacy label goes over top of it it's no longer normal saline, it's a drug in normal saline and the bar code can be read. So I've covered a lot of different things here, but I'd love everybody's comments on that.

DR. LESAR: I'll make a comment about the double bar coding. You know, Mike's reported that in a couple of cases with some other products

but you know if you think about it, if a patient is on D5 or normal saline and the hospital happens to be bar coding the IV fluids, that patient who might be on dextrose, I mean 0.9 percent sodium chloride as an IV infusion typically is product-based. The computer doesn't know if they bar code that, that's an authorized product for that patient. They may be holding a drug that isn't that patient's or is the wrong drug for that patient and bar code simply the bag. The computer is going to say - the first thing if it doesn't alarm, they're going to hang that bag. Do you understand? Or the IV pumps with IV bags. So actually that sets up a tremendous danger and as Mike said, there are certain products that actually have two bar codes actually on the drug products themselves. I think your point is taken very well with that. I think that we're going to see those type of errors as we extend bar coding into the parenteral solutions which I think is an eventuality anyway. I don't know how much that's being done. We decided not to do that at this time because of that specific problem.

MS. BECKER: Does anybody else want to address that? Yes? In the back.

MS. BENYA: Laurel Benyo from Ben Venue

Labs and I do have a question. I also was here with Dr. Cohen about two years ago when we talked a lot about color in this same room and nothing came of it. And I guess my question is going to be rather adversary, but what is going to come out of this meeting? What is the next step? Who is going to take the leadership role? I am a generic drug manufacturer. My hands are tied by regulations in the agency. I cannot change my labels. So what group is going to take the action items from this meeting and go with it?

MS. BECKER: I guess I can open that up to ISMP and USP and FDA.

MS. COUSINS: I was going to say that we have three cosponsoring organizations here who will meet following this meeting and I can tell you one of them will be moving forward. I won't tell you which one, but no. I'm sure you'll see activity. It is the intention of all three organizations to use this information in a way that will benefit you ultimately.

DR. COHEN: And keep in mind please, ISMP is not a regulatory authority or a standard-setting organization. What we do is collect the information from the field, we do investigations, we

try to advocate for change but we have no real authority to do any of that. Even setting standards, you might have heard me say that you know we're trying to set some standards for labeling that we can take to someone else to make it official. So if that's necessary. It may not even be necessary in that case.

MS. COUSINS: And Mike, I would add that you do keep us all honest.

MS. BECKER: Okay. Hopefully we answered your question. Questions? Yes, Carol?

MS. HOLQUIST: Yes, I just wanted to comment a little bit on the color-coding because I heard that come up a couple of times today and that you know what came out of that. Well, I guess what came out of that is that we heard from a number of people that I guess there's inconsistencies in or differences of opinion in whether color-coding is good or not. We heard from some of the front-line practitioners here today that they don't like it. They're not in favor of it. However, we did hear from some other clinicians who said that's all they use, such as the ophthalmologist and the dentist. And so from a regulatory perspective it's very difficult to come out with a statement that says

we're not going to ever allow color-coding when in fact it's been found to be useful in certain circumstances. So I think what we took home from that meeting that day was that color-coding can be a problem and we have to be very careful when companies want to come in and implement new color-coding schemes that haven't been out there already, or there may be some improvements we can make with some of the ones that are already out there. Like for medical gasses, that's a color-coding scheme that's well known and if we went and said you can't use color-coding, that would have a very negative impact. So I think what comes out of these meetings you have to take into context everyone's opinion and sometimes it's very difficult to come out with one standard that works for everybody. So it's not that we're ignoring it, it's we have to tread carefully with any new considerations.

DR. COHEN: I just have one comment about that. Those of us that were here that day I think were - at least the practitioners and the folks from industry were kind of shocked to hear one of the proponents of the color-coding say it's great because that way we don't have to read the label, we can just pick up the container and you know start to

use it. So. And then knowing that within that particular field we actually have had a series of intra-product line mix-ups. In other words, that drug category would be mixed up because the category was color-coded, not the individual drug product which would be very difficult. So you know, and that's still going on too.

MS. HOLQUIST: Right. And I recognize that, and that's some of the issues, but I think - I don't think you're going to see an agency line that says you can't do it because in some cases it is found to be effective, especially with the medical gasses although there has been still mix-ups with that. But I think to revert back you know, we have to look forward and anything new that comes in I think we have to really scrutinize.

MS. BECKER: Other questions? Jerry?

MR. PHILLIPS: Jerry Phillips, Drug Safety Institute. A lot of things today we've been talking about the tall man letters. One of the reasons why we're doing tall man letters is the nomenclature system that's used in established names for generic names. And one of the parties that needs to be part of the discussion is the body that determines generic names which is the United States

- USAN, the United States Naming Council and the INN who approve generic names. We have lots of evidence of medication errors occurring between two generic drug products which is driving the tall man letters. So in order to get to the solution there must be a discussion with that body about looking at this from a safety perspective probably. The system that's in current use uses a stem system which identifies the therapeutic category of that particular drug product. That has a lot of usefulness from a clinician's point of view, but it also introduces similarity. I don't have the answers. It's basically just a statement. Thank you.

MS. BECKER: Thank you. Elizabeth?

MS. MILLER: Hi, I'm Elizabeth Miller with USP. I'm a pharmacist that works with the Safe Medication Use Expert Committee. And there's been a lot of talk about enhanced or tall man lettering today and I wanted to share with you briefly the Safe Medication Use Committee is working on this issue. The committee has some concerns, one being, as many of you have raised in your presentations the effectiveness of tall man lettering, the paucity and lack of data to support not only its use but also what's the most effective combination of lettering.

