U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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PROPRIETARY NAME REVIEW CONCEPT PAPER

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PUBLIC WORKSHOP

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THURSDAY,
JUNE 5, 2008

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The workshop convened at 8:30 a.m. in the Kennedy Ballroom at the Crowne Plaza Hotel, 8777 Georgia Avenue, Silver Spring, Maryland.

FEDERAL PARTICIPANTS:

GERALD DAL PAN, Director, Office of Surveillance and Epidemiology, CDER, FDA
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FEDERAL PARTICIPANTS (CONT.)

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ANDREW EMMETT, Biotechnology Industry Organization
KATHY GANS-BRANGS, AstraZeneca
STEVEN HARTMAN, Novartis
DAVID KORN, Pharmaceutical Research and Manufacturers of America
BOB LEE, Lilly
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MEDICAL/PHARMACY PARTICIPANTS:

ERIC BRASS, UCLA
MICHAEL COHEN, Institute for Safe Medication Practices
DIANE COUSINS, The United States Pharmacopeia
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ACADEMIA PARTICIPANTS:

RUTH DAY, Duke University
FRANK FEDERICO, Institute for Healthcare

Improvement

PATIENT ADVOCACY PARTICIPANTS:

RAY BULLMAN, National Council on Patient Information and Education

PUBLIC SPEAKERS:

JERRY PHILLIPS, Drug Safety Institute
JOHN BREEN, Interbrand Wood Healthcare
SUSAN M. PROULX, Med-ERRS
MAURY M. TEPPER, III, Womble Carlyle Sandridge & Rice

C-O-N-T-E-N-T-S

P R O C E E D I N G S

(8:34 a.m.)

WELCOME AND GOALS OF THE WORKSHOP

DR. DAL PAN: So good morning. My name is Gerald Dal Pan. I'm the director of the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research at FDA.

And I'd like to welcome you all this morning to the first day of a two-day open public meeting where we are going to discuss a pilot program to evaluate proposed proprietary names for drug and biologic products.

I'd like to thank you all for coming, and I'd like to thank especially our panel members who will introduce themselves later this morning.

We have convened a group of panel members from academia, industry, the private sector and government to discuss some of the complex issues regarding trade names or

proprietary names for these products, and we are interested in this because the proprietary name is the main way that the health care system interacts with a product. So our main interest is to ensure that these names are not ever prone, that is, that they don't lead to medication errors and all the unintended and preventable things that can happen as a result of these errors.

This is the first, or one of the first parts, of this program, which is one of our PDUFA IV goals. We are going to discuss a concept paper over the next few days, and then implement a pilot program later in the year. So as many of you know our current review of proposed proprietary names is for basically the proposed name to be submitted to the agency and the agency conducts its own analysis of the name.

This is different from other kinds of data such as clinical data, pharmacologic data, toxicologic data, chemistry data, where

the companies typically submit their evaluations, the result of their research, and FDA reviews it.

So under this pilot program we are interested in having the companies conduct their own evaluation and we would review it much like we do for other parts of the application.

So how did we get to this point here today? We've had public meetings on proprietary name review in the past, most recently in December of 2003, where we learned what other people were doing, we presented what we were doing. In preparation for this pilot program we had a contractor go out and see if there was any update to what people were doing.

And we basically found that there wasn't much new from what was going on in September of 2003. Armed with that information our FDA staff both from the Center for Drugs and the Center for Biologics, worked

collaboratively to develop a concept paper explaining what FDA's current process for proprietary name review is, and we put forth a proposal for what we would see industry submitting as a proprietary name submission.

And our purpose over the next two days is really to discuss aspects of this proprietary name review process, as well as to discuss the logistics of a pilot program through which FDA would evaluate industry generated data on proprietary names.

So this meeting is really about a concept paper. What is it that we are doing? What is it that we can expect of industry? And to comment on what we have proposed in the paper.

It is not a session on, this is what it's going to be like, and do you have any questions.

So this is really - the concept paper is really a starting point not an end point.

So we'll have some opening remarks by Mike Cohen from the Institute of Safe Medical Practices; then we'll have some agency presentations. And our first panel this morning will discuss the safety review of proposed proprietary names.

This afternoon we'll have again some agency presentations, and the panel will discuss the review of proposed proprietary names for non-prescription products.

Tomorrow we will start in the morning with again some presentations, and we'll discuss the promotional aspects of proposed proprietary name review.

And then finally in the afternoon we'll have a presentation of the proposed pilot program from a logistics point of view, how the program will work; and the panel will then discuss the pilot logistics tomorrow afternoon.

So that's it for my introduction.

I'd like to introduce Lana Pauls

who has coordinated this. She is going to talk about some meeting logistics.

MS. PAULS: Hello. Hi, I'm Lana Pauls, and this microphone is clearly very loud.

I have been the logistical person for this meeting. So if you have any questions during the time you are here, please come and see me. We typically, we do have a couple of spots left for the open public times for both this afternoon as well as panel 3 tomorrow. Panel 4 is completely filled.

That being said, earlier we didn't have any sign-in sheets, so if you didn't sign in today at break, if you could please sign in so we can get an idea of the number of people that are attending the meetings.

In regard to specific logistics, if you go out the door and to the right, those are the ladies and mens rooms. We are going to have certain breaks. At lunch time they have set up a buffet, so it should facilitate

eating downstairs.

Other than that, like I said, if you have any questions at all, please come and see me at one of the breaks.

Thank you.

MS. HOLQUIST: Good morning. My name is Carol Holquist, and I'm the director for the Division of Medication Error Prevention in the Office of Surveillance and Epidemiology.

Before we begin today's presentation I'd really like to take this opportunity to go around the room and have each of our esteemed colleagues that are sitting here today on the panel introduce themselves.

So if we could start at the far end with Dr. Cohen.

DR. COHEN: Mike Cohen from the institute for Safe Medication Practices.

DR. HARTMAN: Steven Hartman, Novartis.

DR. SMETZER: Judy Smetzer from the Institute for Safe Medication Practices.

DR. GRISSINGER: Matt Grissinger, Institute for Safe Medication Practices.

DR. FEDERICO: Good morning, Frank Federico from the Institute for Healthcare Improvement.

DR. DAY: Ruth Day, Duke University.

DR. BULLMAN: Ray Bullman, National Council on Patient Information and Education.

MS. PAULS: Lana Pauls, FDA.

MS. TOYER: Denise Toyer, FDA.

DR. TAYLOR: Kellie Taylor, FDA.

DR. LEE: Bob Lee from Lilly.

DR. PHILLIPS: Marjorie Shaw Phillips from MCGHealth and University of Georgia.

DR. KORN: Dave Korn with PhRMA.

DR. NOURJAH: Parivash Nourjah from Agency for Healthcare Research and Quality.

DR. SHERIDAN: I'm Dan Sheridan from Marion General Hospital in Ohio. I'm a

hospital pharmacist.

DR. GANS-BRANGS: Kathy Gans-Brangs, AstraZeneca.

DR. EMMETT: Andrew Emmett with BIO, the Biotechnology Industry Organization.

MS. HOLQUIST: Great. Thank you all very much for joining us here today.

So now I'd like to introduce Dr. Mike Cohen, the president of the Institute for Safe Medication Practices in Pennsylvania.

AN OVERVIEW: MEDICATION ERRORS RELATED TO NAME CONFUSION

DR. COHEN: Well, good morning, everyone. Greetings from ISMP.

I'm very happy to be participating in this meeting this morning. Obviously there has been a great deal of cooperation, I think, between industry and the regulatory agency, the FDA, and also the practitioner community, and I think great improvements have occurred over the years.

But obviously we still have some

way to go. There are still issues surrounding brand names and non-proprietary names and names of over the counter drugs as well, and I want to touch on some of those today to provide background information.

Basically there are many things that can go wrong. We of course for many years have worked with the USP, ISMP medication errors reporting program. And we do receive reports of medication errors obviously involving the nomenclature, the communication of the drug name.

I am going to stick pretty much with the ones that you see here on this slide, and there is a handout as well, although there were a couple of mistakes that we corrected this morning so it's not exactly as it is in your handout.

However, this is really where I wanted to concentrate my comments. And what I wanted to do is provide all of you with some background information about these types of

mistakes that have happened.

So many times the reports that we get are not really mistakes, but more concerns about a drug name that are expressed by the practitioner community.

We do hear through the USP ISMP program from the practitioners themselves. This is not from the institution or the pharmacy organization, the chain pharmacy for example, but from the practitioners directly. So we can interact with them, and there is a lot of good that can come from that program. And all this information is automatically sent to the Food and Drug Administration.

And when it is something like a product-related issue, we do also make sure through USP that the companies are informed as well. So many of you - those of you in industry have been receiving this information all along.

But obviously we are going to cover things like look alike and sound alike drugs,

and I'll have some examples of that both for brand names as well as established names.

Dangerous abbreviations and dose designations sometimes, unfortunately, become incorporated in a drug name - we have seen that happen for example with suffixes, and I'll show you some examples of that, as we go along.

And we also see them in some journal ads, in some advertisements, which if you've taken a look at the concept paper you know that one of the issues that folks are talking about in that concept paper is the advertising.

The suffixes that are misunderstood, or omitted, which I just mentioned.

Confusion related to the OTC brand name extensions; unsafe practices in the journal advertising as just mentioned; name confusion with medical terminology or laboratory nomenclature - we have had issues

like that, and I have an example of that.

Same established name, different substance internationally - that was the subject of a public health advisory from the Food and Drug Administration, and I'll give an example of that.

And then also more than one trademark for a branded item for different purposes, different indications.

To start off obviously we know about the handwriting problems. And there was a study that was actually done quite some time ago, actually in the late 1970s, it was published in JAMA, that showed that about a third of the handwriting - and I don't know that there is any reason to suspect that it has changed since 1979 - is basically illegible, impossible to read, or at least very difficult to read.

That is generally not where the problem is though. Often it's a name that is not so hard to read, but a situation where the

practitioner actually sees in that name what they are familiar with, not what is actually there. And we refer to that as confirmation bias on your handout, I try to define that in the next slide I think.

And obviously this sometimes this situation does result in the patient getting the wrong medication, and unfortunately that does result in harm and sometimes malpractice cases as well.

It does delay medication administration, and obviously can also interrupt workflow.

And obviously it's not just the look alike, but there are these other factors that I mentioned as well.

So this is the definition from our standpoint anyway, and this also applies to labeling and packaging issues as well. And when a practitioner sees in an item not necessarily what is there but what they expect to see, and it's a very strong register in

their brain, and they don't even realize that they have the wrong thing in mind.

Now these are just some examples of different orders that have been written. And you can see the level of handwriting. Some of them are very poor; some of them are perhaps a little bit more readable than others.

But in each case these actually did result in mix-ups. So on the top left, for example, that was actually an order for Provera 2.5 mg that misread as Premarin; conjugated estrogens at 2.5 mg. And I think you can easily see how that could go either way.

The thing that makes this even more likely is when you - and this was in the concept paper obviously - you start including information about the dosage strength, the frequency, how that drug is actually used, the environment - all this contributes to it, and for quite some time actually that has been something that I know the companies have

considered, and that is something that needs to be in the process that is described in the concept.

The one on the top is that Torado or Foradil.

The next one down - maybe I have a - I don't have a laser pointer here, but the next one down, the second one from the top in the middle - is that Tegretol, which it actually was mistaken as Tegretol, but actually it's the antibiotic Tequin that was actually being prescribed.

Avandia or Coumadin? When Lantus, the basal insulin that so many insulin dependent diabetics, et cetera, take as a basal insulin product, was first marketed, basically everybody saw this without being familiar with the new product, the advertising hadn't reached them yet, the information hadn't reached them, and maybe it was used in their area of practice, they saw this as lente insulin, which was something they used all the

time.

So you can see how easily mix-ups like this can happen.

The next one down, Lipitor, Zyrtex, Zyprexa.

The next one down underneath that one is the most recent incident that I can remember in recent times anyway where an item was actually - the name was actually changed. This is a drug for hypertriglyceridemia. It's called Omacor. And there is another product that has been used for many many years for bleeding situations called Amicar, and the dosage strengths were the same.

And as a matter of fact I can actually recall that there was - and I saw this on the Internet in the approval document - that there was actually a situation where the division was actually presented with this information and it did get by, the division of medication technical support at the time identified this as a problem, and

unfortunately it was still approved under this name, and then later on it began to cause problems; many times many reports were received, and it became clear in at least one case of injury that this needed to be changed.

It's not just the brand names; it's also the established names. And here are just quite a few of them that we've had.

And it's interesting to note, as many of you know, the Joint Commission is an organization that accredits many health care organizations - about 80 percent of the nation's hospitals for example - and they actually have addressed this issue of look alike sound alike drug names by coming up with a national patient safety goal.

And what is interesting is, the ones that the hospitals actually have to address on the current list, I think nine out of 10 are these established names, name pairs, not brand name pairs. So I thought that was interesting, and I think probably could do a

better job in assigning these names as well.

They don't go through the same type of testing process that the brand names seem to go through currently with the industry involvement. So I don't need to go over each of these, but some of these have been fatal events, and obviously that's a situation we're concerned about.

The possibility also exists of confusion between a brand name and an established name. In this one, something as simple as heparin, we've had a long-standing problem, even today, where there have been mix-ups between these two IV products, hetastarch, brand name Hespan, and heparin. They share similar letter characters. They are both in IV bags. At one point they looked very similar as well. They are stored on nursing units; they don't go through the typical dispensing process. And for many other reasons that would have to be considered - in fact, I don't think this name today would

be approved. I think this is typical of the kind of thing that we don't see anymore. But you can't be smart enough to pick them all up, but this one I think we would have seen coming if we did the type of testing.

These names have been around for years obviously, Hespan as well. And unfortunately they are still out there, or at least still used, and occasionally we see a mix-up. And obviously giving a product that is an anti-coagulant instead of a hetastarch to expand blood volume in shock can be a real problem.

Just so you know, the Pennsylvania patient safety authority, they have a mandatory reporting program for hospitals. And there are over 600,000 medical error reports in this database since I believe it was June or July, 2004, about 26 or 27 percent are drug related.

And we receive those reports, and also helped to prepare articles for the

advisory. And these are the top names reported by hospitals. This is a mandatory - these are incident reports that are received.

And as you can see it's a mix of generic or established names, generic names, and brand name. It's two very well established non-proprietary names, established names. And we have a lot of problems with this type of mix-up, unfortunately.

There are some things that people have attempted. One thing that we noticed long long ago was that there was a product called Tubex which was a cartridge that had to be loaded in an injector which was very popular; I think Wyeth made it at the time. And they looked very similar. And there were two drugs that we just had constantly reported, diphenhydramine, 50 mg, and dimenhydrinate, 50 mg, that would get confused all the time.

And I remember, this goes back into the `70s, I guess, or maybe early `80s, when

Wyeth highlighted the unique letter characters of those names on the syringe itself. These errors just disappeared.

And that always stuck in my mind. And when we've had similar events, we've requested actually that the companies or FDA consider using what we tagged, tall-man lettering, it's really mixed-case lettering.

The research really doesn't support the use of this, but I'm afraid that the way the research was done was not really - it wasn't well designed. It used more or less the research of these students, for example, rather than practitioners that are more likely to suffer confirmation bias.

And there are many ways to highlight these unique letter characters. And I think you can see that doing something like this makes it even clearer that there is a difference between these two names than something just like this. So we still have a lot of research that still needs to be done;

it needs to be done right. We have a survey out right now. That's not enough, that's for sure. But I think there may be something here to prevent some of the names. And this has been tried with brand names as well; I'm not sure how successful that has been though.

But it may be the way that the characters, the letter characters, were actually depicted. We don't know. We need to do research.

Suffixes, I guess the earliest one that I remember having serious problems with, and I mean patients admitted to the ICU, was the XL designation. Up until then we used SR for sustained release, and then a company came out with XL, meaning to them I guess long acting form. And immediately - and we had an immediate release product called Procardia and nifedipine, which of course is a calcium channel blocker. And at the time it was already being used, and we know today perhaps inappropriately sublingually, where the nurses

would actually draw the liquid out of the capsule, and inject the solution that is underneath the tongue, it was a sublingual dose, where it would be rapidly absorbed; or at least they thought it was that. It might have been swallowing. And it would have an effect of reducing blood pressure when necessary.

Unfortunately almost immediately we had some patients get instead of the telephone order being XL it was heard as SL, so they heard SL and they gave 90 milligram sublingually instead of 10 milligram sublingually.

And we also had times one when it was used in lowercase, 90 milligrams times one, as an immediate release, not the extended release. This can be very, very serious obviously.

And we also had the number 40 in Roman numerals. That was another thing. We had one woman who was very obese go into a

pharmacy aggravated that her doctor had prescribed the extra large Procardia for her. So you never know how these things are going to be taken.

Then we also had problems with numeric suffixes, where this was seen as fix doses of the drug rather than five milligrams of the drug, so now we know enough to avoid these numerical suffixes, like Tylenol No. 3 is a popular way to describe the Tylenol with codeine, and we'd have three doses of Tylenol rather than Tylenol in that particular strength with codeine.

HS is an abbreviation for at bedtime, and this was used here to indicate half strength. This is commonly used, DC, as discontinue or discharge in a hospital; and people might easily see that as discontinue that particular drug.

So all these kinds of things have been reported. And then confusion between different suffix designations as far as the

length or the duration. There is an extended release that USP has designated and a delayed release, but unfortunately depending on the tag, they may or may not correlate between one form generically to another's brand. And unfortunately that sometimes leads to confusion.

Name abbreviations, is this hydrocortisone 250 mg or hydrochlorothiazide, 50 mg, and believe it or not, there are some products that actually use the designation, and I would think this would not be something that would be approved today, I would hope anyway, incorporating an abbreviation that could actually - to many people it means hydrocortisone, and you still have situations where people give single ingredients.

We actually have a list of abbreviations that we think should not be used. I noticed in the concept paper - these are drug name abbreviations - others that were also mentioned with a link to the area of our

website that might have that.

Verbal orders is another issue, the telephone orders, the oral orders face to face or by telephone, that more and more we are trying to avoid those. There is a specific problem here in that a lot of times doctors will leave orders on an IVR, voice device, and the pharmacist can't even ask questions or repeat back or read back the order after they have transcribed it.

And I guess most of you - I kind of screwed this up, I was supposed to tell the joke first. But you see.

All right, sound alike names, Femara, FemRT, Serophene or Sarafem, Invanz or Avinza, these are all ones that have been reported through the USGI or I'm sure MedWatch as well.

Tamoxifen or Tomoxetine - now sometimes we do get word from practitioners, or we know that there is a study going on, we see something in a journal, we can actually

try to alert the system. And these are three that we fortunately we were able to get USAN and other authorities that oversee the non-proprietary name system to change.

Tamoxifen is now - or was in danger of being confused with tomoxetine, and we notified the company and they immediately became concerned and really worked to change that name to atomoxetine.

Fomepizole or omeprazole is another one. Originally torsemide was torosemide, 40 mg, in an ampule, and that obviously would have been confused with furosemide, 40 mg, in an ampule.

So these are just some of many that have been - never really either were there and got changed or never actually resulted in an approved name.

Another issue that we have on occasion - this is kind of an interesting issue. The issue of a brand name that is very, very well known and used for a specific

indication, and then the company gets approval for a totally different indication, and there is a stigma about using the original brand name as far as people's acceptance of this new product. And I can certainly understand that, and FDA has at least on occasion if not regularly allowed a second brand name.

And the other issue here is though that we have, two manufacturers have the same product with two different brand names, and we also have other situations where there are a brand and a generic name.

In this first case we actually had a patient believe it or not take Wellbutrin, which is bupropion, Zyban for smoking cessation, which is buproprion, and generic buproprion, all at the same time.

So this is the kind of thing I think that all of us would be concerned about. Obviously we don't want to see a patient get hurt. We do have ways to pick things up like that now, with computers and the discussions

that hopefully are taking place at the point of sale, but they don't always get picked up. So this does have to be taken into consideration.

Proscar - Propecia was another one, one for benign prostatic hypertrophy, the other one for hair loss. And then Sarafem and Prozac. These are just some.

Here's a drug name-lab test confusion. This actually says, do anti-factor Xa levels, five to six hours after the a.m. dose of Lovenox, which was a low molecular weight heparin. And in fact that was seen as give arixtra five to six hours after the morning dose of - they are both - they would both be thrombolytic drugs, so that would be a particularly dangerous to give to the same patient. And that was the concern there.

So that's another thing you want to look at, is the possibility - and there are many others that we have seen over the years - of a drug name being confused with a

laboratory test or some other clinical terminology in the patient care unit, so when you look at the concept paper you see that they clearly describe the need to position that product in the area that it is going to be used, using live practitioners to look for things like this. And I think that is a very good thing.

Here's an issue that has really bothered me personally because we have seen so many errors with it, and this has to do with biologicals and the nomenclature system that has been around in this regulation since the 1960s, and that is that the proper name of the product on the package label shall be placed above any trademark. It's just the opposite of what we do with non-biological products. We put the brand name, and then in half the font size you need to have the generic name.

What is the problem with this? Well, that inconsistency sometimes leads to serious medication errors. We have had people

repeatedly get the wrong vaccines, for example, and I'm not just talking once or twice; I'm talking in some cases literally hundreds of times. And I think this very much is related to the fact that the brand name is down here, and when people choose a product they are not necessarily reading the entire label panel. Certainly they should, but we know that doesn't always happen unfortunately.

And so just the opposite of what you would expect if you are a nurse on a unit and you've seen all the other drugs that have just the opposite, with the brand name and then everything else.

And many of these are combination vaccines or multivalent products that is. And they are very hard to read the entire label, really, and the fonts are positioned in a way as well that makes it difficult. So we've had a lot of medication errors.

And I know this would probably take an act of Congress or something, because it's

in the Code of Federal Regulation. I really think this should be looked at and changed, and get the appropriate politicians engaged, because I think we've had enough of these errors with the vaccines, et cetera, that we know there is a problem with it. And we didn't have these multivalent products and the number of vaccines that we thank God have today 20 years ago.

Some changes to the brand name as a result of medication errors - there are many of these that have occurred over the years, the latest being as I said Omacor. But we don't see this very often anymore, because I think people have been looking at these names very carefully before they are approved.

The non-proprietary name changes. Amrinone was changed to inamrinone because of confusion with amiodarone; that would be a fatal event in some cases, because they have opposite pharmacological effects on the heart.

I talked about tamoxifen and now

atomxetine and the others as well.

And then we have some issues with over the country drug names which are very bothersome, not just for health professionals but for the patients, the consumers. And we've had for example people that were supposed to have a colonoscopy done, they are given instructions to obtain Dulcolax along with the other substance that they have to swallow over a period of time, and to prepare the bowel, and they go in and they get the Dulcolax right off the shelf, and there it is, docusate. It's a stool softener, it is not a stimulant laxative that was expected.

Why does that happen? Because the name, Dulcolax, is very well known; and in fact it is available in different forms with different ingredients. And so it's so easy for someone to pick up the wrong product.

When patients come into the emergency room it can affect the health care practitioner, not necessarily with this

product, but with some others. I mean what is the patient actually taking? We know Neo-Synephrine as phenylephrine, as a health care practitioner, and if a patient comes into the hospital and you are doing medication reconciliation, they say, I'm taking Neo-Synephrine, you are not going to think it's saline. You are not going to think it's some other ingredient. You are going to think it's phenylephrine, and this leads to the wrong drug being prescribed.

There are many like this; some are potentially dangerous. Kaopectate for years we've known kaopectate as kaolin and pectin. Well, those ingredients were changed long ago, and there is a kaopectate product that has bismuth subsalicylate. If you take bismuth, many of you have probably recognized, you can get a black tongue. You can also get a dark stool, and it looks like you have gastrointestinal bleeding of some type, and we`ve had people get lab tests done as a

result of this without even realizing that they were taking this bismuth product.

The one on the right by the way is again docusate. So it's not - this is really strange, because we always used kaopectate to stop diarrhea, and here is something you are actually giving to soften the stools for constipation. It says, giant relief - great relief of constipation.

This one was very strange too. I don't think you can read this, but this says, great new flavor, same great Maalox. And this is the typical magnesium aluminum hydroxide gel, but how many of you knew that there is another product called Maalox that is called total stomach relief that actually contains not magnesium aluminum hydroxide gel but bismuth subsalicylate and it also says, same great Maalox, same great Maalox.

It's not the same great Maalox. People could be allergic to the salicylate component. I mean this is definitely

different, and this is what worries us about the brand name extensions.

The makers of Tylenol, it's diphenhydramine. We think at the very minimum there needs to be the ingredient that is associated with the original product at least as one of the ingredients. This does not even have that. It is not acetaminophen.

Is that Sudafed phenylephrine, or Sudafed pseudoephedrine with a p-e? Many people were confused by that suffix when they had the - after the legislation was passed that we had to dispense pseudoephedrine products behind the counter, this became an issue, and it still causes confusion today.

There is even confusion between this an a generic name which I will show you in a minute.

The product on the right, Azo, is Phenazophridine. The product on the left is a natural concentrated cranberry tablet.

This one really scared me. Qwell

was gamma benzene hexachloride that you use for lice. You don't swallow that. And here is a company that came out with a quote unquote drinkable called Qwell, which was for cholesterol health. You can't tell me that we don't have to worry about things like that. I think it's very serious.

So here is a Sudafed, or sotalol, the beta blocker? You can see how this could be confused.

So all of this needs to be taken into account.

And then finally the issues with the advertising. One of the most dangerous abbreviations that we used in medicine - we tried to get it banned, the joint commission doesn't allow it, we've made some progress - is the abbreviation U for the word, unit, like insulin, 10 U, becomes 100, and we have people getting 10-fold overdoses. We want to communicate this in medical school, et cetera, and we are doing a good job of that now, and

we have companies that will come out with advertising that depicts these very abbreviations that we feel are so dangerous, and do lead to tenfold overdoses. This is an issue that also needs to be examined.