Dr. Lesar, you pointed out very nicely that the stems might stand out as opposed to what is capitalized. Also, other mechanisms of enhancing lettering, for example we're showing a lot of mixed case, but I saw some interesting use of also mixed fonts. That's why they use the terminology "enhanced lettering."

Another one of their big concerns is standardization. One of you brought up in your presentations the fact that you might see manufacturers using one depiction of tall man lettering whereas you might see in drug information or in a computer pick list another way of representing that non-proprietary name. The last thing that their concern centers around is this dilution effect with the overuse of tall man enhanced lettering and how that could have negative impact on the practitioner using the product.

The committee is getting ready to survey users, nurses, pharmacists and physicians that are actually exposed to this tall man lettering and they're going to broadly disseminate an internet-based survey out to healthcare practitioners of all the allied healthcare professions. And what they're looking for is basically to see what the awareness

and recognition is in the field of the lettering as well as how it's used in practice. Are folks doing their own homegrown tall man lettering in their own systems? And to sort of get some of their perception of the effectiveness of how it's being used.

My question to you and what I'd like to bring back to the Safe Medication Use Expert Committee is do you have any recommendations for this survey? Would you like to see certain things asked of front-line practitioners about how you're using your tall man lettering or enhanced lettering on your products and if you had any other recommendations for things you'd like to see asked of the front-line practitioners?

MS. BECKER: Mike?

DR. COHEN: If you circulated something, you know I'd be glad to offer some suggestions for that rather than going over it right now. But I did have one thought. I was talking to Diane a little bit earlier, just an idea, but this tall man letter has been around now for several - of name pairs. And the companies I guess have been using that now for at least two years I guess on their labeling. Things like dobutamine and dopamine. I'm not sure

when the companies, Baxter I guess implemented that. Others have now as well. But it would be interesting to take a look at the medication error reports perhaps that have been sent either to your database with MedMarks for example or some other databases that exist in the country and then maybe even ask the companies if they've. You know, maybe if you put all this together with several of these name pairs we might be able to see that you know given IMS data showing a certain level of use of the drug and taking that into account, perhaps the number of error reports have actually gone down or gone up or stayed the same. You know, I just don't know. Maybe that's something that we could do that would be helpful to the committee.

MS. BECKER: Thank you, Mike. Any other questions? I don't want to miss anybody. All right, does the panel have anything?

DR. DUFFY: I have one question for the panel. In the international arena, what kinds of solutions to this problem have been arrived at other places? I'd be very interested to hear.

DR. COHEN: One thing they do is they don't use infusion bags as much as we do. They use syringes and syringe pumps for the most part to give

a lot of their IV medications. And that, you know that actually has - it's kind of been a barrier to some of the solutions that we've had. For example, in the United States not only have we changed the appearance of the vials of concentrated potassium chloride, but hospitals, acute care facilities that is and others have removed it from patient care areas. And we've been able to do that because the industry has brought us you know through their technologies pre-mixed solutions which have been great. And we don't have fatalities from injecting potassium chloride concentrate versus sodium chloride as we once did. That still continues in other countries, but there's not, you know there's not a product out there in some of the countries. They don't have a pre-mixed bag and even if they did I don't know that they would use it because they're so used to syringes. But that is really something that you know is different about other countries and that's happened.

MS. BECKER: Well, thank you very much. We will have - oh somebody else? I'm sorry.

MS. BERWITH: May I ask a question please? Yes. I'm Geneva Berwith. I'm from the Penn State College of Medicine. I'm a medical

student. I'm actually going into the field of anesthesiology and I think that this meeting in itself has a big impact on my future career, the future of medicine and the future of nursing, the future of pharmacy, I mean every field. And so but just from my perspective I've seen people say there are various things that work, but they said that those same things don't work. The tall man lettering, the bar code scanning, the color-coding. I heard good things and bad things, and many people have different opinions. And I think that we're a big powerhouse right here in this room of minds that can make some decisions. However, I think that thus far from what I've heard even the panel say decisions are being made based on trends. They're being made based on what the current practices are. They're not being made necessarily based on evidence and we've already discussed the fact that there is not solid evidence out there right now saying what works best. And I think that committees work well to some extent, but in the culture of medicine in this day and age the next generation that's coming up needs to practice medicine based on evidence. I mean, that's - I'm sure you guys have heard it, evidence-based medicine. And I was just

wondering if there is going to be funding to go ahead and research these areas to see if these actually will work instead of just talking about it.

MS. BECKER: Comment?

DR. COHEN: Well, the Preventing Medication Error Report from the Institute of Medicine, if you look at that there's a whole section or chapter rather on research and there's a recommendation actually that people move - that researchers move more towards error prevention strategies and move away from the error rate type of research that's been done so much in the past. Not that that isn't still needed. Certainly in some areas it is, but moving more towards does a double-check work, does tall man lettering work, things like that that would help to prevent medication errors in the case of that particular committee. So I think there's some hope for that. For example, I'm sure AHRQ is taking that very seriously and you know in the future I'm sure some of the funding requests, the RFAs that come from them will probably be in that area.

DR. WILLER: Just one point from me. You've heard all the speakers today, especially Susan Olinger kind of summed it up well. The

ultimate reason there's medication errors is a lack of reading the label. And the things we propose today are ways to try to improve the visibility of the key parts of the labeling. And as you rightly point out, there isn't solid data that any one or all of them have an effect. We are experts in labeling or have a lot of experience in it and we believe that it's better than it was. When I started with Beecham Labs we had as I said two colors, green and blue, and it seemed to work fine then. But the trend came to color-enhanced labeling to improve the reliability of people getting the message. And so until there's more data your idea is a good one. For now we've got to do the best we can until the agency can make changes, until the law can be changed, until we can effect changes on our own. The ones we're doing now are the ones we can do without significant changes in the law. So it's the good ones we're making now. Better ones are going to come.