Now this product on the left had the U, and when it was brought to the company's attention they did agree to actually change that. This is quite old, the ad, but that's the good news.

Then QD, we have QD misread as QID quite frequently, and that's on the list of abbreviations that should never be used, and it's used all over in ads today. These are just some that we cut out of journals. That's a dangerous abbreviation. And FDA and ISMP did in fact come out with a recommended list of abbreviations that should never be used. There is even a slide set that is on the fda.gov website, and QD is highlighted on that website.

The @ sign for atacand, originally

the @ sign was used as part of the advertisement; and may still for all I know. And here is an IV order where it was actually used, and it says, run at 5 millileters an hour; it was seen as run at 25 millileters per hour.

So don't think these things don't really happen; they really do. And that's why we get concerned about them.

Here is another: D5W with two amps of bicarb and 20 mill equivalents of potassium @ 50 ccs/hour, and it ran at 250 ccs per hour.

Made up abbreviations for this class of drug, people don't know what they are, so that shouldn't be in a journal ad.

And here we have IU, which is international unit, and that is seen as IV, and we've had oral products actually, like vitamin E liquid, injected intravenously as a result of using this abbreviation. So we don't want to see that in journal ads, and that's one of the things that I think people

want to look at as well.

Keep in mind, and I think one great thing that is happening here is we are moving more and more toward electronic prescribing. It's starting to grow; it will grow with Medicare legislation over time obviously. And we are going to see less and less - there is always going to be some, but we are going to see less and less handwriting.

But keep in mind that as we've added electronic prescribing, we've also found new ways to make errors with electronic prescribing. People choose the wrong item off of a screen. They use mnemonics or short names which bring up a variety of names that begin with those letters, and easily you can choose the wrong name. So that's another thing that we want to look at when you are doing a review of a new name. How might that actually be used in a real world simulation or in the real world, how might that actually be chosen incorrectly off of a screen? And that

is something that you do pick up as a matter of fact. So again, something to look at.

And then I mentioned the international consideration. I'll just mention that. This is a case that did result in a public health advisory from FDA where a patient who was in the United States and took a product, a calcium channel blocker called diltiazem with an extended - in the extended release version called Dilacor XR, and he went to Serbia and he ran out of his prescription, and he went into a Serbian pharmacy and they gave him a renewed prescription for Dilacor XR, and unfortunately it turned out that that Dilacor was a brand name for digoxin. So something else that you want to keep in mind as you look at drug names is, might there be a situation. And it's a very, very difficult area. You don't even know all the databases that are out there. All the names that are out there, but at least some attempt should be made to see if that issue exists.

And - well, this is just the story on the digoxin and so forth. These are some other drugs that we've run across that the same exact thing happens.

So I'll close with that, and again, I'm really happy to be a part of the meeting, and congratulate all of you for working together to solve this problem of medication errors related to drug nomenclature.

Thank you.

(Applause.)

MS. HOLQUIST: Thank you, Dr. Cohen.

Now I'd like to move to the FDA presentations, and our first presenter for today is Commander Felicia Duffy, who is a safety evaluator in the Division of Medication Error Prevention.

PLENARY SESSION: OVERVIEW OF THE CENTER'S NAME REVIEW PROCESS

MS. DUFFY: Good morning.

My name is Felicia Duffy, and I'm a safety evaluator in the Division of Medication

Error Prevention.

Today I will provide you with an overview of CDER's current process for proprietary name analysis.

Before I get into the nuts and bolts of my presentation, I'd first like to define a medication error.

According to the National Coordinating Council for Medication Error Reporting and Prevention, a medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.

I'd like to point out that the key word in this definition is preventable.

So what is the importance of reviewing a proprietary name? Drugs are not identified by numbers or symbols; they are identified by name. So a drug name is a critical identifier amongst thousands of drug

products in the U.S. market. And because there are so many different drug products, it is important to be able to correctly identify the intended product, because drug name confusion and identification failures can lead to medication errors.

And the bottom line is, medication errors have been shown to cause patient harm.

So now that we understand the importance of a proprietary name analysis, let's get into the overview of our current process.

A proprietary name review may begin at different stages of a submission. It could begin at phase two of an IND, as an NDA, BLA or ANDA. The applicant can submit up to two proposed names for each product in which they identify their primary and secondary choice.

A proprietary name will be re-reviewed when an IND is resubmitted as an NDA or BLA to accommodate any changes that may have occurred with the product or in the

marketplace during product development.

And the name will also be reviewed 90 days prior to approval of an NDA, BLA or ANDA.

There are two primary areas of focus for proprietary name analysis: promotional and safety. The promotional aspects of a proprietary name is conducted by the staff in a division of drug marketing, advertising and communications, or DDMAC. DDMAC will provide an overview of their process in tomorrow's presentation. However, I would like to note that their opinion is included in our safety review.

The safety aspect of a proprietary name is conducted by my division, the Division of Medication Error Prevention.

The focus of our safety review is the avoidance of medication errors. Our analysis is a pro-active approach in a multifaceted process in which we identify error-prone aspects of a drug product. This

includes the name, label, labeling, packaging, and product design.

Although we incorporate the labels, labeling, packaging and product design in our safety review, our primary focus for this presentation will be on the proprietary name.

As I just mentioned, a proprietary name analysis is a multifaceted process which is typically done in two phases. The first phase is hypothesis generation, which consists of generating a list of names which may be confused with the proposed name. This can be orthographic and/or phonetic confusion.

The second phase is risk assessment. Risk assessment consists of putting the name to the test in a variety of scenarios throughout the drug use system. This also includes the use of a failure mode and effects analysis, or FMEA, which will be discussed in more detail later in my presentation.

When we evaluate a proprietary

name, we consider its use throughout the entire medication use system, because drug name confusion can occur at any point within the medication use system, and this includes procuring, prescribing, dispensing, administering and monitoring.

In order to conduct a proprietary name analysis, in addition to the proprietary name, we also need to know the product characteristics of the drug product, because any or all product characteristics can increase or decrease the risk of medication errors.

This list is an example of the product characteristics we consider in our analysis. This is not a complete list, but it gives a general idea of the information we need to know in order to conduct our analysis.

Once we have the proprietary name and its product characteristics, we being with a preliminary screening of the name. If the name fails a preliminary screening, we then

find the name unacceptable for the following reasons: the name contains a stem from the United States adopted names, or USAN list; because the Center's view is that USAN stems should be reserved for established names.

If a name contains a dosing interval, dosage form or route of administration, we may find the name unacceptable, because these characteristics may change at a later date which could render the name misleading.

A name may also be found unacceptable in the preliminary screening phase if the name contains a medical and/or product name abbreviation, because common medical abbreviations and coined abbreviations in a proprietary name may be misinterpreted.

We may also find a name unacceptable if it is misleading or ambiguous. For example if a name includes or suggests the name of one or more but not all of its active ingredients, it is considered

misleading.

Another example is that the proposed name includes or suggests the name of an ingredient that is not included in the product; this is also considered misleading.

So after the preliminary screening, we begin to generate names for potential look alike and/or sound alike confusion. Safety evaluators search through literature, drug references, and computer databases such as the Internet and the agency's internal computer database for existing and proposed names that may look and/or sound like the proprietary name, the proposed proprietary name.

Another aspect of hypothesis generation is the expert panel discussion. The expert panel is comprised of nurses, and pharmacists, in the Division of Medication Error Prevention, and DDMAC regulatory reviewers.

The expert panel meets on a weekly basis, and we rely on our professional and

regulatory experiences to generate additional names of potential confusion with the proposed name.

We also bring to light any potential issues that may be associated with the drug product. For example, if a proposed drug product has a similar packaging configuration as a currently marketed product, then postmarketing experience along with clinical experience has shown that this packaging configuration is problematic, it has been the source of medication errors, the expert panel will bring these issues to the discussion.

So after the expert panel meets, a name simulation study is conducted. Simulated written and verbal prescriptions are given to approximately 120 FDA volunteers who are doctors, nurses, or pharmacists, who in turn respond with their interpretations of the prescriptions.

This provides the safety evaluator

with qualitative information for predictive look alike and/or sound alike vulnerability of a proprietary name. For instance respondents misinterpreting the letters, I-N, in a written prescription, as the letters, I-A.;

So once we've completed the hypothesis generation phase, our next step is to conduct a risk assessment. This incorporates the use of failure modes and effects analysis, or FMEA. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. The safety evaluator applies their clinical expertise, and expertise gained from postmarketing experience, in order to conduct an overall risk assessment of name confusion.

When performing an FMEA, everyone in the medication use process is considered, from the prescriber to the unit clerk who may be transcribing the prescription, to the pharmacy technician selecting the drug, to the pharmacist dispensing the drug, to the health

care provider, caregiver, or patient administering the drug.

Once potential failure causes have been identified, the next step in FMEA is to determine the effect of the failure. In our risk assessment, we evaluate if the confusion can conceivably result in a medication error in the usual practice setting.

We also use FMEA and the principles of human factors, which takes into consideration human performance in the design and development of a product to identify potential sources of error with the labeling and packaging of the proposed product.

So as a brief overview, we have conducted a preliminary screening; we've generated names that may be potentially orthographically and/or phonetically confused with the proposed name; and we've conducted a risk assessment of the name using FMEA.

This process leads us to the criteria for objecting to a proposed name.

The criteria for objecting to a name include but are not limited to the following.

The first two criteria were identified in the preliminary screening phase. This includes names that contain a USAN stem and names that are considered misleading or ambiguous.

If DDMAC objects to a name for promotional reasons, and the review division concurs, the name will not be reviewed from a safety perspective. The applicant is notified and is asked to submit an alternate name.

We will also object to a name based on the Code of Federal Regulation, 21 CFR 201.10(c)(5), which basically indicates, just strictly states, that if a name is too close in spelling or pronunciation with a proprietary name or established name of a different drug product or ingredient, that name is misleading.

Another reason why we may find a proprietary name objectionable is that the

FMEA findings identify a potential source of confusion between the proposed name, and demonstrates that medication errors are likely to occur under conditions of usual clinical practice.

So once a review is complete, our finalized response it sent to the respective review division. In our review we provide overall safety recommendations which include the acceptability of the name; the areas of concern with the label, labeling, packaging and product design; and other safety concerns.

In summary, drug names, labels, labeling, packaging and product design are major contributors to medication errors. And this is why we must adequately assess a name and its associated labels and labeling prior to approval.

We consider the entire product, which includes a name and its product characteristics, and its use throughout the entire medication use system, because

medication errors can occur at any step within the system.

Using best test practices, and capitalizing on the preventable and predictable nature of medication errors, we have a great opportunity to develop better names and product designs that enhance safety with an overall focus on the avoidance of medication errors.

This concludes my presentation of SDER's current process of proprietary name analysis. I appreciate your attention, and I will now turn over the floor to Elle Ibarra-Pratt from the Center for Biologics Evaluation and Research.

(Applause.)

MS. IBARRA-PRATT: Good morning.

I'm technically challenged this morning. Okay.

Good morning. My name is Elle Ibarra-Pratt, and I'm the branch chief of the advertising and promotional labeling branch

within the Center for Biologics.

My agenda this morning is basically to provide you with an overview of our PPNR process, or proposed proprietary name review process, without repeating what Felicia has already presented, and without repeating what will be presented tomorrow in the promotional evaluation presentation.

So but before I do that I'd first like to go over APLB, since some of you may not be familiar with our relatively small group, and go over a little of what we do, which is similar to the Division of Medication Error Prevention and DDMAC at CBER.

Towards the end of my presentation there is a list of resources for your information to get more information on CBER.

This is our organizational chart at the Center for Biologics Evaluation and Research. APLB is located within the office of compliance, and biologics quality, directly under the division of case management. I know

this chart is a little difficult to read, but I want to emphasize the fact that APLB is relatively a small group, but that we do work closely with the surrounding product offices.

As I mentioned, we are located directly under the case - division of case management. We have three separate branches within that division. Currently we have five reviewers. Hopefully within the next week or so, we'll have a total of six reviewers.

Well, what do we do exactly? We do a number of things. As I mentioned we do similar things to the Division of Medication Error and Prevention in that we do evaluate proposed proprietary names that are submitted within the Center of Biologics.

And similar to the division of drug marketing, advertising and communications, we do review promotional materials for CBER regulated products. These include reviewing final promotional materials that sponsors are required to submit at the time of initial

dissemination. We also review draft promotional materials that may be submitted to us on a voluntary basis.

We conduct surveillance activities including evaluation of complaints that come from various sources. We also assist in the review of proposed labeling. These include package inserts, patient package inserts, medication guides, and instruction for use. And last but not least, we participate in the evaluation of blood donor incentive programs to ensure that they are complying with the labeling regulations, and that the incentives are considered reasonable.

So that briefly is who we are, and what we do. Now let's go over our review process which is why we are all here.

Basically our policy at the Center for Biologics is that APLB conducts the primary analysis of the proposed name submission. When a submission comes into CBER, it goes to our document room; document

room then forwards it to the product office; the product office will then obtain a consult from APLB, and we will do the primary analysis of that name.

Although we do conduct the primary analysis, the product office is responsible for making the final decision on the acceptability of the name in collaboration with APLB.

The product office is also responsible for communicating the final recommendations to the sponsor or applicant.

So what are some of the basic differences and similarities between the center's name review process? I think one major difference is that APLB conducts an analysis from both safety and promotional perspective; whereas at the Center for Drugs the analysis is conducted by two separate groups as Felicia has already described, the safety analysis is done by the Division of Medication Error and Prevention; and the

promotional review is done by DDMAC.

Similar to the Division of Medication Error and Prevention, we do conduct a search of the various databases for sound alike, look alike names; and we also conduct safety evaluation, and as I mentioned, we also conduct the promotional evaluation to ensure that the names are not false or misleading or considered overly fanciful.

Unlike CDER, unfortunately CBER does not conduct name simulation studies due to limited resources. However, CDER does conduct name simulation studies on a routine basis.

Because a group is relatively small, and we receive a small number of submissions compared to CDER, we do work closely with the product officers, particularly the medical officers, and the Office of Biostatistics and Epidemiology, to ensure that we have all the vital information we need to conduct a thorough evaluation and

to ensure that we address all of the safety concerns associated with the product or the product class that may impact our recommendation to the product office.

Now once we've conducted and completed our review, we generate a memo and the review is forwarded to the product office. Our recommendations are signed off by the reviewer, the branch chief, our division director, and we do get concurrence by our office director. And as I mentioned, the product office is responsible for communicating our final recommendations to the applicant or the sponsor.

So that briefly summarizes our review process. In summary our process is similar to CDER's with a few differences. The last couple of slides are basically for your information, contact phone numbers and website addresses, if you want more information on CBER.

And now I'd like to turn it over to

Kellie Taylor. She'll be discussing the safety evaluation that is proposed in the concept paper.

Thank you for your attention.

(Applause.)

PLENARY SESSION: OVERVIEW OF PROPOSED SAFETY NAME REVIEW PROCESS

DR. TAYLOR: Good morning everyone.

I'm going to be discussing the proposed pilot program that we have created to evaluate the name submissions.

My name is Kellie, and I'm a team leader in the division of medication error prevention, currently in the Office of Surveillance and Epidemiology. So I'm on the drug side, but I'll be presenting today for both drugs and biologics, the safety review component.

And this is basically what is laid out in the concept paper Section 4A.

So the safety review process is designed to enable pharmaceutical firms to

evaluate the proposed proprietary name and submit the data gathered from those evaluations to FDA for review.

The idea being that this may help to ensure that pharmaceutical firms can choose an appropriate proprietary name for their product, and avoid names that are likely to lead to medication errors.

You will see that the design of the pilot program are based on recommendations and best practices that pharmaceutical firms can use when carrying out the name reviews. And these are largely based on what FDA currently uses.

There's pretty much two components to the safety review process and two objectives. The first is to generate a list of names that could be confused with the proposed proprietary name; and the second objective is to assess the risk of that confusion with the names identified with the proposed name.

And I'll start by going through first how we think the list could be generated.

Similar to what Felicia outlined, we believe that pharmaceutical firms could conduct the preliminary screening to look at their names and see if it includes a dosing interval, dosage form, route of administration, medical and/or product name abbreviations, and names that include or suggest a composition of the product, as some of these names might not be viable candidates for submission.

Also as Felicia mentioned, we recommend that they search a USAN stem list. FDA believes that the stems should be reserved for established names, and names that are proprietary names encoding a USAN stem may not be viable candidates for submission.

When you are generating a list the main things you are looking for is to identify names with orthographic and phonetic

similarities. Considerations would include the spelling of the name, the appearance of the name when scripted - and this can be done by examining handwriting samples; and the pronunciation of the name when spoken.

We are recommending that the sponsor consider both the intended pronunciation along with unaided pronunciation to account for variations that are likely to occur in the real world.

Using these aspects we recommend that you consider those and compare them to existing proprietary and established names and publicly available databases. We have listed the databases in the appendix of the concept paper, and we recommend using a combination of them, because not one database contains a repository of all drug names.

To supplement these searches, we recommend that sponsors employ computational methods. Computational methods have algorithms that can detect the similarity of

product names from a phonetic perspective and orthographic perspective or both, and we believe that this is useful in hypothesis generation but perhaps has limitations for risk assessment.

We also believe that it's valuable to collect medication error data, particularly when an active ingredient is marketed domestically or abroad. Relevant information could include any error reports related to the nomenclature; active ingredient; packaging, and label/labeling of the product. And these data can be obtained from published literature and relevant medication error databases.

In addition we are recommending that sponsors conduct name simulation studies. The goal of these name simulation studies would be to provide a descriptive assessment of how the name could be misinterpreted. This could be done by testing the response of practitioners to a proposed name by asking them to use it in a simulated environment, and

we are recommending that they simulate the real use conditions as near as possible using lined paper, background noise, prescription pads, handwriting, and even electronic order entry if possible.

And we think that the name should be presented with corresponding product characteristics that are likely to be used to communication prescription orders as Dr. Cohen presented, those obviously can influence the likelihood of error.

So the name simulation studies: we look to detect a close to zero percentage error rate with significance, it would require a prohibitively large sample size. So that's why these aren't being used to firmly establish the risk of the name.

FDA statisticians internally calculated it out to be about 26,000 participants.

Instead we recommend that you assess the performance of the medication name

through a well designed parallel group observational study in which each group represents different prescribing scenarios.

The participants of the name simulation studies should include current prescribers, transcribers, dispensers and administrators of the product. It should be representative of the full range of persons involved, and include generalists even if the proposed drug is a specialty product to probable the risk of confusion when it is outside of its specialty area.

Each participant in the name simulation study for the name should participate only once, so within the scenario it should participate only once, but you could use the same group of participants to test across the variety of names.

We're recommending that you employ a minimum of 20 scenarios to represent each possible prescribing condition for the proposed drug, and to test each of these

conditions several times

We are recommending that you embed the test name into a list of two or three other names of marketed drugs to mimic the real world setting, and also consider the verbal scenarios using unaided pronunciation in addition to the intended pronunciation to be reflective of real use.

We are recommending that you collect data at the end of the name simulation studies and interview the participants. This is outlined also in the concept paper. To get qualitative data and record all verbatim responses, and then code the responses and analyze them.

So after completing that we think you probably would have generated a pretty comprehensive list, and could go on to test the likelihood of confusion between that list of names and the proposed name.

And we are - as our current practice is, we are thinking that failure

modes and effects analysis would provide a good tool to assess the risk. FMEA is a systematic, prospective method used to examine the way the nomenclature for possible ways in which a failure - that is, error - can occur.

Consider the intended indication of the product characteristics to anticipate the use of the product in the proposed prescribing conditions, and use FMEA to identify failure modes and analyze the effects.

To conduct an FMEA you will need to assemble a team. The team should be multidisciplinary and include health care professionals with experience in actual use settings, as well as members with expertise in the field of medication error prevention.

And typically this would be about eight to 12 members.

The first step would be to identify failure modes by comparing the proposed name to all of the names gathered during the safety review process, and ask two questions to

assess the vulnerability to confusion.

And these questions are also laid out in the concept paper.

The first question basically is asking, could the similarity of the name to other proprietary or established names cause confusion at any point in the medication use system?

And the second question, probing the - whether other aspects of the name could be - possibly unrelated to the orthographic or phonetic similarity, could be misleading or cause confusion.

When looking at these questions if the answer is no, we are recommending that you provide the centers with relevant information to determine that the similarity would not lead to confusion or error.

However, if the answer is yes, we think that this indicates a failure mode, and the potential effect should be evaluated to determine if the confusion may lead to a

medication error.

When you are analyzing the failure effects, the basic question that you are asking is, could this confusion result in a medication error in the usual practice setting?

You analyze the failure effects. You submit the FMEA and findings if the confusion is unlikely to result in a medication error. However if the effect of the failure is determined to be a source of medication error under the proposed prescribing conditions, we believe that you should consider evaluating an alternative name for submission, or consider justifying why the findings might not lead to error, why the risk of error is acceptable, or suggesting other risk reduction strategies.

And so at this point, this concludes the safety review component of the presentation, and I'm going to turn it back to Carol for clarifying questions.

(Applause.)

MS. HOLQUIST: Thank you, Kellie.

Now I'd like to ask any of the panelists if they have any clarifying questions for any of the presentations you have heard this morning?

DR. DAY: I'd like to ask Kellie to comment on the name simulation studies. It looks wonderful in the concept paper. In terms of who's doing it and the different scenarios and so on. But I cannot tell for sure what the task is that people are asked to do.

DR. TAYLOR: The basic task I think that we are asking them to do is to take the proposed name, work with the - put the name into an actual prescription, a verbal order, written order, what have you, and to run it through each of those scenarios laid out.

So from prescriber to pharmacist to nurse to ward clerk, what have you.

DR. DAY: And then what are the

outcome measures? Are you looking at - do you get a dependent variable out of each person, like what did that person say or do at each point, or just at the end what happened? So what are you measuring?

DR. TAYLOR: I think both. I think we would be interested to have all of the qualitative information about what the interpretations were at each of those points, and what the end result was, did it make it from A to B without being misinterpreted. And if it did get misinterpreted, how was it misinterpreted, and for what reason.

DR. DAY: But what task do they do? Does the ward clerk say or write to someone else, and then that is your observation that you can then score for correct or incorrect?

DR. TAYLOR: Precisely. It would be observational.

DR. DAY: All right, thank you.

DR. FEDERICO: Hi, Frank Federico. I just have a question for clarification. If

in your process, whether it be the simulation or the FMEA or whatever, there is one individual who makes an error. Is that enough now to stop the process and consider that? Or is it just one person? Because sometimes you don't know you make an error until you actually make it.

DR. TAYLOR: I'm trying to understand. So is the question that if the misinterpretation occurred between A and B, would you continue to do C and D?

DR. FEDERICO: If it's just one individual who makes that error, is that enough to -

DR. TAYLOR: I think you would continue the entire simulation process to see what the end result would be. But we would want to know was that error carried all the way through or was it not?

But we are more interested in the qualitative, how is it being misinterpreted, rather than trying to pinpoint where it would

be misinterpreted it.

DR. FEDERICO: Okay, I guess my point just thinking through, when I think of Mike Cohen's reports, it's usually one individual reporting that raises the flag for considerable interest or concern that there might be an issue there, and whether or not in this process that one voice is enough for somebody to say, we've got an issue here.

DR. TAYLOR: Well, all of these findings from the database searches, everything that's laid out is integrated. Certainly if it was a dead hit with another name, that would be a red flag for us looking at the analysis. But also just looking at - is it that they are always mistaking a Z for a B in the verbal study. Should we be looking at more B names?

So it's more of a supplemental qualitative component rather than a hard stop. There is no line where that name is absolutely not a viable candidate just because

you have something happening during a name simulation study.

DR. GRISSINGER: Can I have one clarifying question? Do you also, would you take into account the potential for harm if an error occurs? It looks like through all this was whether confusion would occur, yes or no. Would it also take into consideration the chance or level of potential harm?

DR. TAYLOR: I think in the premarketing I think as Felicia mentioned we very much are thinking that name confusion is a preventable source, whether the harm is going to be grave or not, our stance I think is still that these are preventable errors, and that we should do our best in the premarketing phase, because these are very difficult to remedy in the post marketing phase.

Even as Dr. Cohen outlined with his name changes, those are rare, and it takes a lot of effort, and it doesn't always fix the

problem straight away.

So I think the harm consideration, I'll allow Carol to comment further on this, but I think that it's preventable.

MS. HOLQUIST: No, you're exactly right, that is exactly how we look at it, is that it is a preventable event, and so if we can see that in our simulation studies here at the agency, before it actually ends up going to the real world, ends up causing a problem, it's probably going to be exponentially greater once it reaches the real world, so we are actually trying to minimize those prior to approval.

DR. LEE: A clarifying question. In the 20 scenarios that were discussed, it's to be repeated several times. You did make clear that the respondents in that set of scenarios can look at more than one name, in repeating - in doing the repeat several times I think it says in the paper. That suggests you would do that with different sets of respondents?

DR. TAYLOR: To clarify, the reason we don't want the participants to repeat within the same simulation study is to avoid learning bias that may be associated with that proposed name.

However if you were as a firm had 10 name candidates, say, you could run all 10 names with the same set of participants, and thereby reduce your overall sample size.

So the clarifying point would be that you can - you don't want to reuse the participants within the same simulation, but you can use multiple names for the same participant population.

DR. LEE: It used a number, I think the number was 70, in that one table that was in the paper. So if you were to repeat that five times let's say, that would be 350?

DR. TAYLOR: No, you would have that - what would you repeat it three times for?

DR. LEE: I thought you had - I thought the paper had indicated that you would

run it several times?

DR. TAYLOR: No, each - well, those 20 scenarios laid out actually include repetitive scenarios, so we have like three written sort of scenarios, three electronic order entry scenarios, three verbal scenarios, so the repetitiveness of the scenarios is actually already built into the 20, so you'd be looking at just the 70.