MS. SIMMONS: I think I have an opposing view for you. You know when we first started kind of this journey it was 1999 and we started looking at the demographics and that sort of thing and we were really an ignorant industry at that point.

Other industries where they had high-risk situations and critical situations in the nuclear industry and aviation recognized the limits of human performance, especially in high-risk situations such as anesthesiology which actually has made just probably the best strides for any particular discipline. They've been really ahead of us. What we know now is this. Humans perform in very predictable patterns. That's part of your cognitive psychology you'll go through. One of other interesting things that you learn as you go through working in clinical areas is that we all have minds that work very similar. We also have similar goals. And in the medical field that is doing the best thing we can for our patients.

It has come to my attention as I've spent more time looking at this that there's even more to it when you start looking at the science of causality which established well in very grounded literature and very grounded science and is evidence-based and that causality is not a single point. In fact, there's a term for that called single-point failure, when we assign causality to one particular subject or one particular cause. These errors that you see have multiple causes.

They have multiple factors which makes them very difficult to chase quite honestly and makes them very difficult to solve. What we have done to this point since 1999 is identify many of those and actually been able to reduce the possibility of repeating some of these errors over and over again. It is my hope that your generation after we have done this work will be even braver to speak up when these things happen so we can learn more about them. I think at that point we'll actually be able to make even further strides. Until that point we'll have to keep just chipping away at that multiple causality there to reduce the possibility of failure.

MS. BECKER: Diane?

MS. COUSINS: Just two maybe disconnected comments from each other. One is that the USP's expert committees in fact struggle with that very question. They are always seeking evidence on which to base their decisions. Unfortunately many times there's not evidence, particularly in this area, and it gives the appearance of being non-responsive or providing an untimely response because they are looking for that evidence. So it is frustrating. As Elizabeth said

with the tall man lettering, they were looking for evidence of its effectiveness or not and really found neither even in looking in tangential industries. So I feel your pain on that one. I understand where you come from and I do think it is a challenge to all of us.

However, I will say too that one of the things that the National Quality Forum struggled with when it was trying to develop its safe practices was the fact that as they collected their evidence there were a lot of safe practices that really had no evidence. Taking potassium chloride off the floor and watching the number of deaths diminish to practically zero. Those they called, they had to call them something because they thought they're things that we ought to be doing even though we don't have evidence and they ended up calling them obviously beneficial practices I think is what they were calling them which I guess is the no-brainers that we call them. But you know I think there's a recognition that there are some things that make sense to do and I think it's an incredible challenge for us as we think about changing things like standards that are, you know, these are evergreen kinds of things that we're going to have

to live with for many years. And so there's a challenge for us in where does the line fall between these obviously beneficial practices and the evidence that we have that tell us these are the right things to do.

DR. LESAR: I want to comment that sometimes that evidence would actually be very difficult to get and some of the solutions may have nothing to do with labeling. As you mentioned, you know some of the constraints on availability and choosing may be the thing to do. You look at some of the technology like unit-based cabinets. Misused, those actually produce more errors. And in this case labeling became a critical part of open matrix automatic dispensing machines, I believe a major cause of errors that we saw in those types of machines. We eliminated the open matrix drawers and these things start to disappear. So you can actually look at that evidence. It has nothing to do with how well you can read the label and how many opportunities there are to misread the label as what you change. And those are the practices that would be actually fairly easy to document the effectiveness of and actually eliminate the need of determining how the label should be made. One

problem with that is of course the more you control the risk from any single-point error such as putting the wrong drug in the wrong matrix by the pharmacy actually increases the risk because people then become more dependent on the technology. So you can see where every error is just squeezing the balloon, but some of the answers may not be label in here. It may be practices.

MS. BECKER: Well, I think I heard that the FDA, ISMP and USP would take up the cause of what we heard today. I'd certainly like to thank all the speakers for their presentations and we'll take a break and be back at 3:15. Is that still good with - that sound good? 3:15 and Diane Cousins will moderate the public session. So we're looking forward to those comments also. Thank you.

(Applause)

(Whereupon, the foregoing matter went off the record at 2:54 p.m. and went back on the record at 3:18 p.m.)

MS. COUSINS: Okay, good afternoon everyone. We'll get started again if everyone could take their seat. We're about to enter into the open portion of today's meeting. There are five speakers who will be addressing you. Three of them have

slides and so we'll begin without further ado. We have 10 minutes per speaker and I'll use the clock at the back of the room for the speaker's purposes to timing. So I'll give you a one-minute warning, okay? Our first speaker today is Dr. Gerhard Maher from Schreiner MediPharm. Dr. Maher?

DR. MAHER: Good afternoon. Glad to see so many stuck around for the 3:15 part. I work for Schreiner MediPharm and just a couple of words about the company. It's located in Germany at this point and we make what people have been talking about here all day long. We actually make the labels and nothing else. So I think everybody else was concerned also what was inside. We are the ones that actually make the thing that's on the outside, the label.

Just very briefly the kinds of products. When I thought about this is for IV, an IV focus. We make only specialty items so perhaps there are ways in which these kind of labels can be used for IV therapy that we're not aware of. Most of what we do are removable sections on labels for big areas or vaccines and biotech products. And you can see examples here of wraparound labels with removable sections, integrated texts we have. Products that

have the instructions for use integrated. And we do these for - usually for very small containers, like I say for vaccines and so forth. I was just yesterday in Canada talking to the Vaccine Bar Code Initiative that's going on up there and right now it looks like things are tending towards going towards data matrix codes that would be printed online for vaccines up there including variable information such as lot number and expiration date. So pretty exciting stuff.