DR. LEE: Thanks.

DR. NOURJAH: I have a question about the scenarios. You are - this list of scenarios, the 20 you put, is it set in stone, we have to follow this?

DR. TAYLOR: No, I think we certainly would encourage thoughtful consideration as to how the product would be used. If you had maybe a nuclear radio pharmaceutical or something where all of those scenarios wouldn't be appropriate, and all of those individuals and perhaps other individuals would be more appropriate, such as

wholesale distributors or something like that.

Those are just - we wanted to give a visual image that people could work with rather than just rely on the text. So the simulation scenarios aren't set in stone, but they are given for a guideline. And I think in the paper it was actually for a solid oral dosage form if I remember correctly.

So it's just to show what we kind of envision. So it's not set in stone, no.

DR. NOURJAH: And for each scenario you had a direction, like physician B to a nurse, then to pharmacist, then to nurse D. To you want that direction to be conducted?

DR. TAYLOR: It should be directed in the same way it would in the real world setting. So either physician to nurse, or nurse practitioner to nurse. I mean it should be as simulated, as close to what it would be in the real world setting. So it wouldn't make sense to go back from pharmacist to physician unless it was some drug that you

would need to get clarification on. So yes it should be.

DR. NOURJAH: You wanted our response later about -

MS. HOLQUIST: Right, just right now we are taking clarifying questions.

DR. HARTMAN: Clarifying question: Is the FMEA panel being asked to make a conclusion as to whether the name should be accepted or not? And if yes, if the panel is being asked to make a recommendation, what standard are they to use that a name is acceptable or not?

DR. TAYLOR: The FMEA panel, in going through the FMEA process, would be making a conclusion about whether the name is acceptable or not, and thereby submitting it or not, or submitting it with the recommendations about why the risk is acceptable; what could be done to prevent the risk of confusion; so on and so forth.

So yes, the FMEA panel would be

making a conclusion and recommendation. The criteria which they go, Felicia and Ellie had laid out, are typical review criteria which will remain the same. We will be looking at the data with the same criterion applied as to whether the name is acceptable, based on whether it's the pilot program or our current review process.

Maybe Carol would like to comment further.

MS. HOLQUIST: Yes, I think what you are asking is that once the failure mode effects team does their analysis, and they will come to a determination, what are they using to make their determination; is that what you're asking?

DR. HARTMAN: Yes.

MS. HOLQUIST: Basically they are relying on their clinical practice and their - whoever is on the team that has expertise in medication error, to know what are the typical causality of these things. Because when you

are doing your failure modes you are looking at how things can go wrong, and why they can go wrong. And you will see as you go through these are the - they will know at the end of doing that exercise whether or not something is going to slip through that is not going to be identifiable, and you are going to end up with a medication error at the end of the day.

DR. HARTMAN: So it's fair to say - and maybe I'm stating the obvious - but it's fair to say it's basically a judgment call. They will look at the overall risk attached with various names that they considered, and they will make a judgment call as to whether or not the risk is acceptable?

MS. HOLQUIST: Yes, basically yes.

DR. HARTMAN: Thank you.

DR. GANS-BRANGS: Also for clarification, there are statements about coding, and I was just wondering if there was going to be specific advice about how to code responses?

On Table 3, it's an example of coded responses and follow up questions. So it's got a yes, a no, and then a brand X or a brand Y.

DR. TAYLOR: I believe coding is just a term for capturing the response and correlating the data in a meaningful way. So it's not really like, code it according to some specific MedDRA coding or something like that. It's just really just organizing the data. So it's not coding.

DR. GANS-BRANGS: Thank you.

DR. PHILLIPS: The follow up to Bob's question, the name recognition requires actual practitioners that understand the real world, and a certain amount of naivete would be useful.

Do you see each sponsor developing a panel? And how large a panel of active practitioners would they need to be able to test all the different names over a period of time as opposed to one particular submission

for one product?

DR. TAYLOR: For the name simulation studies? Is that what you are referring to?

DR. PHILLIPS: For a single sponsor that is doing this over time for a number of products, how big a pool of practitioners do you think that they would need to be able to use but not overuse those participants in providing feedback and comment?

DR. TAYLOR: As far as a pool, I think that would be an excellent point to discuss with some of the members on the panel. I think - I don't know what the learning bias would be by reusing the same pool of practitioners. Maybe some of the social scientists from our group could comment about the reuse of practitioners across multiple studies. But I think -

MS. HOLQUIST: Yes, I think that is exactly what we want to hear from the group today, how we would operationalize some of this methodology in real world.

DR. SHERIDAN: When Mike Cohen was talking about the over the counter drugs and the name extensions that are different products, if someone did that with a prescription product, would that automatically fail the preliminary screening? I didn't see it listed.

DR. TAYLOR: I don't think that that could fail the preliminary screening. I think that if you walked it through an FMEA process, I think it would probably fail that. But it's a preliminary screening, it's sort of an easy way to look at the name and readily identify a problem.

To me, although it might seem obvious for those of us working in medication error prevention, that that is readily apparent. The way to work out that would be through an FMEA, and not through preliminary screening process.

DR. SHERIDAN: Thank you.

DR. COUSINS: Kellie, you mentioned

the pronunciation of a name when spoken will be considered as part of the simulation. It says, consider the sponsor's intended pronunciation. Are you expecting that a pronunciation guide would be created for each drug name then distributed? Or is this something that is verbally transmitted and communicated to those that are testing this?

DR. TAYLOR: I think that you would want to use in a simulated environment both what you as a firm believe the name should be pronounced as. I know we've reviewed sometimes names where it's very differently pronounced than what we thought it would be.

And then once the marketing gets out there, then everybody pronounces it as the firm does, or half of the people do; but there are always going to be variations in just natural dialects. So I think a lot of times we do ask clarifying questions even now in our current review process, for the first to clarify how they think this name should be

pronounced, so we can consider it that way as well what we were just naturally - how we would naturally speak that name.

DR. COUSINS: Another question if I may. You mentioned USAN a few times, and we've had at USPS we are creating official titles, we have seen cases where a USAN has not yet been applied for or assigned. Are you expecting to do any kind of screening with the international non-proprietary names, which is a program that the USAN council does look to as it's creating its names? So in other words the USAN name could be created sort of after the fact of all this. And I just wondered, since they used guidance from the international non-proprietary names program, would you be expecting any consideration of that in this evaluation?

MS. HOLQUIST: Actually, no, because we really don't have control over the USAN name. We have an FDA representative who sits on the USAN council. But that is run by - as

you said, it's a different organization. So at FDA we don't really have control over what the established name or the generic name of a drug product might be.

So if we are doing our evaluation and we see a name that might get confused with either a trade name or another established name, we'll actually - we actually have to contact our FDA representative to bring that back to the council. But oftentimes it's a little bit too late, because the name has already been established.

So that is one of the difficulties we have when we are evaluating the names.

DR. KORN: I have a question about the slide where you refer to collecting medication error data. You were focusing on the active ingredient and had a comment about what would be relevant. It would seem that some of it, especially if it includes abroad, foreign data, may actually be using a different proprietary name, and there could be

language differences. Do you have a sense for what the focus should be on that kind of data?

DR. TAYLOR: I think that our sense is that even if it is marketed under a different proprietary name abroad that that would still be useful to know. A lot of companies seem to be wanting to do a global trademark at this point anyway. But it's always relevant for us to know, if not necessarily for the name risk assessment, but possibly if it has modifiers, or product strength confusion, labeling confusion abroad, it is relevant to consider when we are looking at the risk assessment how it's been performing abroad.

MS. HOLQUIST: Okay, if there are no more clarifying questions?

DR. HARTMAN: I have one more clarifying question. I'd like to have a better understanding of how the name simulation groups work.

You list on page 17 in table number

two a number of different possible - the composition of various different groups. The first group contains a physician, a ward clerk, a pharmacist and a nurse. In that group, that group would be given, let's say, one name; let's say you are only testing one name, so that group would be given one name, and each participant would respond and ultimately you would get some data, and make some qualitative as well as quantitative data from that group.

In other scenarios, you also have a physician. Why would you have a physician in another group, when he or she has already appeared in the first group?

DR. TAYLOR: We're trying to collect as much qualitative information as possible using different handwriting samples, different pronunciations. So I think the reason we would have another physician in another group is just to be able to run that same name, that same context, back through the system and see

if different individuals see something differently based on what their practice and experience is.

DR. HARTMAN: You mean with a prescription in a different form perhaps?

DR. TAYLOR: Perhaps, yes.

DR. HARTMAN: But they wouldn't be allowed to see the same name, because that would create some bias.

DR. TAYLOR: It would be a different physician, and they would be seeing the same name.

DR. HARTMAN: I understand. Thank you.

MS. HOLQUIST: Okay, since there are no more clarifying questions, we are actually scheduled for a break at this moment. We are scheduled to be back here at 10:15, so that gives us 10 minutes. And then we will go into some of the questions that we have posed for the panel.

Thank you.

(Whereupon, at 10:06 a.m. the proceeding in the above-entitled matter went off the record to return on the record at 10:16 a.m.)

PANEL 1 - SAFETY REVIEW OF PROPOSED PROPRIETARY NAMES

MS. HOLQUIST: Okay, thank you for rejoining us.

Now we would like to continue with much of the discussion about some of these aspects that we put into the concept paper. We really want to hear, as Dr. Dal Pan mentioned in his introductory remarks, that we are really looking for feedback on what are some of the strengths and the limitations of what we have proposed in the presentations.

And then we'd like to know if there are alternate approaches or methods that FDA might be able to consider in their assessment of these names. And if there are any, please be specific and describe what they can offer that is superior, or even if it's a better or

another method that we can use in addition to what we have already- it'll be complementary to what we have proposed.

So I'd like to start the discussion with focusing on some of the strengths and the limitations of what we have proposed. And I'll open it up to whoever would like to speak first. Parivash, I know you- okay, sorry.

DR. FEDERICO: Carol, is the question around the specific way that you look at the name review, or the entire proposal of putting this on the manufacturers to complete this process?

MS. HOLQUIST: Both.

DR. FEDERICO: Both? Okay, great. So here are some thoughts. One is, I've been thinking about what it means to push this out onto the manufacturers. And I think there is value to that.

One is that it's to their interest to review the drug names in much more rapid fashion, because it will help them get the

drugs on the market much more quickly.

I think that if they do the work up front, when it gets to the FDA for review, conceptually, the whole program, it means that they are not presenting you with something that might get pushed back to say you've got to do this all over again; it doesn't work. Or whatever it might be. So there are many pluses to doing it in that way.

The plus for the FDA I think is that someone else is doing the work. There is the transparency that others are seeing exactly how the process goes, and how it's to be completed. So again I think that's a plus.

And it's been eye-opening for me. I'm a pharmacist by training, and I didn't know all the work that you are doing, so congratulations on that.

The downside that I see is that you now have a standardized process where you know how to do this, and now we are going to be asking each of the manufacturers to replicate

this when it goes out into the real world, and I worry a little bit about that because, not to say that they can't do that, but in our work, as we think about how hospitals implement programs, et cetera, et cetera, even the FMEA process- there is a lot of subjectivity to that. So there are the pluses, of yes, it works. It'll probably speed up the process, and as you think about this in your evaluation process, I think one measure ought to be, did the approval process for the drug name, was it shortened in any way? Did it go any more quickly than it would have gone through the natural channels that you have?

And the flip side is, is there a lot more variability on what we're getting, and how it's being challenged with that.

Just one thing before I give up the mike. Somewhere in here I am going to recommend strongly, and I know we have a representative here from patient group, even

in the FMEA process we need to consider putting a patient there on the panel somewhere.

As we push forward with medication reconciliation, and many of you may know, that is a joint commission requirement. IHI started that as a safety initiative many years ago. As we consider those drug names, we need to consider what it means for the patient, who now we are asking to be much more involved in the process in knowing what medications they are taking.

MS. HOLQUIST: Thank you. And I just wanted to respond to one of your comments, where your concern about pushing this out to the industry.

But do you at least feel that if in fact we are being transparent with some of these processes, that it would help industry to think a little bit more about some of the names that they do submit to the agency, it would at least, at the very least, provide a

little bit of framework for what are some of the things you should avoid.

DR. FEDERICO: Yes, I agree. I think that that is important, if I didn't make that clear. It's putting the onus on them to say, think about this before you send it to us. Do your due diligence, and it makes life a lot easier for everybody if you've done your job. I agree with you there.

DR. NOURJAH: Carol, I think it is a good idea to push it on the sponsor to do this. But until you don't have a good set-up standard, or good standard, I don't think it's going to make your work easy, or the process of the name coming to the market would be shorter.

In fact, I think it would be longer for some time, until you put everything in place and standardize it. I think the company is going to do it, and again you are going to do it and confirm it to make sure it's conducted adequately.

Because the system you have is very well-established. You have the experts that the company may not find. Dr. Cohen may be one of them as an expert, but it's hard to find the type of expert and safety reviewer that should be part of the name evaluation outside of FDA.

So you have the system until the whole procedure is not standardized, I don't see the procedure is going to be fast.

But what I would recommend is that some of the experience you have, perhaps you can train some other people, and I don't know how that training should be composed, but you can train them, you can test them, and then give individuals certificates, so at least there would be some standardization for safety evaluators that work for the- evaluate it for the company.

But for other- for simulation, which is very good to conduct, I believe you are - there is - that procedure, every

procedure that you have has to be standardized, and you are way at the beginning. This is just the beginning of the bigger things. And you have to give yourself more time than two years; maybe four years, five years. But it is- the positive of what you are doing today is that you are engaging the pharmaceutical in the understanding how to evaluate the name. And by making them engaged, perhaps you can get together again and learn from experience, and perhaps put forward standards or establish goals as standard.

DR. PHILLIPS: Carol, I think one of the greatest strengths is involving the industry in doing the FMEA, and looking beyond just the proprietary name to also the interaction with how it's used. Packaging, dosage strength, even the dosage forms, and those are the kinds of decisions that they need to make very early in the process and it's very hard for you to retro-fit.

But as a health practitioner out there, you know, when you see the way things are packaged, or when you see the decisions that have been made by some little silo within the company, I think it would be of great benefit both to the industry and to the health professionals and patients if that is investigated, thought through, discussed, and pro-actively addressed, pre-marketing approval, and even pre-selection of the name. Because it will all fit together much better.

DR. KORN: Hi, there have been a couple of references to the sponsor and industry perspective. So I thought we have some general thoughts on the process. And as well with industry. So I thought I'd offer them now, it may be a good time.

I'm an assistant general counsel for the Pharmaceutical Research and Manufacturers of America, also known as PhRMA. PhRMA is a voluntary nonprofit association that represents the country's leading

pharmaceutical research and biotech companies, which are devoted to inventing medicines that allow patients to live longer, healthier and more productive lives.

We'd like to thank FDA for the opportunity to participate in the panel today to discuss FDA's process for reviewing and evaluating proposed proprietary name submissions.

As you know, as a trade association PhRMA doesn't engage directly in developing proprietary names for pharmaceutical products. However, PhRMA does have views on the policies that are being discussed and proposed to be implemented by FDA, and some of our member companies are present here today, and may be presenting their individual views as well.

Patient safety is a priority for PhRMA and the industry. Our PhRMA member companies have a longstanding commitment towards safe use of medicinal products, and

share a common goal with FDA and the other stakeholders here to better understand causes of medication errors, so that appropriate action can be taken to minimize or prevent patient harm.

We are talking about proprietary names here today. And one of the things we wanted to note is that it's the very essence of a trademark is to distinguish one manufacturer's product from another manufacturer's products. So PhRMA's suitable trademarks in general support medication safety, because there is no better way to- there is no better product identifier than the trademark or proprietary name itself.

PhRMA has devoted, and member companies have devoted, significant resources in the development process toward avoiding proprietary names, causing confusion in the marketplace, particularly the unique and complex marketplace in which pharmaceuticals are prescribed and dispensed.

In June, 2003, PhRMA co-sponsored with FDA and ISMP the public meeting to discuss proprietary name review, and PhRMA itself is a founding member of the NCC MERP, and actively participates in that work.

As FDA develops the guidance documents and initiates a pilot project to which it is obligated under the PDUFA IV performance goals, it's important to remember that medication errors can be caused by any number of system failures, as was noted earlier, or other causes at any one or more stages in the process of describing, dispensing, and administering medications. Indeed, they often involve multiple causes.

At this time there is no scientifically valid and reliable method for measuring the extent to which similarity among pharmaceutical proprietary names might contribute to the risk of such errors, or whether such methods could even adequately take into account the subjectivity and

complexity of human perception that is involved in the processes.

Although FDA and industry cannot assure that a given proprietary name will never contribute to a medication error, PhRMA believes that FDA could work toward development of best practices for naming pharmaceutical products that could reduce the likelihood that proprietary names might contribute to medication errors due to confusion with other proprietary names, generic or established names, prescribing terms, or other related words or phrases.

While we are still reviewing the draft concept paper released by FDA in conjunction with this meeting, and we do plan to submit more detailed comments on that paper in the near future, we want to take this opportunity to provide FDA some general thoughts regarding best practices for determining the appropriateness of proposed proprietary names of drug products.

Following these best practices should help reduce likelihood that a new proprietary name will contribute to medication errors, and offers an opportunity to eliminate the redundancy of FDA data collection, thereby making FDA review more predictable, timely and efficient, which is some of the things that have already been discussed here earlier.

It also should lead importantly to predictability for sponsors in coming up with the names and going through the process.

As a general matter, and in accordance with applicable FDA regulations, PhRMA believes that a pharmaceutical proprietary name should not suggest that a product has greater safety or efficacy than supported by clinical data; include or suggest indications, dosage regimens, dosage forms or routes of administration other than those for which the product is labeled; include or suggest an active component that is not part of the product, or cause confusion with other

proprietary or established drug product names.

PhRMA believes that consulting health care professionals when choosing a new trademark helps ensure that the proposed proprietary name doesn't cause confusion with other proprietary or established drug names.

Now a proprietary name or a brand name is a trademark that designates the source of the product, and FDA should recognize, as part of the process, that the value of the extensive trademark analysis that is done and legal review that is done, conducted by companies in coming up with their names, they already go through detailed searches of appropriate files and records and databases for other trademarks and proprietary names that may be unacceptably similar in sight, sound, meaning or context, of use to the new trademark. And this could involve PTO databases, the orange book and other databases.

FDA in considering the guidance

here today could direct sponsors to have health care professionals review the proposed proprietary name for suitability. The health care professionals should have a range of clinical experience and an understanding of the prescribing, dispensing and administration environment.

Finally, FDA's guidance could suggest that sponsors convene an expert panel of a reasonable number of health care professionals which could prepare written evaluation of the proprietary name from the perspective of the potential for contributing to prescribing, dispensing or administration errors.

This would help predictability if FDA gives appropriate weight in the process to the role of the expert panel.

We appreciate FDA's continued commitment to increase the timely and consistent review of new proprietary names by evaluating its review process and seeking

input from the industry and others here and feedback in this meeting.

We are looking forward to continued collaboration with FDA to improve the review process for evaluating proprietary drug name submissions.

As I mentioned earlier we are still reviewing the concept paper, and we don't want our participation here to be considered as waiving any other thoughts about this, or any legal rights. And although PhRMA and member companies may offer comments here, it's- we may have other comments in the future, and may consider other ways of communicating.

With that I appreciate the time to give some overall thoughts, and we do have some more specific thoughts to go through during the presentation.

But I thought it would be useful with- to get the view of the sponsors in at this point of the discussion.

MS. HOLQUIST: Can I ask a couple of

clarifying questions on what you just said?

From what I'm hearing is that it's PhRMA's belief that the analysis that you conduct through the trademark - the Patent and Trademark Office is sufficient to detect some of the - both the visual and orthographic similarities that we see as contributing factors to medication errors.

Was that a correct understanding?

DR. KORN: I welcome others too, but I don't think-

MS. HOLQUIST: I'm just trying to get a perspective. Because it sounded like when you were talking about that PhRMA already does a very thorough analysis using the patent and trademark as one of their first data sources to look for names that look and sound very similar. It was our understanding from another public meeting that we participated in a number of years ago that in fact the Patent and Trademark Office really don't look at those aspects from the same way that we look

at it from the safety perspective, which is taking into consideration both the scriptability of the name, and the pronunciation of the name, that primarily the Patent and Trademark is looking for like products and similar goods.

DR. KORN: Let me respond to that. I think it's to put it into context the- for those on the panel and those in the room who may not understand that names are not just chosen out of the air and submitted to the FDA because they have good marketing appeal.

Companies do an extensive amount of work including searching, and we have to worry not only about the safety concerns and the linguistic concerns and the cultural concerns of the market, and the meaning it could have to the public, negative meanings it could have to the public, but we also have to worry about legal infringement considerations. And legal infringement considerations require us to go through a trademark registration, or it's one

way to address those is to go through a trademark registration process.

And that process isn't merely searching the trademark databases; it's searching everywhere to find if someone has a registered trademark right, or may have a right in use that gives them rights even though they don't have a registration.

So we have to know whether somebody else is using a mark, or something is likely to cause- that we would cause confusion if we went out on the market, likely to cause confusion in the market.

So we go through a trademark registration process when we do that. It's all about similarity, context, and reducing likelihood of confusion from a similarity point of view, albeit in an infringement context.

And our competitors have an opportunity, the public has an opportunity, to see our mark before it registers, and to

oppose those marks.

So we search, an examiner in the office searches, and the public looks at our marks and has an opportunity to oppose them before they register. It's that kind of a process which we say, when we bring a trademark to the FDA and it has gone through that process, along with other things that we do over the years, we're starting to do more, when we bring a trademark to the FDA it already has a reduced similarity, compared with randomly chosen marks.

Now whether it's adequate or not; whether it needs more work from a dispensing and prescribing context, that's what we are discussing today, what are the details of that.

But I think it's important to know that we don't pick the names out of the air and submit them to the FDA.

MS. HOLQUIST: And one thing I'd like to ask is, have you ever considered

reversing your process, where you might evaluate the names from more of a contextual use in a real clinical practice setting before you submit them through the Patent and Trademark? And if not, is there some reason why that wouldn't be a feasible alternative?

DR. KORN: We can do a lot of work evaluating the mark for other reasons like the medical concerns. But if at the end of the day we find that it is likely to cause infringement, we are going to get an injunction against us for being able to continue to use the mark.

So we do legal clearances early in the process. Companies do it in different ways, we do it. We sometimes- companies will do it sequentially. They will do it in parallel. It always winds up being a give-and-take process, though. Somewhere along the line everything coalesces on certain marks that seem to meet all the criteria. And then there is a give and take as to which mark is

selected.

DR. HARTMAN: Carol, I'd like to add that frequently for Novartis, and I think it's true for every major pharmaceutical company that is looking for global trademarks, global brands, the main clearance, the legal clearance process has to begin long before phase two, often at the beginning of phase one and maybe even a little bit earlier, at a stage when we are not in a position and the FDA isn't in a position yet to evaluate the acceptability of a name. So as a practical matter we can't reverse the process.

MS. HOLQUIST: That's helpful. I think that is important for the group to hear.

DR. HARTMAN: I do have a comment, a general comment, about the - about predictability, which I think is closely related to efficiency which is a stated goal.

By predictability, I mean the ability of a manufacturer to predict whether the results of its name review will be

accepted by the FDA. The rejection rate for the last five or six years has hovered in the 35 to 40 percent range, and that I think has led to a great deal of inefficiencies, not just within the agency, but within the industry, certainly at Novartis.

What I'd like to know is whether the FDA envisions that when a sponsor submits a name that complies with the concept paper, and its expert FMEA panel independently determines in its judgment, because we already said it's a judgment call, it's determined that the name is acceptably safe, can the sponsor be confident that the FDA will accept those results?

MS. HOLQUIST: I can't say that any data you submit will be rubber-stamped based on your analysis. We would have to evaluate it just as we would any clinical trial data. Basically when clinical trials are conducted, the sponsor will submit their raw data, and they will make some analysis and determination

of what that data might mean, and that's actually what we are asking pharmaceutical firms to do as well.

But then we want to in turn evaluate that same raw data to see if we would come to a similar conclusion. I think as you heard from some of the panelists already that given the differences in the expertise and there may be some information that we may be privy to that a pharmaceutical sponsor may not be, such as post-marketing data, or maybe it's a name that is in the pipeline. We would never be able to officially endorse and say if you follow this concept paper to the hilt that we will automatically accept the results verbatim.

DR. HARTMAN: Well, let me ask the question a different way. Put aside that there is data that the sponsor wasn't aware of, which is an understandable situation. But under what circumstances does the FDA look at the expert judgment of the panel that the

sponsor has put together- it's an independent panel, it's met the criteria of the concept paper. In its judgment it has come to the conclusion that the name is acceptable.

On what basis does the FDA say, hey wait a minute, our panel thinks it's not, and since our panel- and they are simply going to say no. Is it simply a question of, your panel looks at the data and says, "Well, we don't care what your panel says, and we think there is a problem?"

What confidence- your concept paper asks sponsors to do a lot of work. There is a burden involved. And what benefit, what confidence does Novartis have that if it goes through the process in good faith, complies with the concept paper, has an expert panel assembled who says we think in our judgment this name is safe. We submit it to the FDA, and the FDA simply says, "Well, our safety evaluator looked at it, and they simply disagreed. We think that the risk is too

high."

DR. DAL PAN: Let me jump in here. I think that that is one purpose of the pilot program is to see how FDA's safety evaluators will look at a company's submission and compare it to their own analysis.

And we will talk about, tomorrow, the logistics of that. But I think that that is what this whole program is about. We don't have pre-set criteria to give you today to say, if you comply with this- and that is sort of a loaded term for a regulatory agency, comply, so I'm not sure exactly what that means.

But I think what you mean is, if you do the analysis that we suggest and set forth, and your professionals look at the data and say, yes, we think this name is acceptable, will FDA predictably and reliably think that the same name is acceptable. And I think the purpose of a pilot program is actually to answer that question, and to see

if the results aren't the same, where aren't they the same, and why aren't they the same?

I think there is subjectivity to a lot of this. This isn't analytic chemistry or something.

DR. HARTMAN: I agree. Let me ask it a different way.

Are you saying that the endpoint is a concept paper, a naming review process that will result in a naming process that the FDA will rely on, they will rely on the sponsors' results? Is that the ultimate endpoint that we are looking for here?

MS. HOLQUIST: I think so. I think the ultimate endpoint is not - that we want sponsors to thoroughly think about what they are submitting before they do it. We are trying to give them the method by which to test their name adequately to what we think are best practices, and at the end of the day hopefully to have screened it well enough to give us some confidence that yes, this name

won't be confused.

But that doesn't mean that we will not do our own assessment of it as well. And I think that is what Dr. Del Pan is saying is that through this pilot we will learn where we differ in our analyses; where we're finding- maybe we find a different name than you might find that makes the name objectionable; it may be that we know about, like I said, some post-marketing data that you may not be aware of.

But during this whole pilot we will be communicating that back and forth to the sponsors. It's not simply that you will submit this data, we will review it, and we'll issue a decision. I think what we plan to do, in the future, with name review, is to have a more open dialog with industry about why we are saying no to the name, and give you the feedback that we are looking at, give you the opportunity to discuss it, just as we would if we were looking at any other data that was submitted on an application for approval.

DR. HARTMAN: Let me say my comment by saying that unless we move towards a scenario in which the agency is willing to place some significant weight on the outcome that the sponsor submits, the predictability and the rejection rate won't decrease.

MS. HOLQUIST: I kind of disagree with that. Because I think the predictability may increase just by the sheer fact that they are being more transparent about the reasons why we're saying no, and if we learn from those reasons, the predictability may increase.

DR. HARTMAN: I'll give somebody else a chance.

MS. HOLQUIST: Let me just ask a housekeeping thing. When you are finished speaking, could you please turn off your microphone, because it mutes everybody else. Thank you.

DR. DAY: I think the strongest aspect of the proposed pilot program is that

it uses multiple approaches. You have seven different approaches from the preliminary screening and the stem search, investigation of potential similarity of orthographic and phonetic aspects, computational methods, medication area of data, name simulation studies, and FMEA, and that's great.

There is no one path to the truth on this, and the multiple ways of looking is really terrific. So I commend you for that.

On the con side, I'm going to have to repeat what I said in the 2003 Drug Safety Risk Management Advisory Committee meeting on drug names, and that is, there is a- still a lack of true behavioral tests. Now it is very good for experts to look at names and predict confusability and do analyses, of various sorts, and I'm all for that.

In addition it needs to be tested with people. People include everyone, because everyone will be involved one way or another with the drug names once they are on the

market. So that goes from consumers to physicians to nurses, pharmacists, et cetera.

Some of our studies in my laboratory show that expertise certainly is important, but there are certain basic cognitive processes that operate in all of us. And we have seen that physicians have problems with drug information showing the same patterns that consumers who even aren't patients and don't have the indication for the drug names and so forth, so they will show the same pattern of problems.

So we need to have a wide range of people doing behavioral tests. So I do have recommendations which I will save for the discussion of alternative approaches; I won't go into them now.

But I would just like to say that there are well established research paradigms from cognitive science about how to test perception, attention, memory, problem solving and decision making. And these are quick,

easy, cheap ways to get data very quickly, and they then have implications for the more complex tasks that go on in the real world.

So I think that - and you can find out very quickly what the - say, the problems are likely to be and actually are behaviorally, with orthographic and phonetic similarity.

So I will save my comments about alternative approaches and how to do some of these things. But I would just summarize by saying, the strengths are the multiple methods, and my major- the major weakness that I find is the lack of behavioral test.

I think the name simulation studies are very interesting, and they are exciting, and sort of speak to that. But there is so much going on, and if you have the basic cognitive processes were that were involved first, then you'd be able to design those better and actually predict them, and actually stop the process earlier if there are problems

that are identified from the basic tasks.

DR. GRISSINGER: I think one thing to consider too, and I don't know what the best time period is, of the initiation of the process of testing. And I don't know whether it involves when the company comes up with the name earlier in the phase.

But one thing to add to confusability, we've seen over the years, is the strength. And oftentimes the clinical trial part of the study comes up with strengths that work best in the clinical study, but then a name is separated. And often you see confusbaility, like Mike Owen showed the slide of the Vanicunin being mistaken, but what adds to the confusion are similar strengths, two and four milligrams. Look at issues with suffixes, like Wellbutrin comes as 150, SR 150, XL 150.

But perhaps if a name is going to have a suffix, and the strength is 165, that may decrease the confusability in some

situations, or in order entry screens where you have a list of drug names, and again you have the buproprion, the Wellbutrin 150s, and the Srs and XL all in a line, the 150 adds to confusability.

So I would maybe suggest - I know it's a total change in looking at how this process may occur - of looking at the strength as part of the component earlier in the process. So that there is a chance that a company could maybe consider getting its strength changed earlier in the process versus worrying about changing a name.

MS. HOLQUIST: Yes, you bring up a good point. And I think Kelly touched a bit on that in her presentation, was that when companies do the testing as we proposed, especially in the failure mode and effects analysis, you would identify exactly those types of errors that you just described, and one of the fixes might be that, oh, maybe if we change the strength here, this may minimize

some of those failures that we are seeing, and in the end may actually make the name to be a more viable alternative.

DR. GRISSINGER: That's why, I know in the pharma world, the clinical studies and trials in determining the strength is really early in the process obviously. So that's why I'm suggesting that we may need to take that into consideration, of the timing of the submittal of the name.

DR. HARTMAN: That's not true at Novartis, I can't speak for Novartis. But we are deciding dosage, dosage ranges, in phase two, which is after, let's say after the naming process is well underway.

MS. HOLQUIST: Ray?

DR. BULLMAN: In doing the background reading preparing for the meeting today, a thought came to mind, I recalled an interview that I saw on television with a sports reporter interviewing George Foreman, the great heavyweight fighter. And Foreman,

he noted in the interview, has 10 children, and he has five of whom are sons all named George. There is George Jr., George III, George IV, George V, and George VI. And then George Foreman, Sr., stated that he was able to distinguish one son from another by the use of nicknames such as Monk, Big Wheel and Little George. And I think in some respects it's kind of an interesting tell for me in that it's a challenge, it's asking a lot of consumers to know the names of all the medicines they are taking at all times.

Oftentimes the medicine list changes, it's adjusted, drugs are dropped, drugs are added, et cetera, et cetera. I'm not saying that is not an important responsibility, and encouragement that we all should continue to aspire to encouraging consumers to do that.

But yet there are ways, right now, for example, that consumers that may not be able to list the proprietary and established

names of their medicines. They may be able to distinguish my little green pill, or my orange pill, or my round pill, or my triangular pill for example.

So I think really from my way of thinking it leads into the fact, and it has already been stated, but I certainly would reiterate it, of the importance of having real world consumers in all of the levels of this testing, and the scenarios as they are worked through.

For example, I'm not a pharmacist, but I've played one in television commercials. I don't know if I did the profession justice or not, but having FDA personnel who are- who live, sleep, eat and breathe either pharmaceutical drugs or food for example, role-playing consumers is not the same as talking to someone out on the street as it were in their particular life scenarios as it were.

So I really would encourage that.

And then a little bit of a change, but I was wondering for example if there was consideration given to other models for reaching the conclusions that you are seeking in the pilot, and that is for example, might there - was there consideration for example of having a independent third party such as an academic center? What comes to mind most readily at the CERTS, the Centers for Evaluation and Research in Therapeutics, for example, playing a role in this kind of a pilot program where the sponsors for example might go through the steps of doing all of the due diligence that we've heard now, and then submitting into one of the centers for excellence, for example, that have established some type of a gold standard process using perhaps what is outlined here but what has been vetted prior to the beginning of the program using them as the tool for developing, for going through the process.

MS. HOLQUIST: I think that is what

we are going to talk about tomorrow afternoon, is some of those pilot logistics, and how would we best evaluate this data.

Mike.

DR. COHEN: Yes, I'm just curious about something. You heard me mention the situation before with Omacor and Amicar, where there was some disagreement between your area, your division, and the clinical division about the approval of that name.

And I'm wondering if people go through the requirements and the concept paper, et cetera, is that approved by you, or does it still involve- in other words, could that same kind of thing happen again? I mean, would that same situation be a possibility? And is there any way to address that?

That actually came up at the Institute of Medicine Committee, and it still causes inconsistency and confusion and so on. And I see it as a problem.

DR. DAL PAN: Yes, let me address

that, Mike. Some of you may have heard that Dr. Woodcock announced this safety first initiative, and one of the features of that is that our office, the Office of Surveillance and Epidemiology that does a lot of the post-market work as well as the trade name and med errors work, we will have an equal voice with the Office of New Drugs, so that if in the past our role was seen as more of a consultative role, that could be- where our opinions could be accepted or rejected, that is changing to one of an equal voice, an equal role, where we will have to work these things out.

We are also working out for our office, and Carol's group in particular, to really take the full lead in this area of proprietary name review, as well as other aspects of med error prevention and review.

DR. GANS-BRANGS: So as a follow up to that, would that mean that the whole concept, which has been successful at least

six times that I'm aware of, of a phase four post-marketing commitment, where there was less potential for patient harm, and the trademark that was approved was able to successfully get through that commitment and remain on the market, would that still exist as a potential post-marketing commitment?

MS. HOLQUIST: We typically haven't been doing those post-marketing phase four commitments for quite a long time. We actually did those early on in our process before we developed more of a formalized review process. And I think what you heard Kelly say earlier from her review, or from her presentation is that really the way we look at it is that these are preventable events.

And so we also heard it from one of our advisory committee panels back in December of 2003 that if we see a risk before it's marketed, we really shouldn't take that risk, because there really is no benefit. It's a name, it's a preventable event, and therefore

we should consider making alternative choices rather than taking the risk on marketing.

DR. GANS-BRANGS: So then just as a very brief follow-up on that, so I'd like to suggest that we send in the documentation that the full definition that NCC MERP uses for preventable errors be included, because it is truncated, and the definition includes all sorts of reasons for error, not just name confusion.

DR. PHILLIPS: Carol, I was quite astounded to hear 35 to 40 percent rejection rate of names. And certainly anything that could be done before FDA submission to improve that would seem to make a lot of sense.

My question is, how many of those rejections are by those basic preliminary screens, so something that should be a fairly easy fix for the industry to go through and check things off, and how many of them are really ones that are only picked up based on the phonetic review or based on a failure

modes analysis, more complex approach?

MS. HOLQUIST: I don't really have a percentage I can give you, but I can tell you, that number encompasses a lot. It's not just- like you said, just the phonetic and orthographic similarity. It also includes the DDMAC objections, so when DDMAC finds any promotional, that objection counts toward that number.

But we also do see a lot of- I can tell you from experience that even though we hear that industry does a lot of these prior-approval screenings ahead of time, we really do see some very avoidable names that come in, especially with the inclusion of like QD in the name, and we know once that is scripted out that that will end up in an adverse outcome.

So that's why we are trying to go out here with much of the reasons that we see, give people ideas of some of the things that we do look at and evaluate in the preliminary

screening; some of the causality that we see, or the contributing factors to these errors that we see through our post-marketing, so that they could do a better job at some of this preliminary screening. Not everyone out there is big pharma, and that's actually why part of this evaluation of this pilot that we are going to have to look at all representative companies, both large and small.

DR. EMMETT: I'd actually just love to jump in and follow up on that comment right there. This is Andrew Emmett with BIO, and BIO represents about 1,200 biotech and biopharmaceutical companies in the United States, academic institutions, state affiliates. And actually nine out of ten of our members have not yet brought a product to market. Of course one day they hope to bring a branded product to market, but are still in the research phases.

And just to take a step back, we'd

just like to thank the FDA for doing this meeting, and thank you for your initiative by pursuing this pilot program.

As Steve and others mentioned earlier, the high rejection rate of trademarks is very problematic, not just for FDA having to go through multiple review cycles, but also for companies having to essentially inefficient use of their resources, particularly very close to the PDUFA action date if there is a late stage rejection of that trademark.

And we really support how this pilot program hopefully will move us toward the new framework of the sponsor doing the actual vetting and setting of the trademarks, generating the data based on the HHS and IOM recommendations, and of course based on the best practices laid out within the concept paper, and hopefully by sharing those best practices, improve the transparency, predictability of the process, and hopefully

bring that rejection rate down as we've mentioned.

And I think there are a lot of small biotech-specific issues that we need to keep in mind, and you know, confidence in the proprietary name for a pilot tech product is very critical especially when a lot of the new and emerging monoclonal antibodies are really a mouthful with the established name, names just, Gemtuzumab and Fliximab or Tezumib, Bevacizuzamab, and you can see how that really can become troubling if there is not a clear and concise trade name for those products.

And also for small companies it is important to resolve these issues, because a late stage rejection really impacts the bottom line of a small company much more than a larger company that can bear those costs.

And we should also recognize that while most small companies do do this type of research, it's not consistently across the board that they are doing this sort of

external vetting before we begin the process.

So I think as we're moving toward the pilot program, we really have to ensure that there is a broad, diverse and representative sample of companies within the pilot program, both small and large companies, pharmaceutical and biotech companies, and to really ensure robust participation in the pilot program it would be helpful to have very defined testing criteria. And I think the concept paper goes a long way toward laying that out, and I applaud the agency for doing that.

And I also think we need to keep in mind the relative burden on smaller companies, and we don't really want to push them out of the pilot if the testing criteria are so extensive that due to resource restraints they may not be able to meet that.

And BIO would be happy to work with our memberships to reach out to them to ensure that there is adequate participation in the pilot program.

DR. HARTMAN: Carol, I'd like to just quickly, sort of an abstract question, has it been the agency's experience that name-related medication errors have - we'll say it this way, names have gotten through that shouldn't have gotten through that caused medication errors in your judgment- a result of a weakness in the hypothesis gathering stage, where you are collecting data and you simply didn't- that the name, the problematic name, didn't come up? Or has the problem arisen at the FMEA level, that is, you were aware of the name, it was in the pool of names you looked at, but when you considered it you simply said, you didn't think that was a problem?

Do you have an understanding as to where the weakness was or has been? The reason I ask is because when I look at the concept paper, it looks as if you've bulked up on the hypothesis gathering, the data gathering stage, but basically the risk

assessment stage hasn't changed.

MS. HOLQUIST: No, I'd actually disagree with you there. Our risk assessment is actually probably the part that has changed.

And you have to look at how name review has evolved over the last 10 years.

Back when I came to this division, before that this was done by committee work, and basically it was representatives from both the Office of New Drugs, some generic drugs, I think biologics, and I think advertising was involved.

And they would be given a name, and oftentimes, they were not given the product characteristics or even knew the full context of the use of the product.

And a determination was made based on a majority ruling. So people would go around the room and say, I think that this name can sound and look like this, but they might be overruled by others on the committee.

That's how basically a name was assessed.

Then in the late `90s, when our division was formed, we began this analysis based on what we thought were some of the contributing factors to error, which of course we knew the handwriting, some of the verbal pronunciations. So we tried to build in some of these simulation studies.

Our hypothesis generation has really pretty much remained the same, that we looked at a number of these different resources in order to come up with a full list of names. We even tried to develop a computational way of trying to come up with a list of names, which is POCA, which is our Phonetic Orthographic Computer Analysis thing.

And in the end we were basically relying on some of the- mostly the post-marketing data that we had seen of some of what we thought were the major contributing factors to error, which was the similarity both visually and when spoken, and also maybe

the product characteristics such as the strength and if there was an overlap in dosing interval.

But we are learning through our post-marketing experience, and from employing now failure-mode effects analysis, that how and why these things can go wrong, where they can go wrong, whether or not they can be detected in the practice setting to avoid an error, or will they just slip through the whole process, and in the end- so I would argue that actually the precursor, the hypothesis generation, has pretty much remained the same, but it's more of our risk assessment that's changed.

DR. HARTMAN: But the question was, where do you find the errors occurring? Are the errors occurring because the names aren't turning up in the hypothesis generation stage? Or is it because the risk assessment stage is not adequate and simply allowing names that turn out to be problematic through?

MS. HOLQUIST: I have to tell you that since we've employed this process we've been able to detect a number of name confusions. And actually Dr. Cohen referred to one of them, which was Omacar and Amicar. I think the problem has been that we haven't had the regulatory decision making, and that they have been made by the different review divisions who don't have this expertise in medication error evaluation, and they are basing it on, well, we don't really think that is going to happen.

So we are trying to base it on more of a scientific approach in saying that, yes, we do think it's going to happen, and we can show you how it's going to happen using these failure modes and effects.

I think a lot of - if we had name confusion before, a majority of what we've seen on the market with name confusion occurred prior to our division even being formed.

So I think we have a bit of a good track record. Early on in our processes we let a few things through that probably we shouldn't have, but we've learned from that. Every name that ends up in failure, once we've evaluated it, we learn from it, and we try and apply those lessons learned to the process.

DR. SHERIDAN: First of all, I really liked the way the program is laid out. The raw structure, there seem to be a lot of good safeguards in there.

I'm curious whether you expect that each manufacturer would do their own tests, or whether there would be a small group of consulting firms that would go in and actually do the testing?

MS. HOLQUIST: I think that's what we want to hear today from you guys, if you think that that is a better approach to take rather than having each pharmaceutical firm do their own testing, that's the methodology and the changes that we want to hear from you.

We are not laying this out and saying that this is the way we want to go. This is what we base this concept paper primarily is on our best practices currently. And so we are trying to improve on that, and that's what we're really seeking the feedback today.

But I hope that everybody will open up and start talking a bit more about, I've heard some of the strengths that, you know, that there are a number of approaches to how we look at this, and we shouldn't use just one particular method. So I'd like to hear more, engage more in the discussion of how we might make this process a little bit better and more fruitful.

DR. SHERIDAN: Speaking as a pharmacist, I would be more comfortable if there were a small number of expert firms as opposed to a lot of different companies getting into it for the first time and trying to feel their way through it.

DR. PHILLIPS: Another pharmacist echoing something similar. I also think there will be a substantial learning curve on the part of the drug manufacturers, and unique expertise developed around this whole process, and a consistent process.

But I also think it's very important to not farm this out but for the drug manufacturers and their representatives from all their different divisions to be actively involved interacting with the consultants.

Because Matt brought up the issue of strengths. It's not only strength, it's packaging, it's promotion, labeling, everything from the use of color, the way things are presented; dosage form, and how the dosage form is formulated in appearance.

And I think it will be an invaluable interaction with the firm to get that input from the consultants, and to build that into a better product, so not just the

name but the other prevention aspects of the failure mode that requires the active involvement of the industry representative, rather than just something that would be consulted out and spit back. I think that is where you have an opportunity to really add some value to the process for the industry and to have a better product for the FDA to look at and respond to.

MS. HOLQUIST: Right, and that's actually what we do at the agency when we do our failure mode and effects, we are looking at the whole product; we're not just looking at the name. Because it isn't just the name that interacts in the health care environment. It's the entire product. And that's what we've been trying to communicate to people.

But we wanted to just focus today just solely on some of these test methods for that name. And if we are hearing that in this paper, that we will need to incorporate some of those other concepts, and maybe that's what

Ruth is referring to, and then that's what we need to do, and that's what we need to hear.

DR. DAY: Is it an appropriate time to start suggesting alternative methods, or are there still other pros and cons that people are giving?

MS. HOLQUIST: Sure, let me just ask if there are others? Bob?

DR. LEE: I just wanted to - we've used a lot of terms like look alike, sound alike, and names that look alike as causes of medication errors. And I just wanted to point out that name confusion is just a subset of wrong drug medication errors. And wrong drug medication errors are just a subset of medication errors in general.

So when we say look alike sound alike names are a major cause of medication errors, we have to put it into context.

We also, and one of the criticisms I have or what I think is one of the weaknesses in the proposed program, not being

a statistician, I know I'm setting myself up, but one of the weaknesses I see is that if we are really talking about look alike sound alike, if we are really talking about similarity, that is different than illegibility, or environmental factors. It's different than the human factors that are involved.

Similarity is what we often refer to as look alike sound alike. And I often think that we are asking an awful lot of a name to ask it to solve the problems of the medication use system. And when we enter into the kinds of exercises that are described in the pilot program, we are not controlling as far as I can see issues like legibility and environmental factors. We are looking - we are trying to put the name into context of all those real life situations to see if the combinations are creating signals to us or names that we might want to later consider as names that this new product - this new name

could be confused with.

But that begs the question as to whether it's look alike/sound alike that is causing the problem. And it just sounds like or seems like you can get an awful lot of false negatives and false positives.

Also there has been as far as I know no measurement of the real rate, error rate, that's due to name confusion. And without that how do you determine whether or not the interventions are really working or not? And I think there are other ways to approach this, but maybe we can - I'd like to hear what Ruth Day has to say, because I think there are other ways that this could be approached.

DR. COUSINS: Thank you. From USP's perspective, you know, having seen these reports over the years, I must say I think this concept paper is an excellent comprehensive framework, but it is to me just a framework.

There is certainly a benefit to having this open-ended pilot. I think the danger in it is that it may not generate the standardized approaches that are reproducible across companies.

I'd like to see a little more structure in key areas like the failure modes and effects analysis.

I also noted that the agency was hoping for 25 to 50 submissions. I would fear that if you didn't get enough that you won't have enough data to really make the decisions to move to the next step. So I would suggest that the companies commit or enroll in some way to give you some assurance that you will have enough data to move forward in the ways you wish.

And then lastly I would suggest - well, and you may have an answer on this one - the shorter timetable. Two years just seemed like a long time in a process, although I recognize it's probably not long enough in

some ways - but it seemed like a long time to be the first step in a process that could be very protracted.

Thank you.

MS. HOLQUIST: Okay, I think we've heard most of the strengths and limitations from the group.

Now I'd like to move to some of the discussion about alternative methods, and focusing on what we've presented and what we could better do.

DR. DAY: I'd like to suggest some methods, and I'm not sure I'd call them alternatives, is if we would delete something and replace this, but additional things to consider.

And I think the last comments about what are the error rates due to look alike and sound alikes is very well put. And we have methods for doing this, and we are actually testing this in my lab now.

So I'm going to suggest about three

research tasks called paradigms that can be conducted quickly, easily, early in the process, can be replicable across all companies could do it or a variation on it; we know what the nature of the data are; and so forth.

So one is called a recognition paradigm. I could do a demonstration with you now if you would just hand me some name that's in the pipeline that isn't known by everyone, and of course it would be confidential within this room.

But what I would do is, there are different ways of doing this. But I might show you one drug name at a time on the screen, very quickly, enough time for you to read it, five seconds, whatever it would be. There might be say 10 of them. And embedded in there is the target item that we want to test.

Then we would have some additional instructions. And then I would say, now I'm

going to show you another list one at a time, and for each one check yes or no whether you just saw it during the first part. So part one is the acquisition phase where you acquire some information; and part two is the test phase. And you just check yes or no. And you can have both the target drug name, and a confusable - you can arrange this in different ways. And you can find out what the error rate is. We could do that experiment in five minutes in this room with these 150 to 200 experts, and we'd know a lot.

And you know at least an initial signal that, gee, there was very high rate of success; it was 95 percent, whatever it is. Or there was only about 60 percent; so 40 percent of the time people could not then recognize this name. So that's a recognition paradigm.

Second paradigm is really a search and find paradigm. And we are currently doing experiments on this. It is kind of a

simulated pharmacy shelf experiment.

That is, you see one drug name, pause, and then you see a bunch. Which one was it? And you click on it, or you say it's not here, all right. And with these paradigms we are able to get error rates. So say for example, we have been testing the tall man lettering that Mike Cohen referred to. And we find that tall man sometimes comes up short. That is to say, that sometimes it helps, but sometimes it hurts.

So to give an example, nifedipine and nicardipine, are on the 2001 FDA list on the website for recommendations for tall man. And the recommendation for nifedipine is to capitalize N-I-F-E, and something else for nicardipine. Well, what happens is, you give people nifedipine in the tall-man version, there is a 30 percent increase in the error rate over just using standard lettering. And that's because it changes multiple linguistic features.

So nifedipine with N-I-F-E really tall goes to mostly pronounced as (pronouncing) "knife-to-peen" so it takes ni-fed-i-pine four syllables, and goes to three, nife-di-pine, and there are other things, the stress, the location of the stress in the syllable can change say with tall man; the actual phonemes can change and so on.

Mike had an example on the screen today of dobutamine and dopamine, but by capitalizing the "but" you get doButamine, and if you capitalize the p-a- for dopamine you get doPAmine. So these things change. So that's just an example of how these testing methods can be used to test tall man, but just to test a given name anyway.

So can you see it and find it on a pharmacy shelf is just one task.

So in general the kinds of tasks that I would recommend would break it down into the types of, A, basic cognitive processes like perception, attention, memory,

et cetera, search and find; but also in terms of the basic tasks that happen in the drug world - prescribing, dispensing and administration.

And it's great that these scenarios put a lot of things together, but you are never going to be able to figure out I think really what is going on unless you have some of this more basic work done for the basic cognitive processes and the basic tasks that are done in the - real-world tasks, I'll call it that.

Last task I'll mention today, and you are going to laugh at first, but please listen, and that is, a pronunciation task. I think a bunch of people should pronounce these names. And let me give you some methods, and then I'll tell you why.

I'll tell you the why first. I was once a consultant for a drug safety board for a company, and looked at all kinds of different materials and so on. And I could

not, when I got my briefing materials, figure out how to pronounce this name. So I did a little of asking people how would you pronounce this and that and the other and so on, and got at least eight different pronunciations. So when I was in the room, after we had done a bunch of other things, I said, oh by the way, how do you all pronounce this, and can we just go around the room. And within the company there were at least six pronunciations.