Then we also have labels with integrated hangers. It was brought up before what's happening outside of the U.S. and what was mentioned I think we also see. Not a whole lot of mini-bags being used, pre-mixed mini-bags being used in Europe at least or Japan. Mostly it's still bottle-based and a big portion of our business is to integrate the hangers into the labels so that when you attach a label to a bottle that you also just integrated the hanger. And then as everybody's concerned with anti-counterfeiting or tamper evidence we have a business group that deals with that also.

I'm going to address here more or less a small piece of the puzzle of what was talked about here today. Obviously 98 percent of what was

covered here today has to do with identifying what's in a pre-mixed bag. But I'd also like to focus a little bit on when admixtures take place and specifically when you add whatever's in a vial to a mini-bag somewhere in the hospital pharmacy or something, that there is some critical information from that medication that somehow does not get transferred to the mini-bag and therefore to the patient bedside. Having such a transfer of information I think is important for a variety of reasons that might make situations difficult at the bedside and we've talked about them a lot today. Just mainly human error and stressful work environments.

So how does this happen? It's fairly simple. There are peel-off - you peel off a section off the vial and attach it to the IV delivery system. For those that would do so and write the information on a tag or something no more errors due to wrong or illegible writing, and therefore things like black box information, specific warnings, "Do not inject this product into the spine" or something like that can be transferred and is accessible right to the patient's bedside. These peel-off sections that I think are a nice way to convey information

have a broad market acceptance primarily in Europe and Japan. They are just now starting up here in the U.S. You're seeing most of them again more in the vaccine area where documentation is pretty standardized. And what are some of the basic features of these? These are not paper labels. Paper labels don't work so all the products that we make are advanced plastic foil-based. So you print the variety of layers and glue them in silicone so the nurse or the hospital pharmacy, you can remove the section that needs to be removed and then when you stick it to the container that it's stuck to it doesn't come off again.

We did some basic research on peel-off labels and at the American Nurses Association just to look and see what do nurses think about peel-off labels. And it's pretty obvious they hate writing down information. They get complaints from their bosses that people can't read what they wrote down. We hear a lot of information about when information is written down that there's a very high level of errors and a very, very high percentage thought that this would be something that they would like to have. And that's all I have. Thank you very much.

(Applause)

MS. COUSINS: Thank you. Our second speaker is Bona Benjamin from the American Society of Health System Pharmacists.

DR. BENJAMIN: Good afternoon. I am a pharmacist. In addition to representing the ASHP today I have practiced for about 20 years in hospital settings and most of that was spent in IV admixture areas and some of it in direct patient care. Most recently before coming to the ASHP I was the quality officer at the Clinical Center for the National Institutes of Health. But today I'm going to be speaking to you on behalf of ASHP in my capacity as the Director of Medication Use Quality Improvement.

ASHP's 30,000 members include pharmacists and pharmacy technicians who practice in a variety of healthcare settings including inpatient, outpatient, home care and long-term care. The issues that were discussed in the workshop today directly affect our members who handle large- and small-volume parenterals as part of their day-to-day job responsibilities and it also affects the millions of patients who are treated with intravenous therapy. ASHP has been an advocate for improvements in drug labeling and packaging for a

long time. We have previously commented in these meetings and in other forums that the incidence of error where the appearance of the product was contributory indicates that current standards are either inadequate or inappropriately applied - current standards for labeling and packaging are either inadequate or inappropriately applied and we have advised the agency in the past to tighten its control over these activities.

ASHP's policies state that practitioners as well as industry should be included in decisions about labeling and packaging. We have endorsed research on the role of human factors and the use of human factors concepts to prevent error. While some of the examples shown today by practitioners indicate that there have been some positive changes and some response to some of these requests, most of them confirm our concerns that there is still much work to be done on the problem of poor differentiation among drug products. ASHP commends the FDA and the organizers of this meeting for recognizing and addressing issues associated with intravenous medication use, a high-volume high-risk process where errors have significant potential to cause harm.

Some of you may already know that ASHP perspective supports many of the views expressed by the presenters today. We would like to comment on four key points on behalf of our membership. The first is the application of human factors, the use of bar coding, collaboration and risk reduction, and FDA guidance and regulatory controls.

First with regard to the application of human factors principles. As this group has heard today, labeling and packaging practices for many large- and small-volume parenteral products continues to exhibit lack of application, under-utilization, or disregard for established human factors concepts for preventing errors as demonstrated by the lack of standardization, cluttered, ambiguous, or poorly visible labeling, confusion about the use of color-coding and dependence on practitioners to note subtle differences among labels. You've seen many examples of this last point. The one that really impressed me that I saw in more than one presentation were those three dopamine infusions, kind of the nightmare of the IV admixture supervisor and people working in the IV room. It's easy to understand when you see these examples how a nurse or a

pharmacist, even one who might not be working in a busy or distracting environment, could pick up the wrong product. ASHP is aware of FDA's current efforts to incorporate human factors concepts in its risk assessments. We recommend that the FDA continue to explore these techniques and maximize their use to detect the potential for error.

Secondly, ASHP is a strong supporter for the use of bar coding technology as one means to accurately identify medications prior to the preparation, dispensing and administration to the patient. ASHP supports current FDA regulations that require manufacturers to label all pharmaceutical product packages with bar codes that contain the NDC number for the medication. ASHP has also received anecdotal reports of situations in which the poor quality of the bar code provided by the manufacturer renders it unscannable, therefore eliminating any patient safety enhancing benefits. We strongly advocate that hospitals and health systems adopt bar code scanning technology to prevent patient harm and call on the FDA and pharmaceutical industry to ensure that bar codes placed on small- and large-volume parenterals as well as all other drug products are scannable.