Furthermore, as a member of the drug safety and risk management advisory committee, and now just a consultant on a lot of the advisory committees, I take little notes during a meeting about the different pronunciations that these experts are using to mention the same name.

For example I'd been on two committees looking at Accutane, isotretinoin. And I've heard (pronouncing) isotretinoin, isotretinoin, it's incredible. So in a group

of experts you have multiple pronunciations.

So here is the method. One person at a time takes five minutes, get a list of say 10 drug names, whatever it is, and have people pronounce it. Tape record it, do a little linguistic analysis, or even a simple analysis, and then you plot a frequency distribution. The frequency distribution plots on the Y axis the percentage of responses as a function of along the X axis the individual pronunciations from most to least popular. So I'm gesturing, I'm pointing at people on this side of the room.

And then you look at the shape of the function. And if it is a steep function with one basic pronunciation, great. That is something you can do with each person, maybe about say 25 - 50 people. You can do it with consumers; you can do it with doctors, you can do it with nurses, pharmacists, so on; very quickly, five minutes of their time. And if you get a steep function which is one

pronunciation, you are kind of in business on this. But if you get two, then maybe you can use some way of tall man or coloring to enhance the one you want.

But if you start getting something where there are several that are high, or it's really flat with lots all at about 30 percent of response rate, then you know you have a problem.

So a pronunciation task is simple and easy to do, and it goes a long way to identifying problems early on. This can be done not only in phase one, it can be done in phase zero, if you will pardon the expression, to get a preliminary idea about what the difficulties are going to be.

So in summary I've talked about a recognition paradigm, a search and find paradigm, and a pronunciation task. All of these have standard ways of doing them. They are quantitative, and the data can be compared across drug names, companies, anything that

you wish. And it could be a gold standard in a sense for these limited types of things, about pronunciation, and visual confusability and so on. And you can get true error rates in the limited laboratory context. It doesn't say exactly what is going to happen in the real world settings. But with these things up front you can predict what is going to happen in your more complex scenarios.

MS. HOLQUIST: I just have a question. Much of what you talked about really seems to focus more on the phonetic aspects of the name. Is there like a simple task similar to that for -

DR. DAY: Can I just say something? We talk about orthographic or phonetic and sound alike/look alike. They are tightly bound. That is something that disturbs me in all these meetings. Let's do a look alike analysis. And everything that you say is good to do it. And we'll do the sound alike analysis. Well, they are tightly bound.

So if you go to POCA, so POCA is the computational method of finding, if there is going to be sound similarity, and visual similarity, and so forth. Last time I looked at that, for each drug name there is a phonetic description that is put into it. So when you get your new drug name you put in the phonetic description and you see if you get a ding, just like in the pharmacy, if you get a drug interaction you get a ding that you shouldn't take these two together.

Well, if some drugs, even that are already out there that you compare it to, that have multiple pronunciations, not being represented in POCA. So I love POCA; it's beautifully designed; the people at Maryland did it well and so on. But if you don't have true data on the - not just that there is an alternate pronunciation, but the frequency distribution of pronunciation. Then what is POCA telling you? It's telling you if you are going to get a ding as a function of what they

put in as the likely pronunciation.

So it's great for FMEA to predict what the likely pronunciations are, but until you get the data you don't know.

I'm sorry, I jumped ahead of your question there.

MS. HOLQUIST: No, that's fine, and that's an important point to point out. I think when we developed POCA there was a misnomer that we actually used that system to make our ultimate determination. And that's not at all what we use it for. We basically just use it as a tool, as another tool, to find some more names that we might think -

DR. DAY: I think that comes across clearly in the concept paper, so I don't think that is a concern. But I'm saying that POCA could be, if you will pardon the expression, more better if it could include the basic data about what the frequency distribution of pronunciations is for a given drug. And you could put it in for professionals and for

consumers, but I'm predicting there is going to be a lot of similarity between both.

DR. SMETZER: Yes, we're talking about alternate approaches right now. And I'd like to talk about a new risk modeling approach that we are starting to use in health care.

It's rather new. It's borrowed from industries, other industries, similar to FMEA that we brought into health care many years go. It's called socio-technical probabilistic risk assessment, STPRA, such a mouthful we just call it STPRA.

It's the new risk modeling technique that is being used in health care in the past several years. In fact we are currently doing some research using that process with some high alert drugs in a community pharmacy, and we are finding it to be an excellent source of information about risk.

It differs from FMEA in that it

builds on FMEA, and what it delivers at the end of the process is a very visual model of all the risks that are associated with both behavioral and system issues that cause errors.

And the really nice thing about it is that it predicts the frequency of those failure rates, and the frequency of error.

Another way that it differs from FMEA, before I describe the process, is that FMEA is really looking at failure modes and how they happen individually one at a time. And this STPRA process looks at all the different failure pathways that could happen, and the combinations of those failures, and puts them together and can give you a predictive rate of frequency of error, and in that way we think it could be used with the name testing process to determine how frequently that error would actually happen with a look alike - with other look alike drugs.

So just to give you a little sampling of how the process works, you first have to do an FMEA. You have to do some testing on the drug name, how compatible it is, how it looks like other drugs. And so FMEA has to be done first, and it can narrow down your possible choices for a proprietary name to several that are more attractive.

And then you can use this STPRA process on top of that that will complement the process that was laid out in the proposal here, and also add some dimensions to it that were mentioned as weaknesses.

The process works by first doing the FMEA, and identifying the type of errors that would happen with a particular drug, and how it could look like other drugs.

The second part of that process is to make sure that you build a model, a fault tree model that really looks at the entire process of how the drug will be used. So if it's a drug that is only going to be used in a

hospital setting, you would need to look at the entire prescribing to administration process. If it's a drug that is going to be used also in a community setting, you'd have to look at how the drug would be prescribed in an outpatient setting, or if it's a drug that's going to be used in a physician office practice and be administered there. So there are different settings, and you need to develop models that really look like the process steps that are happening in real life everyday.

The other part of that model is, building on top of that what we'd call control mapping, and putting into place the different controls that are built into the systems as they exist today. So it may be a double check system that is always in place if a technician is filling an order or filling a prescription, and a pharmacist would check it. Or it could be a control system that is inherent in the system. For example one medication may look

very different than another medication, and its appearance would be a signal or a control for a pharmacist, a clue that something is wrong.

So you take that and you build a model, and then you use a focus group of those practitioners that would actually be using the type of drug that you are looking at, and again, I think it would be the top two or three names that may be viable for a potential submission for a proprietary name.

And then model all the different types of initiating errors that could happen. Start with the type of error, a prescribing error, a physician prescribes the drug, and through real life conditions, how that drug could be misinterpreted as another look alike product, and take it all the way through the system.

At the end of the day the top level event would be that that error resulted, and reached a patient.

So one of the nice things about this STPRA process is that it not only models and puts in qualitative terms or quantitative terms the frequency of the failure rates, and the error that could happen; it also will tell you whether that error can be captured with in the current systems that we have for prescribing, dispensing and administering medications.

So if it's captured it won't be part of the top level event.

So this whole process really looks at whether this initiating error can get all the way through the system. And you use a focus group of these practitioners to estimate the different failure rates that could happen.

Now we have a lot of research out there that tell us that if there is a human error involved, and it's just simple human error, that we can attach a specific weight to it.

If there is an error that has a

greater potential because of the look alike potential similarities of other names, you would use practitioners to try to give you an estimate of how many times that would happen.

And at the end of the day there are different ways of combining the different basic events or the different failures that can happen with either AND gates or OR gates. An AND gates would pretty much say that this had to happy and this had to happen in order for that failure to occur.

So a pharmacist would have to have misinterpreted that prescription and entered it into the computer, and the pharmacist would have had to have done the data verification and missed that also. And all the way through the process that was missed. Those would be types of failure that would be put under what we call an AND gate.

And the OR gates are more or less gates which say, this could happen and lead to a failure, and this is another way it could

happen and lead to a failure.

All of this information is put into a statistical program, an engineering program that can deal with complex computations, and it can multiply all the failures that could happen and lead to the ultimate mix-up of two different drugs, and give you an actual rate at the end of the day.

Now we have been working with this process for about a year, and I will tell you, it was a brand new process to us, and we are not experts in that. And you do need facilitators that are experts in the process. But we are entirely amazed by the accuracy of it. We have been able to verify the models that we've built to date so far with data that is out there, and we are very confident these focus groups actually do produce the rates of error.

The nice thing about the models, too, is that it really mimics real life. It not only picks up human error, just plain

simple human error that can happen that may not be part of the simulations that you are looking at right now.

It also picks up at-risk behaviors. So when you have a focus group get together, and you have a facilitator that makes it easy to talk about the real life processes, you find out how many times those controls that are built into the systems really don't work because people are bypassing them, taking short cuts, et cetera. And that is built into the entire model to give you an actual rate of error at the end of the day.

So I think this is a new risk assessment tool that should be explored, and how it could be used in the name process. And I know that we at ISMP are looking for ways to try to do some kind of pilot with that, to move it forward now that we are about at the end of our current research and using that in community pharmacy settings.

So it is a very difficult process

to explain. I apologize for the shortness of the description. It's a very robust process, and it's really turning out to be an amazing tool that can not only provide qualitative information but visual and quantitative information about errors.

DR. COHEN: I should mention that this is research that is sponsored by AHRQ.

MS. HOLQUIST: I have a question. So it sounds like this process takes into consideration some of the things that Marjorie was referring to, where you are not just looking at the name, you are looking at the whole product. So when you build these risk models, you are looking at where it's stored, all that is taken into consideration.

DR. SMETZER: Exactly. It does not replace a failure modes and effects analysis, and it may not replace some of the simulations that you have set up in your proposal. One of the things I think it would pick up that maybe that does not, is when you are looking at the

entire process, and you are looking at all the steps that you need to go through to actually prescribe and get a drug to a patient, I think even in the simulations you may not have picked up the fact that there could be a look alike drug name that is causative in a drug selection error; or it's not just misinterpretation of a prescription; it could be the prescriber who is actually mis-reading in an electronic format the different drugs available to him.

So there are a lot of ways that one medication with a name that looks like another can contribute to errors, and you would pick that up through this entire process.

But it does look at real world. It looks at what's going on. It is dependent on practitioners that would be using that product, or are using that product if you are looking at a drug that's already on the market, or a situation that is already in place.

MS. HOLQUIST: I just want to ask another question about this process. It sounds like through this statistical analysis that you might weight certain features of what's causing the confusion, and maybe you can fix it whether it's a system base or if it's the name.

Through this whole process, if you are looking at the whole use system, is there a way to say to get back to Bob's point, how much of this is just part of the name component alone, and how much is the overall product as it is on the shelf? And do you think we could ever go to just looking at the name alone, or do we necessarily - will we always have to look at the entire product?

DR. SMETZER: I think the process will look at the entire product rather than just the name, just because it's taking errors all the way through the system as I said.

One of the things that I didn't mention that I think is so valuable in this

entire process is, because you have a statistical program and you have these models built, the program actually allows you to develop some cut sets that will tell you what your risk pathways are.

So instead of looking at one failure and how it affects others, you are looking to say, what is the greatest pathway of risk that that error could actually reach a patient.

Just to give you an example, we know from the research that we've been doing currently that data entry is one of the more vulnerable parts or steps in the process of medication using a community pharmacy. But we were surprised to find that the greatest pathway for an error to go through the system, at least for a specific drug that we were looking at, is for a pharmacist to do that data entry.

And the reason for that is, nobody is doing data verification if the pharmacist

is doing the data entry. Yet when we added a simple tech check pharmacist on the data entry, it became the most reliable way of avoiding an error.

So one of the things you can do with these models is, you can change exposure rates, you can change conditions, and still come up with a predictive rate of error within the models.

MS. HOLQUIST: That's very interesting. I look forward to hearing more about that.

DR. FEDERICO: Just following up with several comments.

One, Bob, I agree with you, and what we just heard Judy say, that it's not just a drug name that solves the problem. There are other problems in the entire medication system that need to be addressed.

And in our work at the Institute for Health Care Improvement, as you try to fix one part of the system you find a problem

someplace else.

The challenge, however, having been at the front line, is that most of the hospitals don't have either the resources or the knowledge to figure out how to error proof some of these situations. So if we can at least help by not making it any more complex, that is, at least doing something, we're trying to minimize the opportunities that can happen with look alike/sound alike drug names, that would be a great benefit to the people at the front line, fully appreciating it's not the only solution to the problem.

The other component that I think is critical, is that I am worried and I think Andrew brought this up about replication; being able to reliably do this each time. And if you are a small drug company and you can't do this, what is the model we should have out there to be able to do this?

And I know that early on when Mike and ISMP were doing this work, and I was on

the front line, I would participate in the drug name review. And whether it could be done independently with an additional component that was just brought up this morning, that there are other aspects that should be considered like the packaging, and the drug strength, and all of that.

I think when we did it, and I was part of it, I wasn't considering all of that. I was just thinking, does the drug look like something else.

When we added the drug to the formulary, the initial process was that the pharmacy and therapeutics committee was a good ole boys' breakfast meeting. We had a couple of bagels and coffee, and somebody said, I want to add drug X to the formula, and everybody said, agree, disagree, and it was done.

We reorganized the committee so that the formulary group actually did an in-depth investigation around not only the safety

and efficacy of the drug, but we conducted a simple FMEA. Is it likely that this will confuse us with something else? Can the prescriber make a mistake? Can a nurse make a mistake in administering? Can a pharmacist make an error in preparation? All of these components.

So it is complex, and I can tell you that if the drug name added to that complexity it was just going to make my work that much more difficult at the beginning in being able to do that.

But I want to reemphasize, not all of us have the capacity or the skills to be able to do that at the front line, so we owe it to our patients and our health care providers to try to simplify this process.

DR. LEE: Before this session ends, I would be remiss if I didn't say something about handwriting. It's a pet peeve of mine, and that is, I think that Mike amply showed that handwriting throughout the whole medical

system - it's not just in prescriptions, but handwriting shows up in doctors' notes, and in a lot of areas, and the IOM report found handwriting to be a substantial problem as well, the latest IOM report.

And it did urge new prescribing. And I just wonder that if you don't have some standard on the handwriting samples that you are going to use in the simulations, if you aren't in a way fooling yourself into thinking that you are actually checking a real world condition, that the name can do something about, if the handwriting is so distorted that the person looking at it can't even determine what the word is, not that they don't respond - they may not respond with another drug, but if the overwhelming percentage of the respondents is not getting the word right, and it's more a comment on the legibility of the script than it is on the name.

And I think on the issue of stress and preventable in the error definition, that

definition goes on to say that a medication error is any preventable event, et cetera, it goes on to say that preventable events are related to - and then it lists a whole bunch of factors, including nomenclature, including the name, meaning that, it seems to me that that means that medication errors in which name confusion is part of it will never get you to zero if you just - zero or minimal medication errors if you just stress the name. It's a preventable event if you address all of the factors; not - all of the causeways, all the ways in which the medication error can occur. It isn't a preventable event if you just attack the name.

DR. DAY: A brief comment about handwriting. I agree with what you said. The converse is also true: if in the simulation studies the handwriting samples are fine, and don't include the ones that are going to be more problematic out in the real world, then there could be a false sense of security that

there wasn't as many errors through the whole scenario.

So I would request some thought be given to getting a lot of handwriting samples generated up front. I mean I'd get 50 people in a room. I'd write the name on the screen; I'd type it on the screen. And then use this in a sentence, and some other tasks, and then take a look at what the handwriting variation is again.

It's like - it's like a visual, not pronunciation, but a visual production task. So there is always perception and production, okay. To perceive something, and then to be able to produce it. So before I was talking about the pronunciation task. That is oral production. You need to have visual production as well, and to know, you know, what the frequency distribution is around that in terms of illegibility and interpretability.

So anyway, however you do these scenarios, without careful attention and

control to what the handwriting samples are that you are going to get, you could get a false sense of security - I mean you could get both a false alarm and a hit rate as it's called that are not true.

DR. GRISSINGER: Just one comment. I'm a little concerned, I want to make sure that people understand, especially the FMEA process.

The key question in evaluating names is, what could go wrong? And so reproducibility is not really - is somewhat - reproducibility - sometimes whether they even know the drug name exists.

The other question that has to be asked is, I keep hearing this is, what could go wrong. So I think it's kind of a combination of some of Ruth's things that she was saying earlier as well as other things as well.

DR. SMETZER: I just wanted to mention that the model I talked about, the

STPRA, would be able to determine the risk that would go with each pathway, whether the drug came in by fax or by handwritten or by verbal order; whether it's left on a voicemail system. But each of those conditions that allowed for the receipt of the prescription would be a separate pathway up through the model and give you a rate of error so you can actually determine you know how that error rate was derived, and the different conditions underneath it.

Similarly, you would have the difference between whether you are using a bar code system or not a bar code system; or whether you have robotics fill that drug; or whether the robotics wouldn't necessarily be involved in it; et cetera. So you could turn off and turn on different conditions in the model and really be as accurate as possible as to whether or not there is going to be an error that reaches the patient.

DR. SHERIDAN: I think we need to

keep in mind with the verbal orders and recognizing the names, at least in the practice setting where I am at, at least half of the physicians are not native English speakers, so they tend to have various accents too. So probably when you are going through scenarios to pronounce the names, it should include some people that are not native English speakers.

DR. NOURJAH: Going back to your concept sheet, and give one suggestion. Your concept sheet, as I said, it's just a framework not very specific. And that makes it more subjective and causes more variation among companies.

So one way to do that is to form a consortium or an independent intrastate reliable bodies that carry on these - conduct this type of study for FDA. By this they use - they try to come up with the most reliable more valid as time goes, maybe they improve more on their methodology. But it's more

consistent. I mean the simulation that you suggest can be done in many, many ways. Unless you can say, I want it in this type of writing, this type of voice - noise in the pharmacy, at this level of task - multitasking of pharmacies is doing, you cannot really assess the review - assess the quality of the study that comes to you for name confusion.

So it's good to have a body to do that, which they use a standard method, and you would keep working with them, and see if you get a situation or condition that is acceptable to all scientists and FDA.

MS. HOLQUIST: Who would you see as the makeup of this consortium? What type of individuals?

DR. NOURJAH: Right now, there are a number of people when I listen to them, I think they are qualified to be part of that, as well as people with expertise, as I said, like FDA staff. If you can train some people, that would be ideal. And also academicians,

which are very - that is their - you know, their work, research work, to establish gold standard, to improve validity and reliability of the method. So I would bring in that consortium, that type of individuals, and perhaps pharma to be part of it, and also other industries have some representative, just to be engaged.

MS. HOLQUIST: What I think I also heard loud and clear is that patients need to be involved in this type of evaluation as well.

DR. HARTMAN: There have been some suggestions by panelists that the process should be more - well, should we very well defined, and not allow for a lot of flexibility. And just as a general comment, I would tend to think we ought to have more flexibility ultimately. The reason why is because this isn't a science. We don't have anything like or analogous to a double blind clinical study that will tell us whether a

name is safe or not. All of these different approaches that are part of the concept panel, and that other people have suggested, reflect the fact that we are in some ways grasping for straws. I don't mean to say that we don't understand a lot about name safety, but we are not there yet; it's not a science.

And what I am concerned about is that we shouldn't lock ourselves in. Because if we lock ourselves in so that there is always one method that all of the sponsors will use, and that the FDA will rely on, then we are going to perhaps we are going to hinder the development of better name evaluation techniques. So we really want a system, I think, that ultimately allows for sponsors and for vendors to take what is coming out of research to incorporate that into the work, and have it be considered by the agency.

DR. DAY: So we have before us in the last two comments, should the procedures be fixed, and standardized? Or open and

flexible? And I think the answers are: yes and yes.

There could be a few simple easy to conduct core tasks that everyone would do, and then there are some general recommendations about other things, and so the industry could develop their own methods for that. Very often new and creative approaches come forth when other people are in the room, and that often happens, and that can move quickly.

So I would recommend some things that are well tested, and they are scientifically based, some of them; they can be replicated and validated and so on and so forth; and some core tasks that everyone does, and then some general recommendations, general framework, so you don't have to say you have to do 20 scenarios, but you need to have scenarios of this type, or whatever; and then allow for the flexibility and creativity that has just been suggested.

MS. HOLQUIST: And I think with

respect to the fact that this is not science, I think some of the people at the FDA might take that a little personally, because it is a science, and it's more of a social science than it is what you traditionally see with your approval of a product based on safety.

So I think that is what we're actually trying to do is build the science behind this, to look at what's out there in the literature, we will look at some of the accepted methods that are there, and build on that. And yes, we don't want to squash ingenuity here. That is the goal to really get the best test practices.

DR. PHILLIPS: Part of that issue related to creativity, high reliability, organizations, use rapid cycle improvement. And I think you really ought to look seriously at avoiding the down side of this long time period, and finding a way to cycle back the improvements. How do you take the best practices, the innovative ideas, that an

individual submitter would have and share those with all the participants in a pilot so they could integrate that in their processes, not waiting for the two-year period, and then sitting down and analyzing that data, but really making it a continuous improvement process as it goes along. And I think that might help you gain a better outcome at the end of the period.

DR. FEDERICO: Marjorie, thank you for those comments. As I'm thinking of this and saying, how would we do a test, just one test, with one sponsor, one manufacturer, one time walking through this process to see what it would look like? I notice that here there is an evaluation of the submission itself. Are there other questions around how to evaluate this whole pilot? Do you have other set up that I think are critical for us to also understand?

MS. HOLQUIST: I think that is what we want to talk about tomorrow afternoon is

how would we best evaluate this overall pilot, and what should we be looking at, and should it be FDA.

DR. KORN: Just a follow up. There has been a lot of discussion here about different tests. There have been tests discussed before in 2003 and the like, and FDA made statements about there being no gold standard, and that this should be a combination.

Is there an FDA assessment of tests? Or is this whole process part of the follow up to 2003?

MS. HOLQUIST: This whole process is the follow up to 2003, and I think that is what we've learned is pretty much the state of science has been pretty stagnant since 2003. And so we have used the methods that we know best at this appropriate time. And so what we are looking for are, are there new and better ways to evaluate what we are doing now. That is the whole purpose of this.

DR. LEE: Carol, could I make - it's a little off the topic. I think we are probably going to end. But it is about stems. And for many, many years, pharma companies have been speaking with WHO and with USAN about the respecting stems. And there has been kind of an unwritten guideline about stems that are reasonable end stems, like five or six letter stems, or multiple syllable stems, but certainly avoiding those stems and the stem position in names particularly where you are not in the same therapeutic class, that those stems are things that could be respected.

But when you start looking at two and three letter stems, one syllable stems, particularly two letter, you take - and if they were to proliferate, those two-letter stems, you would take an awful lot of possible combinations of syllables, letter combinations, out of the vocabulary. It's not the same as saying, I will refrain from using

a six or seven-letter combination. That is pretty easy to do. But a two-letter combination is often very difficult.

And I would suggest that we look at ways to work with USAN and WHO about the way in which stems are created, because the opposite can happen as well. If it really is a safety concern, then what happens when a new stem is created, and its found in names that are already on the market, and that the stem is in the stem position of existing names? There doesn't seem to any concern about WHO and USAN making sure that when they create stems, they create stems that don't already appear.

And I think if they started to do that, this problem - this issue of - I have an issue anyway - with stems would go away.

MS. HOLQUIST: Yes, I totally agree with you. And that's been one of our pet peeves for a long time as well. The only thing is, we don't have control over that.

And so we've been trying to work with our USAN representative to bring forth some of these concerns. And that is primarily a number of the reasons why we try to avoid them in the use of the proprietary name.

Okay, I think we're at the time. And so thank you all for your participation in this panel. It was a very rich discussion, and we really appreciate all of you coming here today. And we are going to break for lunch now, and we will reconvene at 1:00 o'clock when we will discuss the evaluation of non-proprietary names.

Thank you.

(Whereupon, at 12:03 p.m. the proceeding in the above-entitled matter went off the record to return on the record at 1:06 p.m.)

PLENARY SESSION: SAFETY REVIEW OF PROPOSED NONPRESCRIPTION DRUGS

MS. PAULS: Good afternoon, everybody. If I could please have everybody

take their seats, so we could get started with panel two.

I just have a couple of housekeeping reminders. Several people have asked about the slides today. The slides will be posted onto the website after the meeting as well as to the docket. It may take a couple of weeks because we have to make them 508 compliant before they can get posted.

In addition to that the transcript will also be posted as soon as I get it and we make sure that it's accurate. So that usually takes anywhere from three to four weeks after the meeting.

As a reminder out in the front and in the panelists' packages there is a sheet talking about how to post comments to the docket. We have a new regulations.gov website that is pretty easy to do, and I tried to leave some specific directions in there.

Also in regard to housekeeping, when you do want to speak, please make sure

for transcriptional purposes that you state your name and your organization before you make a comment, and in addition we can only have six mikes on at one time, so make sure that you turn the mike off when you are done.

That being said, we are back on panel two. We have a couple of people that are different this time. If we could start with you, Dr. Sheridan, and go this way, to have everybody introduce themselves please.

DR. SHERIDAN: I'm Dan Sheridan, I'm a medication safety pharmacist from Marion, Ohio.

DR. HORN: Hi, I'm Donna Horn with ISMP.

DR. BRASS: Eric Brass, Department of Medicine, UCLA.

DR. PHILLIPS: Marjorie Shaw Phillips, pharmacist with MCG Health and University of Georgia.

DR. SPANGLER: Hi, I'm David Spangler with the Consumer Healthcare Products

Association.

DR. TAYLOR: Hi, Kellie Taylor, FDA.

DR. DAL PAN: Gerald Dal Pan, FDA.

DR. LEONARD SEGAL: Andrea Leonard Segal. I direct the Division of Non-prescription Clinical Evaluation at FDA.

DR. JOHNSON: Sue Johnson, Associate Director, Office of Non-prescription Products.

MS. HOLQUIST: Carol Holquist, FDA.

MS. TOYER: Denise Toyer, FDA.

MS. PAULS: Lana Pauls, FDA. And Ruth, if you could please join us up at the panel, I have a seat for you on the right-hand side.

DR. BULLMAN: Ray Bullman, National Council on Patient Information and Education.

DR. FEDERICO: Frank Federico, the Institute for Healthcare Improvement.

DR. DAY: Ruth Day. Duke University.

DR. GAUNT: Michael Gaunt, Institute for Safe Medication Practices.

DR. COHEN: And Mike Cohen, ISMP.

PANEL 2 - NONPRESCRIPTION REVIEW OF PROPOSED PROPRIETARY NAMES

DR. JOHNSON: Good afternoon.

Thanks for joining us today. I know a lot of people may still not have power at home. When I was driving in, I thought that last night was the night the lights went out on Georgia.

(Laughter.)

My name is Sue Johnson. Don't trust your soul to a backwards southern lawyer. I'm the associate director for the Office of Nonprescription Products, and I'm here to give you a short background on nonprescription drug regulation.

We in our preparation for this decided to focus on some very specific elements. There is a lot more to it, and if anybody has additional questions today I can add comments about the process, but if you would like additional information the website

is also listed here.

Non-prescription is the term that FDA is moving towards, but most folks are familiar with the term, over-the-counter, or OTC, so we will use those interchangeably.

There are two regulatory processes that apply to OTCs - let me get this out of here. The first is the new drug application process, and when you hear on the news that FDA has approved a new drug, they are talking about a drug that is being considered under the NDA process.

The second regulatory process most folks who don't deal with OTCs know less about and that is the OTC drug review process or the monograph process.

And I'll talk a little about both regulatory processes, and about labeling and proprietary names for both.

I just wanted to mention, based on Mr. Cohen's slides this morning, that neither of these processes relate to dietary

supplements. So between the prescription realm and the OTC realm, neither covers the dietary supplements, and those were present in some of his slides this morning.

So let's start with the NDA process. And to market under an NDA process, it's pretty much the same for OTCs and for prescription products. Industry applicants send an NDA application to FDA, and that contains the data that are relevant to support safety and efficacy.

In that application the industry proposes a tradename, and other labeling, so there is a formatted labeling that is submitted to us with the application.

For OTC products, there is also sometimes special studies, consumer studies, that help us understand how consumers view labeling. So do they understand the words on the label? Can they use the label to choose a product which is appropriate for their condition?

And then can they use and follow through based on that label? Do they take the medication right? Do they understand any drug interactions? Do they understand potential adverse effects?

So after an NDA is submitted by an applicant, FDA is required to review that NDA application, same as for prescription drugs, on a Congressionally mandated timeline. And most folks have heard of PDUFA, or prescription drug user fees; that is the same for NDA and OTC products.

So a favorable FDA review is required, and an approval is required prior to marketing for NDA products. It's specific to a drug product, and depending on the information within the application, it may provide for marketing exclusivity, which means there is only one product of its type on the market.

You are probably most familiar with NDAs for OTCs as the mechanism for Rx to OTC

switches, so that was the instances in which prescription medications become available OTC. Some of our recent switches are for alli for weight loss, which you have seen, and MiraLAX and Zyrtec, all have a lot of promotional information out there these days. I'm sure you have seen those products.

So safety review for proprietary names is conducted by the Division of Medication Error Prevention, the same way as it's conducted largely for prescription products. So at the end when we go to take an action on an NDA, we approve normally one or more trade names with that NDA approval.

The industry has also been allowed to change or add a proprietary name to a specific product. And line extension I think has different meanings to different people. In this scenario what I'm talking about is marketing the same product, the same formulation, under different trade names. Industry is allowed to do that. And in the

end you end up with a drug store shelf with duplicate products with different names essentially. And that includes distributor names, which may be specific to a retail outlet like a chain drugstore.

Okay, let's switch then to marketing under the OTC drug review. This process is different than the NDA process in that it's organized around active ingredients rather than specific products. It was established in the early `70s to deal with products that were then being marketed OTCs. It does have provisions for new ingredients to be added, but that hasn't happened to any significant extent at this point.

The whole process is a series of regulatory steps based on public notice and comment, so it's all a public process rulemaking, and the rulemaking steps are interspersed with OTC Office of Non-prescription Evaluation of the data that has come in.

In the end what's the product of this review is a monograph, and in that monograph the FDA defines allowable conditions for that active ingredient to be marketed, and that would include things like drug combinations that are allowed.

Part of the monograph review process is determining whether a drug is generally recognized as safe and effective, or GRASE, and when a drug is determined to be GRASE, all of this information gets finalized in a monograph.

The monograph process does not allow for drug products to be reviewed before they are marketed. The conditions for marketing again are set up in the monograph, and as long as the company is following the pertinent regulations including manufacturing and labeling, et cetera, they are allowed to market the product without prior approval.

So in follow on to that, proprietary names for OTC monograph products

are not reviewed by FDA prior to product marketing. And this is distinctly different from the NDA process in which they are.

Labeling, and these comments pertain to all OTC products, both NDA and monograph, is directed to a consumer. It is intended to be in plain language, and consumer comprehensible. It's intended to convey everything the consumer needs to know to adequately figure out if what symptoms they are experiencing meet the conditions the drug is intended to meet. It is intended to be used, to be able to be used, without health care provider supervision.

The drug facts format is the consistent requirement between NDA and monograph products, so all product information is required to be in that format. And FDA regulates OTC labeling. We don't, however, regulate OTC advertising, which is distinct from labeling. The Federal Trade Commission regulates OTC advertising, and that is

different than prescription products where FDA has regulatory authority over their advertising.

Here is a template for the drug facts format. And if you use any OTC products at all, hopefully you recognize this. I've turned the box around to see this. It has the familiar box format, with subheadings for active ingredients, uses, warnings, et cetera, all information that we think the patient needs to use the product properly. The agency emphasizes the importance of the drug facts portion of the labeling for patients to select and use their products properly.

Proprietary names for both NDA and monograph products are considered to be part of the labeling. While we think that trade names may affect consumers' ability to identify and use products properly, we really need additional data to understand those relationships.

It's the existing regulations that

dictate much of our interaction with OTC trade names and our ability to make decisions. So I'll just focus this discussion on OTCs this afternoon on the fact that we are largely guided by the existing regulations. But having said that, the existing regulations do allow us to take enforcement action if we identify products with proprietary names that are found to be false or misleading. And I'll be happy to take clarifying questions, but first let me introduce the questions for panel two.

The first thing we would like to know is since non-prescription products that are marketed under an NDA can participate in this pilot program, we are looking for feedback on whether the mechanisms for reviewing safety issues associated with proprietary names for prescription and non-prescription products should be the same, or should they be different?

And in addition if we are not quite

sure exactly how to do safety reviews of OTC trade names, what additional studies would help us generate data to figure that out. And that's all I have to say. If folks have questions about the OTC process, I can address those.

DR. HORN: I have a question for you, Susan. Can you give me an example of an OTC drug that has gone through the monograph process recently so I can understand what the difference is?

DR. JOHNSON: The vast majority of OTC products that are marketed are actually monograph products. They are the older moieties, some of the more common ones are antihistamines, decongestants - Sudafed is a monograph product, acetaminophen is in the monograph. Many of the products we saw this morning were monograph products if not all of them. Docusate is in the monograph as a laxative. Bisacodyl is in the monograph. Bismuth salicylate is in the monograph.

DR. GAUNT: Hi, this is Mike Gaunt from ISMP.

I just, curiosity, why you would approve more than one name for an NDA?

DR. JOHNSON: I'll go back to the regulatory basis for our decisions. And one of the things we didn't want to focus on at the meeting today was a lot of regulation because the purpose of the meeting is to get feedback on how to do this analysis. So the attenuated discussion of that is really the regulations do not prohibit it, and therefore it's allowed.

I think that the focus on - one of the issues that has come up recently was one sponsor was interested in having two trade names for a single NDA. And our attorneys brought up - the question came up as to whether or not that was going to be confusing to patients. The attorneys brought up the fact that that moiety, that very same active ingredient, was marketed by many different

sponsors.

So why in particular were we worried about the confusion between two names from a single sponsor? And in fact, you well know in the marketplace, given all the - they are not generics, but they are generic-looking products that are marketed under the monograph - there are many tradenames for the same active moiety.

DR. LEONARD SEGAL: I can also add that there are many issues that the attorneys frequently will put into the mix regarding First Amendment issues. And we need to listen to their interpretation of the regulations in all decision making that goes on at the agency; that is paramount.

The other thing is that the entire generic process, which offers the opportunity for less expensive drug products, puts us into the situation where you can have an approved NDA that has one particular active ingredient, and then a generic that has the same active

ingredient but will have a different name. And there can be multiple generic products.

MS. HOLQUIST: Yes, I think the clarifying comment to that, though, is that most of those are not from the same manufacturer, or the same sponsor, and I think that was what you were asking about.

DR. JOHNSON: If this started, has less to do with the monograph than it does just to marketing in general, I think it started way back when the generic process opened up in that sponsors found that if they marketed their name brand product at a higher price, they would get that end of the market going, and then they could change the trade name, and market a seeming generic of their own product, and capture the generic end of the market as well.

So it's been a longstanding practice.

DR. HORN: Just let me understand. So if a company has a name like you say

Kaopectate for instance, the name is already there. If they want to use that name, Kaopectate, with another active ingredient, different active ingredient, like what we saw on the slide this morning, do they have to go through the FDA to do that, or because the generic has already been approved, and the name has already been approved, they can do that without going through the FDA? That's the part I don't understand.

DR. JOHNSON: It is confusing because the instances, while they seem the same, are actually incrementally different from one another. So the instance in which Kaopectate's active ingredient changed is different than some of the other examples we saw this morning, where a name like Kaopectate would add a different ingredient in a combination, and use their sort of family name with an extension.

In the instance - well, for Kaopectate very specifically, that is a

monograph product; they were allowed to do that without prior approval. Had we found that there was sufficient reason to act on that, we could have taken a compliance enforcement action on it.

The issues related to each of these individual scenarios are something that the attorneys take very seriously on a case by case basis. They are not willing to make generalizations, and we actually asked them to present today. But the generalizations they are very uncomfortable with because, in fact, each is incrementally different than the next.

MS. HOLQUIST: I've just been asked for a housekeeping matter, that when you speak if you could say your name before you speak; this is just for the transcriptionist. Thank you.

DR. COHEN: Mike Cohen from ISMP. I have a question about the first question. So before we can discuss that, can we ask the question about the first question.

Are you talking there about - when you say, given the differences between non-prescription and prescription product regulation and use, should proposed proprietary name review and methods be the same?

Are you talking about the DDMAC issues there as well being the same? Because we are looking for that, or you are looking for that, rather, with the prescription drugs. And I have concerns about the safety of some of the ads, some of the website information, et cetera, et cetera, with over-the-counter drugs.

For example one of the major manufacturers of acetaminophen chooses not to include the fact that it contains acetaminophen in some of their ads and some of the depictions of the product. And that concerns me, because we have so much duplication. That is a major issue that came up at other advisory committees. And I would

want to see somebody taking a look at that.

So if you are including advertising, I'd be in favor of that.

MS. HOLQUIST: I'll defer this to Michelle Safarik and Lesley Frank. But I think what you heard is that this really right now, as it stands, it's not under FDA's authority. It's under the Federal Trade Commission, and I think we are also concerned about that as well. And we have to look at ways in which we could communicate that to the sponsor while working within our regulatory framework.

I think if you have concerns about it, I would say go on record with your concerns and we can take this back.

DR. SHERIDAN: I'm Dan Sheridan from Ohio. I just want to clarify, when we talk about the products that are - when a different drug comes out with the same name, like, not necessarily Kaopectate, but the Maalox example where there are different Maaloxes, or another

example of a time my brother was watching his grandchild at home, and the little girl had a fever, so he went to the store to get her some Tylenol. Didn't have his glasses. He was in his 40s, and his eyesight wasn't as good as it used to be. So what he came home with was actually a form of Tylenol that had Sudafed in it. I don't know if it even had Tylenol, but it had Sudafed. So he gave the child Sudafed for the fever and ended up with a little baby that was bouncing off the walls all night long, and he had to sit up and watch the baby all night.

But is that something that just happens without you being able to do anything about it, or is it something that you can only react to after the fact?

DR. LEONARD SEGAL: Well, I can start with a question like that. I mean you are talking actually about a monograph ingredient. But in general the question is about a - the same family name that covers

products that have different active ingredients.

One of the things that we have tried to do is we have tried to get data on confusion within that family name, comprehension in terms of potential consumers' understanding of what the active ingredients are in those individual products. And we collect those data and see whether they show us that there are major confusions.

One thing we can't control is whether somebody wears glasses when they go to the pharmacy to actually pick their product. And -- but when we see that there is confusion, we can make recommendations to the sponsor that they change certain things about the way that they are presenting the information on the front of the box, in essence, to try to highlight and emphasize certain elements, certain active ingredients that are in the product.

We do do testing for this, but

there are things that we can't control. Another thing we can't control is, when people walk into a pharmacy, how distracted they are, whether they have their sick child with them, and whether they are in fact paying attention when they pick something off the shelf, or whether they avail themselves of a pharmacist to answer a question when they are choosing a product.

There are things that we just simply can't control, but we make efforts to learn about the comprehension of the ingredients in these products by consumers when we think that there may be an issue of confusion.

DR. JOHNSON: Can I just add, at the outset of this discussion, let's make it clear that the FDA does not in any way, Office of Non-prescription or Office of Safety, want to back away from the fact that there are potential confusions here for family trade names or whatever issues are in the public

interest.

What we want to emphasize today is that we don't have a lot of data to link all of these relationships and to really understand what is allowable under the regulations at this point. What is the impact of that, and we do know that people get confused, what is the ultimate safety problem, what is the risk analysis of that. What would the prevention be? Does getting rid of family names actually help us? Or doesn't it have an impact at all? What we would need are the data. And so the first step towards that is allowing - we have made a determination internally that the way the regulation was written for the pilot program, OTC products are allowed to participate when they are NDAed, in this pilot program.

So specifically what should we be doing under this pilot program to try to sort some of those things out.

DR. PHILLIPS: And given the

understanding then that this is limited to the NDA products, over-the-counter non-prescription products, I will take a stab at question one. And I think you do want a similar or almost identical process, except that the focus is going to be much more largely on consumers, and also with the recognition that a lot of the processes for product selection, dosing, and use is under control of a different group of folks.

That said, these products are also ordered by physicians, recommended by pharmacists, and then administered by nurses. So I don't think you want to totally divorce the process from a health professional review, but it really has to look a lot more strongly on the patient self use or the consumer self use and their perceptions and what they see.

But because you have the interaction between non-prescription drugs and prescription drugs and confusion among those, as well as the issue of medication

reconciliation when you are gathering information from patients, I think you still want to involve the same health professionals in the process, but you are going to need to involve a whole variety of consumers, and the same kind of thought process you had when you were involving multiple health professionals in looking at a failure mode, or looking at name recognition, or looking at pronunciation. You are going to need to do that more heavily weighted toward the consumer and patient end because of who the primary users of the products are.

DR. BRASS: I think before we get too much depth into question one, I think it's important to expand on some of Dr. Johnson's comments that detail the data that are available when making decisions about OTC drugs, specifically the large amount of behavioral research which is done to support the decision making, that unlike the hypotheticals that were talked about this

morning, in the case of OTC drugs, there are well - well in quotes - established behavioral clinical research paradigms to collect data not with model panels, but truly representative consumers, and study how the proposed packaging, which includes the front panel and proprietary name, the drug facts labeling, allows the consumer to understand the label, appropriately select the product, and use the product in a real world, as best we can, setting.

So in these kinds of studies, consumers will take the drug home and use it. They will have to make the decision about, based on what they know from the packaging, whether they should use other drugs. So we are actually measuring the outcomes in an integrated way and not in an isolated way.

Now I'm in no way suggesting that those methodologies are perfect, but they have evolved tremendously over the past 20 years and provide a context for thinking about the

isolated question of the proprietary name that is very different than what we were talking about this morning.

So that whether or not the name engenders confusion with other OTC drugs or other Rx drugs, that that consumer population - now we are talking about hundreds and sometimes thousands of consumers in these behavioral studies, we know what they actually do.

So we can use the type of fundamental baseline research that Dr. Day was talking about to help inform the design of those studies going forward, but by the time we are talking about names, it's in the context of a large amount of behavioral data.

I would also say that that experience is not irrelevant to the discussions of this morning. Because first of all it's important that everybody recognizes that within the agency there is in fact a cadre of expertise in social and behavioral

and comprehension research that can be used to help design studies for other groups; but also the concept that some data is better than no data, and we'll get the data and look at it, and then we'll figure out what it means, is not always a useful paradigm.

And before one embarks on a data collection exercise and behavioral research such as the simulation types of studies that were talked about this morning, whether or not they will in fact be robust and informative to the questions of interest has to be addressed before you embark upon them. And that's a lesson we've learned somewhat the hard way in 20 years of behavioral research for OTC drugs, but it's a lesson that has been learned, and that I think is critically important that the potential for misinterpretation of data, and making bad decisions because it's the only data available, may outweigh any benefits to the data collection exercise per se.

But central to what Dr. Johnson was

setting up, I think it's just really important to understand that this is a consumer driven process, but one in which we have actual behavioral data that includes the consumer's interaction with the proposed proprietary name during the development process.

DR. SPANGLER: If I could just make three quick points. One, Dr. Brass has just articulated the fact that there are studies when these products switch from prescription to OTC. You just articulated it a heck of a lot better than I ever could; so I'll second what he said.

Second, as was pointed out in the second ISMP person who was speaking this morning, when she was talking about not just the name, but the package, all the steps, again, using the brand name as a code - now to quote another person from this morning, Bob Lee - using that brand name to bundle up everything you want to communicate and get across there, that is definitely the wrong way

to think about it. You've got to think about that entire package, that entire label because that is the communication tool that the consumer is making their end use decision on, that brand name, yes, it is trying to get their attention, it wants to get their attention when they walk into the store and see a crowded shelf to cut through some of the clutter. But that is just that initial little hi, I'm here, shortcut; it's nothing more. There is no substitute for reading the label, and that is true for a health professional of being aware of what ingredients are in there, just as it is for the consumer.

And yes, there are instances where someone would be handwriting. But again go back to what Bob Lee said this morning, I hope we are approaching an age where we have less and less handwriting of medical records, and more and more of it electronically transmitted.

DR. GAUNT: This is Mike Gaunt from

ISMP. Just as a counter point there, a point that Dr. Cohen had mentioned today is the whole idea of confirmation bias, and it happens to us as practitioners, and it happens to us as practitioners and as a consumer.

When you walk into a pharmacy and you see a whole row of products that have the same family name, the likelihood of you confusing that and in your mind's eye ignoring some of those other details that are on the box or the package, is increased I would gather compared to even probably prescription drugs. Because you have many different tablet formulations, many different strengths - PM, nighttime, daytime, extra strength, regular strength, things like that. So I think the name - you know, having that same name - increases the likelihood that you are going to have some of that confirmation bias in the aisle at the drugstore, because you are looking at the whole section of products that have the same root name, you know, same parent

name. It doesn't - you're right, people would -- we need to do a better job of reading the boxes and the labels. But having that presented as the main panel in a whole section of products, I think, can lead to confusion.

One of our colleagues at ISMP just made a mistake and came out with a PM product instead of a regular product. And she is someone who is a safety expert and has been doing this. And to expect the patients to not fall into the same traps or have the same issues, I think they will.

DR. BRASS: Having said what I said earlier, and now kind of moving in that direction, I think first of all the points that Dr. Johnson and Dr. Leonard Segal made earlier about our paucity of data on the true prevalence or consequences of these types of mistakes handicaps us a little bit, so one might legitimately revert to anecdotal experience and common sense because I think just -- there is a face validity problem.

And there is one example which parallels this where there is better documentation of clinical concern. And this was addressed earlier this century, `02 or `03, concerning the safety of the OTC analgesics, where when one looked at issues related to acetaminophen hepatotoxicity, or NSAID-induced GI toxicity or renal toxicity, a nontrivial percentage of the cases involved ingestion of more than one product with the same active ingredient, where the consumer relying on the proprietary name, the more prominent, seemed not to be aware that they were taking multiple products with the same ingredient.

And that led to much discussion at that time about how naming and labeling could be altered to mitigate or minimize that risk. But I think it is the most tangible example of where we have clinical adverse outcomes, suggested data, where name confusion is not simply a bad night with a kid, but really

potentially irreversible or a high degree of morbidity associated with the drug product.

MS. HOLQUIST: And if I can just interrupt here, that is exactly what we are trying to test. How would we best test that? Because from our perspective, from a medication error perspective, we see that as a root cause of error, and typically how we have tested that in the past are the methods that we have outlined in the concept paper.

I think we've been criticized that those methods may not be the best test practices to test in this type of environment, and that's sort of what we want to focus today's discussion on, are what we propose adequate, or are there other methods that we should consider that will better get at a lot of these things that you guys are talking about.

DR. BRASS: That's right. Because there is a dichotomy at least that is historical that as our methodologies have

gotten better, our confidence in more recent NDA approvals has gotten better, but we still have the monograph and other even earlier NDA products which haven't been exposed to the same standard. So one of the other lessons I have learned from behavioral research is that it is much more like traditional clinical research than lots of people would like to think.

So if you want to answer a research question, you start with a hypothesis, and you form the hypothesis that labeling A or B or something else will decrease a certain behavior, and then you design an experiment that is based with adequate design features and adequate statistical power to address your hypothesis.

And it turns out there are large numbers of behavioral questions which have been successfully studied using those types of methodologies. So if a question is important enough, there are in fact behavioral

methodologies that would allow a real world assessment that would have high face validity and circumstantial real validity to predicting marketplace behaviors.

Right now there is nobody who is adequately incentivized to say that must be done to somebody with adequate funds to actually do it. And that is the barrier to getting it done.

If somebody said it had to get done, said that to somebody who had the money to do it, I guarantee it would get done. But right now it's talked about, and it's not been elevated to a high enough priority. I'm using that as an example, but the more important point I think is that there are in fact behavioral approaches in the consumer marketplace that are sufficiently well understood that would allow relatively definitive scientifically valid conclusions to be made on the impact of labeling and name changes and other interventions on how

consumers use these products.

DR. JOHNSON: Could I just respond to that, the latter part in particular, about being incentivized.

One of the things that may change the current equilibrium, if you will, is recently, at the end of last year, sponsors have begun to be required to send in what we call 15-day reports, reports of serious adverse events for the monograph products. That had been neglected in the regulations up until this point. And Congress acted on that to change that.

So we will have a new safety database associated with these products. It will be interesting to understand whether these confusions are inconveniences or whether to a large extent they are causing serious safety problems.

We know now that there have been serious events. We know now that we have a smattering in the literature and in our own

databases of some aspects of these various scenarios causing problems. We don't know what the real impact of that is overall, and the 15-day reporting may help change our understanding of it, and therefore the incentives.

DR. BRASS: No, I agree with that. But this is a challenge in the entire area, I think, for the entire day. I mean you live in a world of finite resources, and you want those resources invested initially where they are going to have the highest impact on public health.

And so you want to address problems that are associated with the highest public health risk. And for the reasons you've said, we don't have enough epidemiologic data to understand the true public health burden of a variety of these issues.

We all understand or feel that it is nonzero, but how nonzero it is in a universe of billions of doses dispersed, et

cetera, and compared to other tackleable problems, is one of the things that I think creates inertia around these issues.

DR. DAY: I agree with everything that Dr. Brass has said.

DR. BRASS: That's a first.

DR. DAY: Yes, it is.

(Laughter.)

Moving right along, we actually are doing testing of OTC labels in my lab, and we have the drug facts label versus an enhanced version, and it's an experimental head-to-head test, and we get dramatic improvement in whether people know that there could be liver toxicity, or not, or GI bleeds or not, however it said on the label.

And we can get 80 percent, 100 percent improvement, just by doing things in different ways.

And so this is absolutely the case, and in terms of - and there is no incentive for it. We have no funding for it. This

comes out of my pocket and time and so on. So you are absolutely right.

And the point that he also made is that there are millions of people taking these things, and that Dr. Cohen said about where people don't realize it when they take this product and that product, Vick's cough syrup and something, something, something, they could be getting multiple doses of acetaminophen is really important.

And I thought one of the outcomes of the 2003 meeting was that we recommended that the labels, whatever the name is it says contains acetaminophen in it. And I saw that for awhile; I don't see it all the time anymore. Again, that's an issue I suppose with FTC and so on.

But there are very clearly developed methods for testing these things, and many of the tasks that I proposed this morning, when we come to alternatives, I'm going to propose again here in this context.

But there is another one. I think the major thing about OTC products is it's a self-selection process. And so I've developed a task for testing self-selection based on the different kinds of naming procedures, which I will bring up during the alternative discussion.

MS. PAULS: If I could please remind everybody to introduce themselves before they speak.

DR. LEONARD SEGAL: Ruth, I was just going to comment that what belongs on the label is not an FTC issue.

DR. DAY: I'm sorry, I did mis-speak. I understand that drug facts label comes from an act of Congress and FDA - I'm saying that FTC would step in for any advertising promotional aspect. I did mis-speak that; sorry.

DR. LEONARD SEGAL: Right, and when we become - again, acetaminophen is predominantly a monograph ingredient, so we

are not reviewing - there is no mechanism in the regulations to require that we review the packaging for those products.

When we become aware of a problem on a monograph ingredient product where they are not doing something that they are supposed to do in compliance with the regulations, then it's a compliance issue, and we need to track it down in terms of safety in that regard.

There are NDA acetaminophen-containing products, and they are NDA products because they may have a different formulation that makes them extended release, or for other reasons - maybe they are combined with an ingredient that is not covered in the monograph, and therefore they are regulated by the new drug application process.

I just wanted to clarify that.