Third, ASHP supports a collaborative approach to risk reduction, similar to what we've heard in this room today. The answers to questions being asked at this meeting are critical information for all the stakeholders and can help determine what changes are needed. And meaningful change must arise from a common understanding of all the issues. ASHP believes that workable solutions can only be developed by consensus of all these stakeholders. And we again commend the FDA for collaborating with ISMP and USP and including manufacturers, practitioners, regulatory and accreditation agencies and patient groups in the meeting today. We would additionally advise the group that any proposed changes should also be evaluated by human factors experts and most importantly by pharmacists, nurses and physicians who actually handle these products to ensure the best chance for effective solution.

Lastly on the issue of guidance and regulatory control, the FDA should accelerate its efforts to incorporate relevant findings from today's workshop and other fact-finding meetings into more specific guidance on packaging and labeling and into regulatory standards. The agency should then rigorously monitor for compliance and

any adverse events associated with regulatory changes. Further, while acknowledging that changes represent significant challenges in implementation, ASHP reiterates that because patient safety is at stake, the importance and the urgency of addressing the issues presented today cannot be overstated. ASHP will be submitting more detailed written comments prior to the April 12 deadline. I would like to thank you for the opportunity to comment on this important issue on behalf of the ASHP membership.

(Applause)

MS. COUSINS: Thanks Bona. Our third speaker today is Jerry Phillips representing the Drug Safety Institute.

MR. PHILLIPS: Good afternoon. My name's Jerry Phillips. I am the President of the Drug Safety Institute which is a subsidiary of Brand Institute, a pharmaceutical consulting company that is involved in the naming, labeling and packaging of pharmaceutical products. And prior to me joining this company I was with FDA for 16 years and today I want to talk a little bit about some of the stories behind medication errors, my personal experience at the agency and then some recommendations.

The first thing I'd like to point out is that while at FDA we published an article in the American Journal of Health System Pharmacists in October of 2001 in which we looked at deaths associated with medication errors. In this we looked at the adverse event reporting system at FDA for a 6-year period from 1993 to 1998. And we identified some 5,366 medication error reports were identified for that 6-year period. Sixty-eight percent were classified as serious and approximately 10 percent were - resulted in death. The product characteristics we identified and it's important in today's discussion that close to 50 percent of all deaths associated with medication errors in this timeframe had to do with injectable drug products. When we looked at pharmacological drug category, the CNS agents, the opiates of course lead in the number of deaths. Acetaminophen, cisplatin, vincristine, Brevibloc, lidocaine and the anti-infectives and antibiotics.

Seventy-three deaths were associated with one product being given for another. Examples, potassium chloride instead of furosemide, heparin instead of sodium chloride in eight patients, cisplatin versus carboplatin instead, et cetera.

And lidocaine being put in stock bins for Hetastarch.

Now, prior to me - when I joined FDA, today we had some discussions about being a labeling reviewer in the Office of Generic Drugs. And I actually was a labeling reviewer and one of my products that I was reviewing was metronidazole. So I want to tell you a little bit about from my experience as a labeling reviewer inside the FDA. On July 8, 1993, four products at a VA hospital received mivacron simultaneously at the same time on a hospital ward. They were intended to receive metronidazole. Instead they received mivacron which is a neuromuscular blocking agent. This resulted in two deaths and two serious injuries. Now, the packaging of this particular mivacron was in a foil over-wrap like we've seen today, but the foil over-wrap had no drug identification on the main panel as we saw today. So what you see is the opaque picture window there that you can identify the drug product sometimes. And what happened in this particular case was that mivacron was a new formulary item, came into the pharmacy. The pharmacy tech knew that he only had one product in his formulary that was foil-wrapped and that was metronidazole, so he put

the things into the bin for that product. Then it got to the pharmacy. The pharmacy pulled it out of the bin, put a metronidazole label on the window as you see it there. It went to the floor. It went up there in the foil over-wrap and then the patients received it. So a lot of things went wrong here.

The agency actually looked into this. Since I was one of the reviewers for metronidazole I was looking at a paper label like you just saw and it seemed like it was a logical label to approve. But what was happening in different areas of FDA was 11 different products being reviewed and approved by different people of the same sort. We of course went into negotiations with Abbott at FDA and it was negotiated for changing the labeling from all 11 products that included the drug name and the strength and also alerting hospital pharmacy directors. And this of course is an example of the solution. And on the back, although you can't see that very well, metronidazole is on the back of the label. There were many lessons learned in this case including from the pharmacy and the hospital system to what FDA does. And if you look at it, we were approving drugs at FDA and still do in a silo-type system.

Now, I'd like you to think about CDER and FDA as a hospital. We know that medication errors occur from one hospital to the next and I'd like you to think about FDA as one big large hospital system with different therapeutic drug products. Nineteen separate hospitals working together, 2,000 employees, common set of operating principles, but sometimes communication doesn't occur between one division to the next division, et cetera.

So my intervention strategies include that both FDA and industry must be able to consider the actual environment in which the product will coexist and interact with other products and the end users. And today I'm proposing that FDA think about an FDA pharmacy which would serve as a human factors lab where you basically would have an inpatient pharmacy just like you would walk into a hospital and an outpatient that would be equipped with all the labels of those products. FDA already has the authority to ask for labels, labeling and packaging to be sent to the FDA. And that human factors lab would be used in a pre-marketing arena so that you could - any reviewer could walk into that pharmacy and look at how their label is going to fit into the

environment in which it would be used. Also, in a post-marketing arena you could look at it from a medication error perspective.

Industry should adopt a failure mode and effects analysis which is a tool used in the engineering and the device world quite a bit, but hasn't been incorporated into the drug world as much. And use root cause analysis to determine the potential error causes of these intravenous solution errors and then implement appropriate solutions. Practitioner input is paramount via market research, getting expert opinions, focus groups, or any type of a market research design to redesign the labels and packaging.

Now, some particulars. We heard this today. The strength needs to be very prominent. You need the total quantity of the active ingredient for injectables. Color and boxing or those types of things can help to differentiate between one strength and the next strength. We should avoid using confusing expressions, such as Fosphenytoin equivalents, PE units, using different types of salts. We should try to standardize our units of measure, milliequivalents versus millimoles versus micrograms, et cetera, and issue an FDA guidance

accordingly. Color. We should avoid color-coding whenever possible and use color only to differentiate important information on the label. And I think it's important to avoid standardized color formats for all labels within a company line which happens regularly. For content, the most important things are the proprietary name, the established name, the strength, the route of administration and any special warnings and that's what we should see. We should think about standardizing the placement of that information. FDA has standardized the placement of information for consumers in the over-the-counter drug products and maybe we should be considering standardizing the location of these important things on prescription drugs. I also would recommend that we amend 201.100(b)(5) that requires inactive ingredients to be on an IV label but keep that in the package insert. Thank you very much.

(Applause)

MS. COUSINS: Thanks Jerry. Our next speaker is Dr. Miriam Klein from Woodhull Medical and Mental Health Center.

DR. KLEIN: Okay, my name is Dr. Miriam Klein and I'm the Medication Safety Officer and

Clinical Pharmacist at Woodhull Medical Center located in Brooklyn, New York. The reason for my interest to improve injectable medication labeling is the result of a personal tragedy during infancy. I had experienced irreversible profound severe bilateral central neural hearing loss due to a medication overdose by a newly licensed pediatrician. This inspired me to become a clinical pharmacist and to help other healthcare practitioners avoid medication error. With the support of my pharmacy director Sheila Neiman we have spearheaded a national campaign with pharmaceutical manufacturers and national patient safety organizations to improve medication labeling system in order to avoid medication errors.

The purpose of meeting today with the FDA, ISMP and USP on improving patient safety by enhancing the container labeling for parenteral infusion aligns with our mission. This is one of the important facets of improving medication management system. It is the injectable vials and ampules that requires more attention. The FDA should support the concept that IV labels on injectable medication should be removable and transferable to syringes, medication containers and

IV fluid. This will be an additional feature supporting patient safety. It will help avoid medication error. By correct labeling, we can help assure the delivery of the right drug, the right concentration and the right dose.

All healthcare facilities across the United States face the same common goals, patient safety and by extension preventing and avoiding medication errors. One of the continuous challenges they face is maintaining compliance with the JCAHO medication management standards and its national patient safety goal. A critical part of JCAHO national patient safety goal number 3 is medication safety. Requirement 3(b) states, "Label all medications, medication containers, that is syringes, medicine cup, basin or other solution on and off the sterile field in perioperative and other procedural settings."

One troublesome area that affects every single healthcare facility is the management to ensure that all injectable drugs transferred to syringes, medication container or IV fluid are properly labeled at all times. This dramatically affects patient safety. Although much education is given to healthcare providers, there is still a flaw

in the system. Whenever the patient arrives, they transfer medication from the injectable vial to the syringes, medication container or IV fluid bag, there will be instance of non-compliance in labeling medication.

One of the biggest challenges facing anesthesiologists and surgical nurses in the OR is labeling medication. Handwriting the drug label is time-consuming, it causes delay which compromises patient safety. To hand-write the drug name and concentration on a syringe label, medication container or IV fluid bag is prone to error and can be labor-intensive. Illegibility, incomplete medication name or writing the wrong concentration can be dangerous to patient safety. Because the path is so arduous that those that handwrite the drug's name on the labels often do not write out the full generic names of the drug. Some providers may take shortcuts by writing drug's names with nickname, abbreviation or acronym, leading to dangerous medication errors compromising patient safety. When the injectable drugs are withdrawn from the vials and unlabeled syringes, many times these unlabeled syringes are administered to patients and the problematic area that these occur

are in ambulatory surgery, critical care and emergency department. This safety gap exists in many areas of the healthcare system.

In the FDA Patient Safety News website dated May 2003 the FDA issued a warning report titled Drug Errors Caused by Abbreviation. It documented the type of medication error caused by abbreviation and acronym. Another report dated December 2005 titled Preventing Errors with Neuromuscular Blocking Agent details the ISMP safety alert Paralyzed by a Mistake: Profiling Errors due to Look-alike Packaging and Labeling. In one case it described how pancuronium, a neuromuscular blocker, was administered by an emergency department nurse instead of a flu vaccine because the vial and label looked very similar. That patient recovered. In Indiana, 16 patients received a thousand-fold overdoses of heparin. The nurse mistakenly administered 10,000 units per ml heparin instead of HepLock 10 units per ml. Three infants died and three survived.

The problem of unlabeled syringes is a widespread issue. How many more patients need to die or suffer harm before the implementation of removable and transferable labels? This label

requirement changes may help to reinforce patient safety. The pharmaceutical firm must step up to take a collaborative role in providing safer medication labeling option and the FDA should mandate removable and transferable labels. The 2006 Institute of Medicine in July titled Preventing Medication Errors, Chapter 6 details that in four years from January 2000 to 2004 there were 32,000 medication errors that were linked to look-alike, sound-alike drug names. Thirty-three percent of these errors were due to label and packaging issue and 30 percent of fatalities were due to these label and packaging issues.