DR. JOHNSON: Acetaminophen has been brought up a couple of times. There was an advisory committee in 2002 or `3, I always forget the date because I wasn't in the office

then, that highlighted specifically the hepatotoxicity associated with acetaminophen and the GI bleed risks associated with aspirin and nonsteroidals. Those are high priorities. Those are not something that I think we understand are not in the same equilibrium as the rest; that they are high recognized safety considerations, and we are working really as fast as we can to try to put out regulations that deals with those specific problems.

DR. DAY: there's a quick easy solution, and that is to pull the liver toxicity, for example, out of a chunk that says, alcohol warning. So you will have a chunk on the drug facts label which is called something like alcohol warning. And then it goes on and on and then it says, and it may be in the GI bleed one I guess it is, that it may cause - and it's the end of a chunk, and it needs to be pulled out as a separate thing and say, you know, whether it's a stomach problem or if it's a liver problem, whichever product

we are talking about, it just needs to be pulled out and be in its own little chunk with a name on it. And that solves it, and that's what our research has been showing.

DR. SPANGLER: If I could make three points. One, on this issue - I'm sorry, David Spangler, Consumer Healthcare Products Association. Sorry. I'll try better next time.

Three things. First on this issue of what's on the principle display panel on the ingredients. Under current law now, existing regs now, for a single ingredient you have to list your active ingredient. For combinations under the existing rules, you don't.

However, for a lot of NDAs recently, FDA has encouraged within the NDA negotiation around the label to include all the ingredients if it's a combination. And so you are increasingly seeing switch NDAs if it's a combination with all the actives on the front.

Second, we have been talking a lot about acetaminophen, and on that, the major manufacturers of acetaminophen products, and that includes the world's largest store brand manufacturer, have voluntarily added acetaminophen to the front panel even in combination. And as Dr. Johnson pointed out, there is a pending rule to try and change that, so that would be a requirement.

We think that is a great idea. We are trying to expand that to other categories, as issues arise, where that comes up as a cause of potential confusion or concern of saying, "Okay, let's step up. Let's put the actives on the combination on the front."

So I think you will be seeing more of that, not less.

The second thing, I don't know if- more than anecdote, less than data, somewhere between those two: a couple of years ago, in fact it was after the 2003 meeting, following up from that meeting, in late 2004 we surveyed

a number of our members who made 20 different brand families. I happen to be holding a Neosporin. This happens to be a Neosporin pain relief. Okay. So if you had three Neosporin varieties, that would be a family.

So 20-brand families, over a year and a half, representing 109 million units, so that's 109 million packages sold of 20 brand families, and this is just consumer complaints. So somebody decides they are going to pick up the phone, they are going to send an email, they are going to write a letter to the company; 680 complains about confusion or requests for clarification. Of that, two of those, the company attributed a serious adverse event to the confusion.

Now again this is not an analysis of an AER database. This is not everybody in the universe. This is 20-brand families. Consumer complaints. A year and a half.

So this is not zero. Zero would be better. But it's not, you know, it's not a

through-the-roof number.

The third point, you had asked a very direct question of, okay, how do we marry what we are talking about here today with the pilot project on naming? And what we've heard Dr. Brass talk a lot about on some of the consumer studies. And I guess I would say, I hope you guys are talking to one another as the office of non-prescription products develops its guidance on what it would consider some of the best practices in a label comprehension study. Because that's the place where these two things really intersect, so that when you are doing your label comprehension study, you are trying to be as holistic as possible in your tests, and get at those core communication objectives that you are trying to achieve. One of which is obviously to not confuse.

DR. BRASS: If I could just follow up, David, because I think I applaud the industry's effort to move the ingredient,

particularly acetaminophen, to the front display panel. But I think it also highlights a missed opportunity. Wouldn't it have been great to know the prevalence of use of multiple acetaminophen products prior to that change, and after that change, to know whether or not we had in fact done good, and if we had not done good, we misdiagnosed a problem and better look somewhere else.

But we don't consistently quantify the problem, and quantify the success of the intervention, and I think that if we are ever going to make really not only substantial impact, but learn from our experiences how to do better in the future, we have to understand the impact of these kinds of interventions in a quantitative, clinically relevant, scientifically valid way. Nonetheless, I applaud the effort.

MS. HOLQUIST: I'd like to take that Neosporin example and throw that out to the group. So if we were faced at the agency with

a similar scenario like that of having to name these products like this, and trying to test how much or how little these things would be similar, how would we do that?

DR. SPANGLER: Could I - before we go there - this is David Spangler, Consumer Health Care Products Association - before you go there let me just make one observation that has always struck me whenever there is a discussion of the supposed bad sides of brand name line extensions.

We don't seem to talk about that in the context of, if I walked into a Wal-Mart and about every fifth product on the shelves is the Equate brand. Doesn't the same thing apply there? We don't- we don't worry about that, because we understand. We are shoppers, we're in the store making selections. We understand, this is the store brand of something else. This is everything; every one of those packages is not- it's an individual entity that has its own communication depths.

Sorry.

DR. BRASS: But again, that is a very interesting hypothesis, very valid. I just wish I could know if it was true.

And coming back to your question, one of the things that I think is important, again in general study design, one designs studies to challenge hypotheses, not to confirm hypotheses. The bias has to be toward failure, not towards success.

And so that if I was interested in a brand line extension, or whatever the proper terminology, I apologize, I would try to understand where the highest risk behavior conditions might lie that would be of interest to me, and I would design a behavioral or comprehension or self-selection or some type of real-world experiment that created that worst case scenario, maximized the risk of error, maximized it in a clinically relevant context. For example, if it was a population of people who if they made this mistake would

be the worst off, I'd study that population.

So again, I think the theme I'd like to just continue to reiterate is to find a problem that is important enough, to find an hypothesis around that, and design an experiment that is designed to test that hypothesis.

DR. COHEN: One thing you have to keep in mind that was mentioned before too was, it isn't just the single thing, just the name. But the packaging, for example, it also can contribute to the errors. And with a lot of the over-the-counters that I have seen, including some that I showed this morning, the Maalox for example, you would be hard-pressed, I think, to find that name, the name of the ingredient, on the label. You really have to look for it. And that's the case with a lot of- even though the ingredient might be listed there, the graphics are so attractive, calling your attention to the brand name, that it is very easy to miss other information on the

label.

And again I'm not sure exactly how you would look at that, but that is a contributing factor to overlooking something that someone may be allergic to.

I remember long ago, we published an incident involving Excedrin, and the ingredients- it resulted in a fatality, because of an allergy to one of the ingredients that was overlooked.

So it isn't just the fact that it's on the front label panel. Sometimes it's very difficult to see it, and that's a problem.

DR. HORN: Donna Horn with ISMP. I want to follow up on what Mike is saying.

One of the things you were looking for, you said, was data. And at ISMP we do have a reporting system, a voluntary reporting system, and we do get reports to us from consumers when they have made a mistake. That's consumers that know they have made a mistake. There are a lot of consumers that

don't know if they've made a mistake, and even if they do know they wouldn't know who to report it to.

There was an example at my son's school where the school was given Motrin as a stock, liquid Motrin, for the children if they needed- if they had permission from their child's doctor to have it administered at school. The school did stock it.

It wasn't until my son needed it and I happened to be there, because I didn't have a note - I went in with them - that we realized that the Motrin was actually Motrin Cold. All those children were getting Motrin Cold. So, is that an adverse effect? Well, yes, I guess if you have children taking pseudoephedrine during the school day that shouldn't be, that could be an adverse effect. But did that school nurse know who to report it to? No. I mean, I reported it to ISMP because I was there, but she would not know who to report that to, and there were a lot of

children affected by that.

So I think we have to have a campaign that if you want data the people have to know where they can report those things to.

DR. BRASS: Or do a more active surveillance for questions that really matter.

MS. HOLQUIST: Okay, I hate to break up this discussion, but we were scheduled for a break. So do people want to continue, or do you need a break at this moment in time? Keep going? Okay.

DR. SHERIDAN: This is Dan Sheridan again. You mentioned the Equate, and as a pharmacist working in a hospital pharmacy, I frequently see medication reconciliation. That's where a patient comes in the hospital and a nurse writes down all the medications they are on. I don't know how many times I've seen Equate, 10 milligrams. So that does cause a lot of confusion, not just among patients, but among health care workers too.

DR. BRASS: A couple of other points

I'd like to make in the context of the pilot that has been proposed, and again, applying the learnings from the behavioral research in the OTC area.

One is that I think it would be highly desirable for you to have failures submitted as well as successes. You don't only want to see the successes; you want to know what's failed, so you can begin to understand why it's failed, and get a more generalized understanding of what's going on in this type of research, so that over time, iteratively, you can make better recommendations in terms of that.

And then again another thing that we have learned in the OTC area is that there is no behavior you can imagine that won't occur. And setting a zero error rate may be a worthy goal, but is not going to be what you find. So understanding, for example, what a negative control behavior is in the experiment. So a drug name that clearly

everybody agrees has no intrinsic confusion. But I guarantee errors will occur some place in the process when you use it to provide some kind of background rate to allow interpretation of error rates when you see it.

And it'd be nice to have a positive control as well, so you take a name, if you are trying to validate an instrument, you take a name that you really do believe causes problems, and show that it differentiates from a negative control in the experimental paradigm that you are trying to apply to new learnings, to try to see whether or not your assay methodology has any dynamic range to distinguish meaningful errors, and allows you to differentiate a rare non-meaningful error with an otherwise appropriate name from a signal that is truly meaningful in terms of safety.

Because again, once you start talking about- the closer you get to a real-world situation, the more unpredictable small

rate behaviors become.

DR. HORN: Donna Horn from ISMP. I wanted to move a little bit towards the RX to OTC switch, because those are the products that would come under this concept paper. And bringing your attention to box two on page 15, it says in part submit line listing and narrative of medication error case reports identified in the post-market period.

And Zantac has been over the counter for a number of years now. Zyrtec just went over the counter. And if you were to apply this rule to Zyrtec, I think the post-market, from an RX standpoint is, there is lots of data to suggest that that name pair has been confused many times - Zantac and Zyrtec. So I'm wondering if you did subject Zyrtec to this rule, would Zyrtec then have to change its name? Would that name not be effective or not be allowed, because we know that Zantac and Zyrtec get mixed up.

And now that the consumers are

going out there to purchase it themselves, they may get a call from their doctor that says they are supposed to pick up either Zantac or Zyrtec, and I know for instance my mother would never ask the doctor to spell the medication to her on the phone. She would just think that she could remember that and go to the store, and might run into the wrong product and buy the wrong product.

So I think that there is a problem with Zantac and Zyrtec over the country, because they will be confused by consumers. So I'd like for you to let me know, what would be the results of that name submission based on post-marketing tests?

DR. LEONARD SEGAL: It's unfortunate we don't have our attorneys here.

MS. HOLQUIST: Yes, I think that is one of the problems we have. Because once a name is established in the RX world, and we know that there are problems, even when there is a product line extension in the Rx world,

we take that into consideration.

But the problem is, when you are going from the Rx to the OTC, it's the same product, so can you change the name? It's not like you are introducing a new product.

And actually some of the errors, at least what we learned from Zantac and Zyrtec, a lot of them dealt with the pediatric suspension, and a large majority of that were related to the fact that these products were packaged in very similar packaging configurations, you know, the bulk bottles that sat on the shelf.

So as we were talking about earlier, we have to examine not only the similarities of the names, but what are the other contributing factors to it. And if there is a way to minimize those other contributing factors when we introduce it into the marketplace, into the OTC realm, we will consider that.

We may not be successful at getting

a name changed, but we would consider other measures that may help to minimize that type of confusion.

DR. BRASS: I would just like to highlight - this has been a very stimulating and very useful day. But there has been one aspect of it that I personally found incredibly depressing.

As part of the cohort that tilts against the windmills of trying to get physicians to use established or generic names rather than proprietary names, the concept that 10 years from now proprietary names might be safer than established or generic names because of an improved process to prevent errors of medication errors is quite depressing.

So whoever has the power to ensure that these same standards are eventually applied to established names would make me feel much better.

MS. HOLQUIST: I think Dr. Cohen can

probably speak to that, because I know he's been doing some work with WHO and other organizations, and again, when we come up with names that are similar in the non-proprietary scheme, we do tell our FDA representative who goes to this USAN committee, but they are very far from that mentality. And I think it's going to take a joint effort here to really - for them to hear that this is also an issue.

DR. COHEN: I don't really have anything to add. I've attended some of the USAN meetings. I'm not on that council. So I'm not a member.

But they do take into consideration look alike issues, but nothing as far as testing, field testing or use of practitioners or anything like that. It's just a committee. That's what FDA was doing 15, 20 years ago, and unfortunately there is no funding to go beyond that.

But it is a serious problem; it really is.

DR. DAY: Is it all right to move into alternative approaches?

MS. HOLQUIST: I think we've been hearing a mix of it all, so.

DR. DAY: Well, there are plenty of things that are recommended for prescription drugs that wouldn't need to be done here, and I think that is fairly obvious. So it's already a simpler process. But to add some things in, some of what I talked about this morning, but something new, I do think a pronunciation test with consumers is essential. Just since this morning's meeting, two people in this room have come up to me with interesting cases in the OTC world.

There is a product called Golytely, a preparation for colonoscopy, and it's spelled G-o-l-y-t-e-l-y, and this person in this room who will not be identified said for a long time he or she was calling it (pronouncing) goolie-tellie.

(Laughter.)

And it's supposed to be (pronouncing) go-lightly as in - you can figure out what that means.

There is someone in an office who is always talking about something like ibuprofen, or something, some other variation on it, and when you think about all the dialect differences in the country, and the people with different language backgrounds and so on and so forth, I just think it's, to me, a no-brainer, if there is going to be a new product come out, get some people to look at it and say it, and get the frequency distributions I described this morning, if there are multiple alternative pronunciations, either do something to enhance the way it is presented, so it won't, or go on to something else.

DR. SPANGLER: Could I ask for a clarification?

DR. DAY: Yes.

DR. SPANGLER: David Spangler, CHPA.

On having the pronunciation, I'm not arguing, I'm asking a question.

DR. DAY: Certainly.

DR. SPANGLER: What does it gain if you know that 50 percent say tomato and 50 percent say (pronouncing) tomato. I'm - help me understand.

DR. DAY: All right. So in that case it's not likely to lead to any consequence of not getting a tomato, and getting a cucumber instead; so you have to look at that context.

But the frequency distribution is very revealing. There might be one that is very strong, 80 percent and then 20 percent. It's the cases where you have like 40, 30, 20 and so on and so forth. There is going to be a lot of confusion in going say, go pick up the such-and-such, and then actually finding it.

DR. SPANGLER: And it would also certainly be true if you were going to do any

automated analysis of the pronunciation, you would have to know the universe of pronunciations in order to do the analysis of it.

DR. DAY: That's right. You are defining what the universe is, and you are not just predicting what it might be. Right, exactly. And from the real people who are going to use it.

Task number two I would do, I would do a search and find with consumers. And I do a visual experiment; I do an auditory experiment. So I put up on the screen or somewhere or a piece of paper, nicely printed, the name of the product, and then either have a simulation with lots of names, as far as the actual packages, you can have in my lab for example shelves where you put packages and go find that and pick it out.

And then you do the hypothesis testing by putting in what the foils are, so the target is one they are really supposed to

find, which is the drug name you are trying to test; but the foils are the other ones you put out there that might be confusable and might not be confusable.

And then what you do is not only get percent correct data, you find out what the errors are. So I want to reinforce it; error analysis is essential. It's not just that you had an error rate of 30 percent, but what did they choose instead. And if it's totally random, and has nothing to do with the foils and the targets in terms of what the names are, then you don't have a name problem in the same way as if you are doing the Kaopectate and the, I don't know, Kaopectin, or whatever thing that might be similar.

So you do your hypothesis testing in a search and find way, and sometimes you give it to them visually, and sometimes you give it to them auditorially.

Last task is a new one, and that is version of a self selection task, and it's

based on scenarios. And you say, okay, you have such and such a condition, and if someone tells you there is product out there, so now I am going to find it. And you can either give the name or not give the name, various variations, and then they go and select it.

But then you give other scenarios, so you don't want to get sleepy, or you want - you do want to go to sleep at night, and so on. So you can have all these products like all the different neosporins, or all the different ones that are the AM and the PM.

So a self-selection task where you are given some scenario of what the health condition is, and then the different products, and whether the name confusion is going to cause - I mean the name variation is going to cause confusion or not, will tell you something. And you can then put in the different types of foils on the shelves to find out what's going to happen.

DR. LEONARD SEGAL: Ruth, you

brought up a couple of interesting things, and I'd like to ask a couple of questions, actually one of you and one of Dave Spangler.

On the first, in terms of prefacing, one of the requirements, and you mentioned the terminology several times and Eric has mentioned it several times, for an OTC product is that it has to be a product that a consumer can understand how to use, and know to use, and be able to use, on his or her own, without the input of a health care professional to advise and to tell how to use.

So that is the standard by which we have to determine whether products can be over the counter. And we do that by these label comprehension testings. We self-selection test. We actually use studies. This is part of what we do for products that are going to be new to the OTC market. Might have new indications; might have new warnings; might have new directions for use, things that we know have not been tested previously; landing

on that ground, because I want to just move on to one thing that you said.

DR. DAY: Can I just comment? I do know that you do that, and it's wonderful. All I'm saying is, now you just fold in the name variation.

DR. LEONARD SEGAL: Well, this is what I want to ask you, because you made a comment in your conversation that many of the things that we are talking about for Rx products are not needed.

I wanted to get a little bit more information about that, and based upon that today, it's a two parter, do you have any sense of how often the OTC selection process is in fact not a self-selection process, and becomes more a prescription process whereby the physician is saying to the patient, not the OTC consumer but the patient in the office, go out there and buy Ibuprofen over the counter for your knee pain? Versus the consumer walking into the pharmacy and saying,

I have some minor aches and pains with my knee. I'm going to buy acetaminophen or Ibuprofen. So it's a two parter, and the cross discussion would be helpful.

DR. SPANGLER: No, David Spangler with CHP, I don't have a good feel for that. It certainly has happened. It's going to be fairly category specific. And I think if we just think kind of logically, if you think about a category like analgesics, allergy, a very few others, you are going to have a fair amount of that. Also, the H2s and omeprazole PPI, those categories you might get a little more of that. But I don't have numbers for you, I'm sorry.

DR. DAY: I don't have numbers either, but I know it's very common. Having had a wasp bite a few days ago, and a bad reaction locally to it, I had to consult with a physician finally, and he started suggesting OTC things.

It happens a lot of times. So for

allergies, and all the categories that you said.

But did you want some comment on what kind of testing did not need to be done in the OTC domain also?

DR. LEONARD SEGAL: Well, we're discussing methodologies here for assessing trade names, and I think it's useful to hear what your thinking was.

DR. DAY: Well, I was thinking in terms of those name simulation studies with all the chain of all the people in it would be greatly reduced. So that was one of the things I had in mind.

DR. BRASS: And the - if you went the NMEA route, the composition that would be very different, that it would have to mirror the decision-making process.

And while I agree that clearly in many situations physicians are in the loop, or pharmacist is in the loop, the question is, where is the greatest risk lie? Does the risk

go up or down when you impose a health professional?

Again, I don't know the answer, but the hypothesis, the face validity assumption would be, the greatest risk is the consumer operating independently, and that if you could pass that barrier everything else would be safer.

But that's an assumption too, and I acknowledge that.

DR. COHEN: Let me - this is Mike Cohen - let me just point out too that, keep in mind that a lot of the OTC drugs are used in patient situations. They are ordered in the hospital; they are used by nurses in the hospital. You have an FDA barcode rule that includes OTC drugs used in the hospital. So there is a good number of them.

MS. HOLQUIST: Yes, I think that's one of the things we have been grappling with at the agency is, that we know that these things can be ordered through the traditional

channels, and so how would we weight that along with consumer testing.

DR. COHEN: And I would imagine sometimes patients come into the OR, and you probably know more from the poison control centers, the ER rather, you know, where physicians are told they are taking a certain product, and they really don't understand exactly what the ingredients are.

DR. SPANGLER: David Spangler with CHPA, I think it goes back to the point that was made by Dr. Day and others this morning about, you do have to have some flexibility. Let's take for example switches that occurred, or new product introductions in 2006. One of them was a sunscreen. On that you are not going to go through 20 health care professional scenarios. On the other hand if you know to Mike Cohen's point that it's going to be continued - is already being used in a hospital, and will continue in a post-switch environment, yes, then I think some of that is

probably fair game to think through, because it fits that case.

DR. PHILLIPS: Marjorie Phillips. I have a clarifying question, since we are talking just about the NDA products, and not the monograph products, it sounds like most or all of those are prescription OTC switches.

I guess the question is, how many cases would you actually truly have a new name that was being introduced, or one where you could have the same level of impact of saying, please choose another name; that name is not acceptable for safety reasons. Is it more that you are asking a different question in the non-prescription environment of really more - again, what are the potential safety risks of this product name, and packaging and labeling, being out in the public, and what can we do to analyze those up front and mitigate them.

So I guess my question is, does it even more put us in the realm of looking at

overall failure modes analysis, or more complex analysis of saying, what are the potential risks, and what can we do proactively to address those. How many cases is there really an option to make a name change? Or is that going to be something within the agency's purview?

DR. SPANGLER: We'll give two examples anecdotally without naming names, David Spangler, CHPA. I can think of one example of a pretty high profile switch where the sponsor had their name, planned name, which included a suffix, and FDA told them no. So they changed the suffix. So there would be an instance.

Another profile fairly recent example would be where the company for a variety of reasons did not find the formal prescription name appropriate, so they therefore went, had to go through a review of their new name.

Now I don't know how extensive that

was, but I do know they did have to go through that process, because the prescription name, to their way of thinking on what they wanted to achieve with the product, just was not going to be a good name.

So it does happen and those are two instances.

DR. BRASS: Is Dr. Phillips' premise correct that monograph names are completely off the table, or it's just simply a different process?

I mean obviously for new names, new names are always likely to be switched. But if there were safety concerns raised about a monograph product's proprietary name, is it - you are not saying there is no mechanism by which that could be redressed, I hope?

DR. LEONARD SEGAL: No, there is always a mechanism to address safety concerns. The thing about the way the current construct for the monograph is, is that these concerns, the safety concerns, would need to be

generated. They are not an upfront deliberation.

And to change that would require changes in the law.

On the NDA side, Dave has given you some examples. There are a lot of examples on the NDA side where there are new names for the NDA OTC products.

But there are a lot of examples where the prescription name gets switched with the product. And there are many legal implications to not allowing that, which - and so we have a lot of conversations with our attorneys.

MS. HOLQUIST: I think just one thing, if that is a concern of yours, the monograph names, we actually would like to hear about that, and if you could submit comments to the docket on that it would be very helpful.

DR. HORN: Donna Horn with ISMP.

I am not sure if Benadryl, which

was a prescription and is now over the counter, has been sold for a number of years. I don't know if that would be under NDA process, or if that would be a monograph. But the example that I would use is that if we are looking at your concept paper, and if you look at box one, where it says that you can't use a drive that is considered misleading if it includes a suggested name of an ingredient that is not included in the drug product.

Benadryl, non-drowsy, does not contain any Benadryl, and to me that would follow - that would have to be eliminated if they went into a concept paper.

DR. SPANGLER: Benadryl isn't an INN.

DR. HORN: I don't know that that means; I'm sorry.

DR. SPANGLER: It isn't an international non-proprietary name. It isn't a generic name, so I'm not getting the point.

MS. HOLQUIST: I think what she is

meaning is that Benadryl, in and of itself, causes drowsiness. So by using it the name implies, people who know diphenhydramine know the side effects.

DR. HORN: What I mean is, if you pick up a package that says, Benadryl, non-drowsy, you may think you are buying Benadryl that doesn't cause drowsiness.

DR. LEONARD SEGAL: Benadryl is a family name. It oversees the family name, as many of the family names that cover a variety of OTC products do, this one covers diphenhydramine, which is a monograph ingredient; the non-drowsy that you are referring to, I'm not certain which one that is. It might have phenylephrine or pseudoephedrine, which is a monograph ingredient. So you are talking about a family name in the monograph series just for clarification.

DR. HORN: Okay, so I guess it's sort of like a loophole. Because Benadryl

used to be a prescription product, and went OTC; the Benadryl itself. So once it goes OTC, the name can be used for anything?

DR. LEONARD SEGAL: Diphenhydramine I think is marketed by prescription as well. It is available in parenteral formulations and IM formulations. And so it's - I don't - I think it is marketed under that same family name in both settings, but I couldn't tell you for sure.

All I can tell you is that on the OTC side the family name covers a variety of different products with monograph ingredients in them. Which is the quirk of the law. And that's where it is right now.

DR. JOHNSON: Can I add something? This is Sue Johnson.

In giving the example of the Rx OTC switch in my slides, I may have confused folks. Let me be clear that not all the NDA products are switched products first of all.

And I think it's a misperception

that the family trade name is just associated with switches. In some instances the line extensions where different products are made using that family name happens when it goes into the OTC environment, but it also happens with things that have been in the OTC environment for a long time.

The family trade name issue is one of those scenarios that I spoke about earlier where if you look at the regulations, and you look at how the various cases are interpreted, you have to look very specifically at the increment that you are talking about.

With our attorneys here, I believe what they would say is, Benadryl non-drowsy is a different trade name than Benadryl. And the fact that they are interrelated is not necessarily an illegal actionable event, but the burden then is on the safety realm to assess whether or not that is problematic to the extent that we have an enforceable action that requires, just because it's not intuitive

perhaps doesn't mean that it's not a problem.

Now I'm saying that all again on the background that the FTA doesn't want to back away from the fact that there are potential safety problems associated with these things. But the allowing sponsors to use a brand that they have put significant money over decades and decades in is part of what our attorneys of necessity are having to look into.

DR. JOHNSON: I just add one more thing? With regard to those scenarios, the NDA process would look at those ahead of time; the monograph process would not. But were it actionable, we do have the resources and the regulatory purview, to take action on that.