The FDA had issued a statement on July 20, 2006, that supports the Institute of Medicine 2006 report Preventing Medication Errors. The FDA look, quote, "forward to using the occasion of this report to continue to work with stakeholder and partners to build on these efforts." It is my hope that the FDA will in the near future be able to mandate pharmaceutical firm to follow the IOM action agenda and that USP and ISMP support this innovative and unique system of removable and transferable labels on all injectable medication which will help to validate the proper identification of medication

and reach the larger goal of reducing errors and preventing fatalities. Due to my tragedy and the tragedy of these infant deaths, I wanted to take up the challenge to improve medication safety. My lifelong disability is the impetus that fuels my passion to helping others to avoid such errors.

The exciting label safety features that some European countries implement allow for simple label enhancement, that is a removable and transferable label for all injectable medication. The label that we wish to introduce to the United States is one that will address a critical area of patient safety. In the United States there are two products that have removable labels. On this side, this is Zemuron vial from Organon and the other side is Gardasil vaccine from Merck. Now, you notice how hard it is to remove that red label that's superimposed on top of the white one. This drug is used in the OR and all healthcare professionals use sterile disposable gloves and it's very hard to remove. You need long nails to remove it. On the other side, this has a pull cap that is very easy to remove and I find it the much more user-friendly system. By showcasing this label enhancement I would like to end with this line, better safe than

sorry. Thank you.

(Applause)

MS. COUSINS: Thank you, Miriam. Our final speaker in this segment is Dr. Dennis Tribble of ForHealth Technologies Incorporated.

DR. TRIBBLE: Thank you. I'm from out of town but I don't have slides so I guess I can't be an expert. ForHealth Technologies gives me the opportunity to get inside a lot of pharmacies. We do an IV robot. And so our interest in this particular subject has to do with a couple of observations, the first of which is we're seeing a change in practice some of you may not be aware of. And that is with the increasing cost associated with compliance with USP 797 and some of the other requirements for IV production, we're starting to see a lot more centralization of IV admixture services to the point now where integrated health systems are actually building separate facilities to centralize that. The value to that process of course is that that means they can distribute the benefits of best practices to all of their member facilities and the patients served by them, even if those facilities would otherwise be economically unable to support those practices on their own.

What we're seeing as a byproduct of that is at least one we're aware of, and in fact there's someone here from this site, is already registered as a manufacturer by the FDA. And we're seeing a kind of dichotomy in the industry where some of these facilities are being governed as pharmacy practice under state boards of pharmacy and others are seeking licensure as manufacturers under the FDA. So the rules and ideas that we're considering today may ultimately wind up affecting the way we practice pharmacy in our pharmacies especially in these centralized facilities. So we probably need to keep that in mind.

The other thing that kind of came home as we were talking is we have the same problems producing labels for things we make in the pharmacy that the industry does. And one of the things that occurred to me as I was thinking about this, I have a number of customers who put clutter on their labels because that clutter is demanded by their state boards of pharmacy. Those state boards of pharmacy don't distinguish between an IV label produced for an inpatient pharmacy and a prescription label produced on a bottle of antibiotics going out the door at Walgreens. And

the result is that those labels have a tendency to be fairly full of things that most nurses would really rather not see. So there's probably some effort here that needs to occur to involve NABP and to get them to look seriously at some of their model practice acts in order to get them to do things with labeling requirements that are a little bit less arduous in this particular environment.

And finally, as a guy who's been playing with software for the last 15 years, there are some rules you see in medical device software that do in fact seem to be applicable here. This is the point I need to look at my notes so you'll forgive me if I too have to put on glasses. When you develop a medical device, you have to start with a hazard-based approach. You ask two questions, is it safe and is it effective. If it's effective it does what you want it to do. So to Diane's challenge to me earlier in the day, we must first decide what it is our labels are intended to do. Until we answer that question, we will not know what those labels ought to look like.

The second thing we have to look at is say what are the biggest hazards associated with our labels. We've had some good discussions about that

today. When you think about the hazards that we have, the first big hazard you have with any system is asking people to do things that they do poorly. And there are certain things that people do poorly, especially when they're in a hurry. One of the things that they do poorly is they don't read novels very well. People don't read labels like a John Grisham novel. They read labels the way they read a reference book. They look for key phrases. Why do reference books mostly have tables and figures in them? Because that's the easiest way to see the data. So we have to organize the data on our labels so that it's easy to read in a hurry. We saw some interesting examples of that today. Okay?

The other thing they don't do very well, and forgive me, but this is especially true of nurses. They don't do math in a hurry. Okay? When you present the data in a way that's ready for them to use so they don't have to do mental arithmetic, they usually do it right. But if they need to know that the concentration is 500mg per ml but you tell them that it's 5g - forgive me. In a 100ml. I probably just blew the calculation. But you get my point.

That means there isn't a one-size-fits-

all for this labeling because if the drug is dosed by frequency or administration rate, concentration is more important than the amount of drug in the bag. But if it's dosed as a single dose, I don't care what the concentration of clindamycin 600mg is in that pre-mixed bag. I want to give 600mg of clindamycin. The amount of the drug in the bag is important. But if I'm setting the infusion rate up and down based on a clinical response, what's the most important thing to me? The concentration in the bag. So one rule that works well in one instance is not always going to work well in others.

And finally, there's some other things I guess we've got to look at. ISMP has some really wonderful rules for expressing measurement. You know, you put commas, a thousand separator in there so people don't have trouble counting zeroes. You never put a trailing zero. We saw three bags up here where the concentration was 0.30 percent. I was waiting for Mike to come crawling over the table. Those rules have been out there for a long time. Why aren't those written into our pharmacy systems, our labeling systems? Why are they not part of the standards that we apply to labels that we make?

Judicious use of white space. It turns out again if you look at well-written reference material, there's lots of white space. The information you're looking for is always in the same place. I know exactly where to go to read it. I develop habits around my confidence in the layout of that information and those habits actually make me more effective in reading that information. Those are all things I think I we need to think about here.

Finally, let's talk about special effects, tall man, color, whatever. I'm sorry, I've got to tell my grandmother story. I had a grandmother, God rest her soul, she's dead, that I learned quickly as a child never to tell her I like that. Right? I like that cookie. Because I would wind up with so many of them I could never stand looking at it again. I think we can do the same thing with these special effects. Tall man lettering makes sense in certain selected instances. We should apply it judiciously. Color may make sense in certain instances. We should apply it judiciously. Warnings, when they are exceptional, when they really need to be seen are effective if they're applied judiciously. If there's a warning

on every label people stop reading it. We've had the same experience with software systems that do drug interaction checking. If I get a drug interaction check on absolutely every order I place, sooner or later I learn to hit the delete key before it even finished displaying. And we see the same effect on printed material that we put on the labels. If warnings are rare, they will be read. If warnings are common, they will be ignored. Anyhow, those were some thoughts from experience from the software industry I thought I would share. Thank you for your time and attention.

(Applause)

MS. COUSINS: And they said I'd have a difficult job. Thank you all for staying on time, I really appreciate that. Thank you for the time you put into preparing your comments, I appreciate that.

Well, we're about to wrap up our meeting and we have two final folks to address you from the Food and Drug Administration. So let me turn the podium over to Carol Holquist, Pharmacist and Director of the Division of Medication Errors and Technical Support in CDER at the FDA.

MS. HOLQUIST: Well, thank you. First I think we can all agree that we had a very productive

meeting today. We really identified many of the challenges and constraints faced by all the stakeholders, whether it be industry, healthcare practitioners, regulators and even the public. When I was thinking about what really were the key issues addressed today, actually the last speaker did a very good job of summarizing many of them. But what I came up with too was a lot of the information that we came out of.

First was the clutter, the real estate that's available for these labels and really what really is considered clutter. It really depends on what stakeholder you're speaking with. Most of this clutter comes from a lot of the regs, some of the USP regulations that are put out in General Chapter Number 1, but also some of the legal considerations that we heard from industry. So I guess what's still really unclear to me at the end of today is you know what can we remove from the bag. You know, what can we remove, what can we de-clutter that will still be safe and everyone will feel confident that we're not going to go forward and make any more errors.

And in trying to do that came like the second thought of the day is can we standardize

these things and how best to do it. And I think we do have to be very careful in our considerations of standardization for some of the things just mentioned, that you know one size may not fit all areas. So we're going to need some testing in this area, whether it be with the human factors. I think also with label comprehension that's going to have to become more prevalent in the review process. We're going to need to look also at - when we talk about standardization we heard a lot on color differentiation today. We heard from manufacturers that it's very helpful for them to differentiate their strengths, but then we heard from some practitioners that when you look at everybody's together it may not be that helpful.

We're also going to need to look at where we put the bar code, do we put it in a standard place. You know, is there going to be a standard place for a pharmacy label that goes from an inpatient setting, can it cover that bar code so you don't end up with some of these errors where you have dual bar coding. Also tall man lettering was a huge issue here today. We heard that there is some need for standardization of that, but it shouldn't probably be used you know this willy-nilly approach

you know. Let's be proactive and make everything you know tall man lettering. I think we really have to - we heard today that we do have to reserve it and we have to have some gatekeeper for that.

And also I think in the end we heard about the timeliness, the timeliness that it takes for all these things to happen. If it is a regulation change and you all know it can take several years to do that. So what can we do in the interim? Do we do a guidance? We all know that guidance isn't regulation so it can be followed, it may or may not be followed. Is that the best approach? Is it something that we need to change in the USP general chapters? If it's changed there, FDA would have to follow it because we have to follow whatever's laid out in the official compendium. So I think all of these issues that we've heard today we're going to have to take back as a group and look to move forward so that we're not here 10 years from now discussing the same things that we heard 10 years previously. And I think you know the sponsors of this meeting, USP, ISMP and FDA, we're all very serious about trying to make some difference. And as everyone stated, the IOM report has given us all a great sort of thrust

there to move forward with these things and hope to give us some ability to really make a difference. So with that I'm going to turn it over to our director, Gerald Dal Pan.

(Applause)

DR. DAL PAN: Okay. Well, I first would like to thank everybody who participated, our organizers, our speakers, everybody who asked questions and everybody who came here to attend today. We certainly have our challenges set forth before us. I think that Carol and the other presenters clearly delineated what they are. The clutter issue I think is a straightforward issue. How to handle it might not be so straightforward. Other things are a little more complicated, like Carol say, tall man letter and coloring. But I look forward to our office, our agency working with ISMP and with USP to move this issue forward. We'll clearly need continued input from all the stakeholders and the fora that we do this, guidance development, regulation-writing, whatever one of those avenues we take does allow for public comment and we'll certainly be seeking that and looking forward to what different stakeholders have to say in that. And finally, I'd like to thank Mike Cohen

and his colleagues at ISMP, Diane Cousins and her colleagues at USP and my colleagues at FDA for organizing today's symposium, today's public workshop. And with that, thank you.

(Applause)

MS. HOLQUIST: I'd just like to add one more comment that I forgot to say, that you can - if today, if you didn't get your full say here that you still have the opportunity to submit comments to the public docket until mid-April. So if you have a burning desire to you know give added input in here it would be greatly appreciated. Thank you. Oh, the slides will be available as well on the web after today's meeting.

(Whereupon, the foregoing matter went off the record at 4:07 p.m.)