DR. HORN: And I'm not a lawyer, so I can't interpret the regulations. But it does - when I read that the name cannot suggest an ingredient that is not in it, and the answer is, well, Benadryl is non-drowsy is a different trade name, it still has the name

in it that suggests an ingredient that is not in it.

So I think that is very confusing to consumers, and it could be a safety issue.

DR. JOHNSON: Then let me continue that thought just a little bit. Because this is something that we knew would come up at this meeting that is of interest, because it is a common point at which selection of various products happens mistakenly to whatever end in the clinical scenario.

What we don't quite understand, and what we would like some additional feedback on and to have additional data on is, why is it that people know that Pepsi has sugar in it, Diet Pepsi doesn't? Now I'm not comparing the risks associated with making those confusions, bu9t I am saying that in very many environments - I think somebody was talking about a cosmetic environment; you can name 40 Oil of Olay products.

Why are those - and maybe you would

like to take this question, Ruth - why is it that in some environments we understand this, and in some environments this relationship between products isn't clear?

DR. DAY: It's a very good question. I'll have to think about that a little more.

DR. BRASS: Don't you think it's just education, cultural and experience, how we learn about those things?

DR. SPANGLER: Precisely, and I would argue the same thing applies again on a brand family even when it's medicines. Again, I'm not equating the two. I understand the medicines. There is a different set of risks.

However, it's the same - it's our experience, it's how we're acculturated, it's about choosing something off the shelf.

DR. PHILLIPS: It's a prefix and suffix issue too. And how many people have grabbed Pepsi Free thinking it was the stuff with caffeine, or without sugar, when they intended to grasp Pepsi, when they didn't see

the suffix as opposed to diet-something. So I think it has a lot to do with a lot of those behavioral and human factor things that we haven't fully appreciated or incorporated.

DR. COHEN: I think it's also frequency of use. I mean Diet Pepsi, you drink it all the time compared to regular Pepsi; you are asking for it, you know that product. You are asking for it all the time.

But when you do in to get Dulcolax for a colonoscopy, what is that, every three years or something after you are 60 years old? Or a cold medication or something like that. It's just not that frequent. It's a whole new array of products at that time for you.

DR. SPANGLER: Just continuing a little bit more on this line of thinking. And again I recognize risk is different.

But I only buy one jar of cilantro a year, and one jar of chives a year, but they are both the McCormick brand. Yet when I am buying cilantro I am buying cilantro; I'm not

buying chives.

DR. BRASS: So before the chairman of Pepsi-Co lands to defend his product line (laughter), because is where, again, understanding the real clinical risk.

See, I have my own acquisition bias. I work in an inpatient setting in a county hospital with a busy ER. So when somebody comes in saying they took Benadryl when they really took Benadryl whatever, and they get treated for a diphenhydramine overdose when they were really overdosed with something else, that is something I see. That is an acquisition bias. That is something I could extrapolate very easy.

But I have no idea whether that truly represents a substantial public health problem or not, or simply reflects my frame of reference for thinking about clinical problems.

And as I said earlier, part of the core data we're missing is definitions of the

most clinically relevant problems. And for those of us who identified in 2002 analgesics as the major OTC, public health problem, and six years later are assured you are working on it, it becomes hard to understand where we should devote our efforts.

DR. JOHNSON: Sue Johnson. Can we get feedback then, in lieu of having specific data about that, the question that is number one is, should OTCs be included in this, and should we be focusing on OTC trade names as a large part of causing any safety problems that occur in association with this?

Or is this a different acquisition problem, or a different comprehension problem, than trade names?

DR. BRASS: Well, again, I think we have seen one example recently, and I don't want to over speak the example. But the concept that brand name extensions contributed to confusion in pediatric dosing, where the infant formulations versus the other

formulations, and infants were being given inappropriate formulations.

Again, we don't have a good root cause analysis of that, but I think it is suggestive enough that one should at least raise the question about brand names.

But I think that going forward in most cases the issues are addressed in the context of routine clinical development.

So my answer to you would be yes, they should be included. But as Dr. Day pointed out, that the flexibility to set the standard in a product drug-specific way, in the context in which it is to be used, including whether it's in the hospital, outside the hospital, what population, I think would allow a very rational approach to this in the OTC setting that is much more linear than it is in the Rx setting, because of the history and tradition of doing behavioral studies with the product labeling.

DR. HORN: Donna Horn from ISMP.

I'm just wondering, the concept paper is for a pilot, and it's voluntary. And I'm just wondering, would any of the OTC manufacturers, or the Rx to OTC, that's mostly what you would be dealing with, would they even want to go through this process because they have a name that you like. So I don't know that you would get too many people to actually go through it.

So then if the lawyer says, despite all the errors that have been reported on the prescription side, you can still use that name, what is the point?

DR. SPANGLER: David Spangler, CHPA. Again, if you - there could be any number of scenarios where you might. I'm not saying they will or they won't. It's going to depend, to Eric Brass' point and Ruth Day's point, it'll depend on the case and what they see the needs as being.

No one is going to want - you are not going to get the switch if it's an unsafe product. You have to have the label designed

through and as seen in the label comprehension test; the actual use trials; sometimes a self selection trial; that you are going to have data on how it's going to be used in a - what simulates a consumer environment.

And you are going to have to generate that anyway. So it might well be, especially if they kind of dovetail where their light may be headed on guidance for those types of studies, and what they are talking about here.

You know if they marry up nicely, you can get even more information, and that's a good thing. A company will embrace that if they are going to get better information out of it.

DR. PHILLIPS: Marjorie Phillips. Could you just educate those of us that really aren't involved in non-prescription drug approval, what is the label comprehension testing? What is actually required versus optional before the product submits for that

non-prescription approval?

DR. LEONARD SEGAL: Label Comprehension 101: the studies are designed with each specific product in mind. So what we focus on is comprehension of what the use of the product is; the directions for use of the product; the warnings; drug-drug interaction issues. Any of the warnings, the specific populations that can and can't use the product.

The labels are tested. Generally we like to see a few iterations of testing. It's very nice if we can see labels compared, so we can actually see if one particular label with certain messages is comprehended better with another label with another wording for those messages.

We look at the general population and the low literacy population to see if there are major discrepancies in the comprehension that each of those groups displays.

Sometimes there are targeted studies that look more at specific populations that we are particularly interested in; ones that we are particularly worried about. The studies generally have many hundreds of people in them. The low literacy population generally is somewhere between 150 and 200.

And these studies have morphed over time, and they have become more and more sophisticated. We've been learning as we go along.

Then what we do with those studies is, depending on the nature of the product, either the studies stand along - because we had one particular concern over a particular piece of the label - or in fact the study is designed to develop a good label that can then be used in other kinds of behavioral studies - for example, the self selection study, or the actual use study. Because one thing that we have come to understand is that comprehension does not predict use.

And if we have as I repeat a very specific target comprehension question, then we may just do a label comprehension study. But if we are really more interested in the ability of the consumer to be able to look at the label and be able to determine for his or her self, whether the product is appropriate for his or her use, in other words, in self selection, we hypothesize that that self selection decision will be best tested with a label that is understood well.

So sometimes that label comprehension study becomes the tool to develop the good label that can then be used in the more definitive study.

The same for the actual use study, which is a clinical study, where the other two are not clinical studies. And the - in the actual use study, the consumer actually gets the medication, either through some simulated drug store situation, and purchases it and brings it home; or gets it through some other

mechanism, and brings it home, and uses it and adverse event data is collected, and the studies are designed to, as best as we can, develop the situation that is most naturalistic in terms of what a particular over-the-counter situation would be.

So we try to eliminate in those actual use and self selection studies as much as we can, health care provider mediation. So that we actually see what a consumer will do. Obviously these studies are not perfect. You have to collect data, and that does interfere to some regard with the process of conducting the study. But we try to do it in the most naturalistic way we can.

Does that help you?

DR. PHILLIPS: So these studies are generally developed and conducted by the sponsor that is doing the submission; but sometimes with FDA guidance or feedback to address specific concerns that you have asked them to?

DR. LEONARD SEGAL: We take these studies very seriously in our division, and we actually encourage very strongly sponsors submission of these studies before they submit them.

The clinical studies they have to submit. The label comprehension study because it is not a clinical study we really don't have to advise them on, but we have developed a certain expertise. We've got social scientists in the division. And we look very carefully at all the medical issues, and the language of the questionnaires that are being used so that they don't introduce bias into the responses of the consumers, so that we hope that at the end of the study, with our - with our comments to the company, that we will develop very good data.

The other thing that we are very interested in, and Eric alluded to this earlier, is that we are very interested in why people make mistakes. So we have gotten very,

over the years, much more vigilant about asking sponsors to tell us, not just what answers people got right and what answers people got wrong, but why they got them right and why they got them wrong, so that we can then use that information to develop a better label, and potentially retest that label.

The more that we collect verbatim responses from consumers that participate in these studies, whether it's the label comprehension or the self selection study or the actual use study, the more we learn about how difficult it is to predict how people think, and that is very educational to us.

So that's the nature of the consumer study work that we do, and we are always thinking of other kinds of studies that can help us along the way, and sometimes we get interesting products that bring up interesting questions.

And just this week we decided that maybe for a particular one, we ought to be

requesting a purchase study so we understand why somebody is actually purchasing a particular product for a very specific reason which I won't go into here.

But we are always thinking of new opportunities to help to define what consumers do and why they do it.

DR. BULLMAN: Ray Bullman, NCPIE, since the written word is central or key with comprehension and understanding for the drug facts, for the OTC with the drug facts label, is there consideration given or encouragement to include consumers who are blind or visually impaired? Because when you think about it, it brings up a whole different set of issues, and it relates not only to label comprehension but to selection and use issues as well.

DR. LEONARD SEGAL: You bring up a very important area that we have not been very sophisticated in, but we are - one of the problems that we frequently face, and industry is very interested in expanding different ways

to help consumers self-select, one of the things that we are regulatory bound by at the current time is, the definition of labels and labeling, and the way the regulatory construct is set up, if something - and again, it would be helpful if we had an attorney to speak to that, but I'll do the best I can without that expertise, but the message is that we get from the attorneys is that if a particular mechanism for education of a consumer - and that's what a label does, a label educates, package insert educates, a shelf talker educates - if that cannot be considered part of the labeling, then it's not enforceable. So we get into the OTC arena of what becomes enforceable in terms of the approval process.

So that if a company were to provide some kind of information for someone with a particular kind of a disability, like blindness, somehow that education would need to be deemed - would need to be deemed enforceable as part of labeling or we couldn't

really even look at it. It would be nice and voluntary, but we would not be able to comment on it as a mechanism by which we could approve an OTC product.

DR. BRASS: But also, with that specific example, operationally the cop out we use, like when I was on the advisory committee, is that a blind person would either know to shop at a pharmacy where they could ask a pharmacist for assistance, or be with a person who was sighted and would assist in the selection. In either case, the label would be directed towards the person actually using the label to help inform the decision making to assist the disabled person.

MS. HOLQUIST: And I think that is why we are also concerned about including health care practitioners in this evaluation as well. We get a lot of push back that, no, it should really just be strictly the consumer, where I think we do have to build in health care practitioners as well.

And Mike, I want you to be able to talk to this.

DR. GAUNT: Yes, Mike Gaunt from ISMP. And I think the proprietary names for non-prescription drugs should go through a testing process. We see case reports, we get error reports, that confusion is occurring. We get that on the inpatient side, the prescription side, as well. So I'm not sure why we would think name mixups wouldn't occur on the out-patient side, of non-prescription drugs.

Now I agree with Carol that, to me non-prescription drugs are probably almost more complex in some ways than prescription drugs. Because you have all the interactions of many different practitioners like you do on the prescription side, but then you throw in the consumer side and the self-selection piece. You have interactions with pharmacists, with nurses, now with nurse-practitioners and clinics, who are prescribing

these things or suggesting these things, yet there are fewer safety checks built into the process than there are on the hospital side and the prescription side.

If a doctor prescribes something and it is misinterpreted by the pharmacy, there is still a chance that a nurse verifying the order on the floor, knowing the patient's clinical criteria, will be able to intercept that.

That is not going to happen on the patient's OTC non-prescription side.

So there are fewer safeguards, once that product is on the market, that someone else will be able to catch that mistake.

Yes, there are safe and effective OTC use, but they still are potentially dangerous if they are misused. There are growing numbers of people who are elderly, who have visual impairment, who are taking many many products, both prescription and non-prescription. So you are creating a situation

where not only do non-prescription drugs are confused with one another, but you are having homes where the patients are on 10 medications, prescription, and they might go to the pharmacy to get some other things that may contain some of the same products that they have for prescription products, or name confusion might occur - you know, Zantec, Zyrtec, whatever.

But I think it is critical for these to go through a testing process. You know we have had the errors of different products leading to serious harm. And I think you do need practitioners involved. I think you need that failure mode type of process, at least as part of it, that involves practitioners, because they are counseling people, they are interacting with patients on how to select these products, or what they are suggesting to them to take once they get to the pharmacy.

Now of course you also need the

consumer piece to that. Now is that outside the failure mode process? Or do you include them within that expert panel as another person, that might be the possibility.

From the hospital side, when they are doing root cause analysis, or even some failure mode things for new product, bringing products or changing clinical services in a hospital, they include nonclinicians in that process, because it impacts more than just the clinicians.

So adding those consumers to that might be beneficial, would probably be beneficial in those failure modes, because you are also dealing with other storage issues. Pharmacy, they are all on the shelf grouped together. You go to a grocery store, they have fewer, they might be separated. You go to a gas - you go to a 7-Eleven, there are non-prescription products there. In the home you have a whole other set of storage issues which complicates the issue.

So I think you need both pieces, clinicians and patients, along with medication safety experts, to be able to coalesce all that and be able to identify where the failure points are.

And it's going to incorporate more than name in the end, but the name plays a part.

DR. BRASS: I agree with everything you've said, but I just want to reemphasize the greater quality and quantity of data that this kind of process will interdigitate with for an NDA approval.

I mean for the specific example that you cited, for example, a natural use study will determine how many people who self selected and actually used the proposed name product were simultaneously taking other drugs, OTC or Rx, that contain the same ingredient.

So there would be the real world data, so I think the challenge would be to

find where there is value added to the differential approaches when you have such relatively robust estimates from the clinical trial data that define what that risk would be in a representative consumer setting, the kind of data we simply never get for our Rx drugs in how consumers obtain drugs from multiple sources, and may encounter the same kind of problem.

So I agree with the added level of complexity, and the benefit of additional ways of looking at it. But again, it's against this background of a much more robust dataset that we are used to seeing for a lot of these kinds of decisions at the time of approval.

DR. JOHNSON: This is Sue Johnson. Somebody earlier ask the question in the morning session, is one failure in these scenarios enough to block the use of the product name.

I guess I have a similar question in the complex scenario that you have been

talking about. If a trade name were to fail in the health care provider scenario, it would not be allowable in the OTC realm. If it fails in the consumer realm, it would not be allowed to be used in the consumer realm.

Is that what essentially what we are hearing you propose?

DR. GAUNT: This is Mike from ISMP again. I think it's a combination of things. I mean I think you are paying the price. I think you could have - we talked about this this morning - preventable errors. I mean I think you could make that suggestion. It could be a combination of both. I mean I think if it happens with the health care practitioners, they are also consumers. So they have more knowledge of the products conceivably, but it's still the same, you are still talking about consumers of that product as well.

So I think you could potentially say, yes, you could have one failure that

would cause you not to have a name go forward.

DR. FEDERICO: Frank Federico from IHI. A couple of things as I have been observing this. We asked the participants three or four times to identify themselves before they spoke, and half of us didn't do it. So we expect patients to go and read labels and understand what to do, and they are not going to do it for a variety of reasons.

And I agree with what Rick is saying - Eric is saying, we really need to understand more what some of the causes are and some of the problems.

But I also think about my own experience as a pharmacist at the front line, my experience with my family, looking at some of these drug labels, what Mike put up on the screen today, there are some basic things that we ought to be considering, like simplicity, simplifying some of the label is a key way to make things safer; it's just the first step. It doesn't mean that it's the only step.

There are so many other things - advertising pushes people to buy products that they don't really even need. That is a different problem; that's not what we are addressing.

So I would strongly recommend that there be an opportunity to understand a little bit more what is a good label; what might help with patients not getting confused when they are choosing products. There is a bigger push for patients to choose their own medication, HMO plans, whatever plan you may have out there, if the product has gone over the counter, the doctor will say, go buy it over the counter, because your plan won't cover it any more.

So that is going to happen more and more. So if again we want to engage the consumer, we need to understand what helps the consumer do the right thing, and what is not working.

On the flip side of it, having worked with one of the clinics that supported

the professors from a very well known university in Massachusetts, we found that the literacy issue isn't just amongst people who are illiterate - the help literacy issue I should say - it's amongst also people who have very high literacy level, because health literacy is very different. It's the ability to take that information and use it, and to interpret what is on the packages, and understand, if I pick up this product is this the right product or not.

So it is a complicated process, and I agree, we need to learn more about it. But also, let's not forget that there are very simple things that we ought to be considering to make it better.

When I saw that Maalox bottle today, I say, would I know the difference between the different Maaloxes? Could that have been something done earlier on in the process to say, wait a second, let's not do it that way; let's do it in a way that somehow it

is easier to read.

So I also asked about the drug facts. Is it helping? Does anybody know whether or not that really works or it doesn't?

DR. LEONARD SEGAL: We don't have the data to tell you if it's made a difference. And the rule actually was put into play just about the time that I came to FDA, which was in `98, I think a rule was in the beginning was `99, wasn't it.

And there were some - I know that in the development of the rule historically there was pilot testing, and they did some consumer group reads and reviews of these new labels to get an idea as to where things would go.

This is something we have talked about doing internally to do a repeat view. But the problem is that the base data I don't think really was there in a substantial way to show the - in a rigorous scientific way the

problems with the old way.

It's just that people knew that people couldn't read the label, and they were looking for a simplification, and more categorization and standardization across all OTC products, so the people would develop a sense of, if I look here, I will always find the purpose, and if I look here I will always find the warnings. And these are the standard headings that I can get accustomed to.

But you bring up a very good point, and I think that is it important for us to have a more comprehensive look at drug facts, and see if there is another iteration of drug facts that we can be using to improve the comprehension and use of OTC products.

But that is not a trade name question, and that is a topic for a different day.

DR. DAY: Just a brief comment that we are doing those kinds of studies and find big differences. And one of the concepts that

we've found is that people need to know some things before they take a drug, and then while they are taking it.

And we've reorganized the drug facts label for before taking, and there is information there where you would have contraindications and so on; and then while using, and that does seem to aid them finding what they need to know when they need to know it. Again it's not the drug main issue. But just wanted to mention.

DR. PHILLIPS: I guess that's the only thing that I could - I'm Marjorie Phillips - the only thing I could take away from today and the discussion this afternoon is that particularly within non-prescription products it's hard to isolate the drug name issue, and perhaps we just need to recognize that the drug name safety issue needs to be considered, addressed and looked at in an organized and systematic way in conjunction with the other activities already being done

as part of the assessment process.

So I think it makes a lot of sense, as Dr. Day was saying, to include some of those recognition, different things in addition to the other work we are doing with consumers, but also to involve health professionals. And I think it also makes sense, as Mike was saying, to get a panel fo experts that would include consumers but also health professionals to do the failure modes analysis looking at what are the possible ways that errors can occur with this product; how likely are they to get through without being caught, and causing harm? And then are there some mitigating factors or some things that can be done with product redesign, with marketing, with labeling, with other things to include the drug label and the drug facts that would mitigate or prevent those errors from occurring.

So I think it is extremely worthwhile to happen, and it seems like a lot

of the same activities would be happening but incorporated in a slightly different framework.

MS. HOLQUIST: Any other proposed alternative methods to what has been discussed? I forgot to say my name, Carol Holquist.

(Laughter.)

Okay, since we didn't take a break, I think we'll break now. And I thank you all for your great discussion.

We are going to return at 3:20. Thank you.

(Whereupon, at 3:05 p.m. the proceeding in the above-entitled matter went off the record to return on the record at 3:28 p.m.)

MS. PAULS: Okay, we are going to go ahead and get started with our last section of the meeting for the day, and that is the open public meeting time.

OPEN PUBLIC HEARING ON PANEL 1 AND PANEL 2

MS. PAULS: At present we have four people registered to speak. The first one of our speakers is Jerry Phillips, the president and CEO of the Drug Safety Institute.

Jerry, if you come to the mike over there and address the panel please.

MR. PHILLIPS: Good afternoon.

My name is Jerry Phillips. I was the former associate director of the Office of Drug Safety, and now I'm the president and CEO of the Drug Safety Institute, which is a subsidiary of Brand Institute. Brand Institute has been in business for about 16 years, and the Drug Safety Institute was created in 2004, and is the leading consultancy in the arena of proprietary name safety testing for the pharmaceutical and the device industry.

We've been preparing FDA data submission reports for our clients for many years, and have continually evaluated and revised our name safety research methodology.

DSI appreciates the opportunity to offer comments on this important subject, and shares the agency's goal of reducing medication errors associated with similar nomenclature, labels and packaging.

I will focus my comments specifically on three improvements made to DSI`s methodology since the 2003 FDA public meeting. And also we'll comment on the name safety testing methodology proposed in the draft concept paper that was discussed this morning.

The most important change is the recent development and introduction of a DSI proprietary tool utilizing the principles of failure mode and effects analysis, which differs from that proposed in the concept paper by FDA.

DSI recognizes the importance of learning from past experiences and previous medication error reports. The DSI-FMEA tool utilizes a regression model to assign a

weighting to certain known risk for failure modes. These failure modes were identified by analyzing proprietary names in three different situations or scenarios.

The first scenario, we reviewed proprietary names on file with DSI that were previously rejected by the FDA.

The second was the evaluation of proprietary names recently approved by FDA.

And the third was the evaluation of USP-documented name pairs that have been involved with medication errors.

These risk for failure modes that were identified with these scenarios include sound alike or look alike similarities; product profile overlaps; prescription misinterpretations; severity of outcome; probability of detection; promotional issues; linguistic concerns; and USAN or INN stem issues.

A numerical value was then assigned to each possible failure mode to calculate an

overall risk score for each group of names. Thus we have determined an overall FMEA score or threshold for names that have been rejected by FDA. Those names that have been approved by FDA, and those names that have been involved in actual medication errors.

WE are now using this FMEA tool to calculate an overall risk score for each proprietary name being evaluated in a name safety research project.

The overall risk score of each proposed name can then be compared to the medium risk scores of FDA-rejected names, or those names that are associated with documented medication errors.

The next important change in DSI's name safety methodology is our ability to use our computerized orthographic and phonetic analysis tool, which uses the ALIGN algorithm to determine the phonetic similarity of one proposed proprietary name in relationship to a marketed product name using nine different

languages.

These languages include English, Spanish, French, Italian, German, Polish, Portuguese, Dutch and Czech.

For U.S. name safety data submissions, DSI has been recommending and submitting phonetic name similarity results in both English and Spanish.

For Canadian submissions we submit our COPA results in both English and French. And for EU submissions we submit in all nine languages.

Recognizing the need to improve data to support a proprietary name from a promotional perspective, DSI implemented a third change to its methodology by developing two separate reports for submission to FDA to support the approval of a proprietary name, the first for safety purposes, and the second to support a promotional perspective. And that was a separate report.

Within the aided portion of our

surveys that we conduct with health care practitioners, DSI constructed five different questions aimed at determining whether a proprietary name was promotional or not.

The more elaborate proposal that will be discussed tomorrow we are very impressed with as far as the concept paper for promotional testing.

Now I'd like to address certain elements contained in the draft concept paper.

DSI encourages the agency to reconsider its initial position requesting confirmation that a proprietary name does not contain a USAN stem. Consideration should be given to USAN stem exceptions, such as the two letter stems such as a-c or i-o. This is mentioned earlier today by Bob Lee.

In addition the location of the stem within the proposed name should also be considered. For purposes of harmonization, the FDA should also consider the INN stem decision tree that the FMEA has incorporated

in their December 11, 2000 name safety review guidance document.

DSI believes that reviewing medication error reports can be useful in understanding the etiology of why certain proprietary names are confused. However, we question the reasoning behind requesting medication error reports based on the active ingredient of the product.

We understand how reviewing the medication error reports of errors that may be occurring with a base brand name, in which a modifier was being proposed. However, this would be based on the proprietary name of the product and not the active ingredient.

Furthermore, we believe this type of requirement will present a burden for applicants and companies, such as ANDA holders or 505(d)(2) applications, that do not have access to such data.

As an alternative we encourage the ABC to publish a list of known confusing name

pairs, and redacted case report narratives, so that the industry can continue to learn and adjust its risk assessment methodologies accordingly.

DSI has been performing name safety and promotional assessments utilizing a sample size of 160 to 250 in the U.S., which we would recommend as a standard. We usually recommend a confidence interval of 95 percent. At that level the margin of error on a sample size of 200 is plus or minus 6.89 percent.

However, there are times when drugs will have limited distribution or use, such as a drug that is injected into the retina, and administered only by an ophthalmologist. Therefore, a variance of the sample size, and a variance in the type of health care professionals, should be considered, based on the intended use and/or the distribution of the product.

In performing prescription simulation studies for a manufacturer, we

routinely test approximately 15 to 20 names at a time, due to a wide array of challenges that may be encountered in the studies and risk analysis.

The agency is recommending a minimum of 20 different scenarios representing different prescribing conditions, which we consider problematic. We believe that these studies should be created around the mode of communication, which means verbal, written and computer order entry; with the appropriate communication vehicle, which is the inpatient order, and outpatient prescription; the clinic order; and a computer order; and to utilize an appropriate sample size with the relevant users of the product.

We believe that this is also similar to the model that FDA is currently using.

We would recommend that the draft concept paper be revised to be similar to the methods currently used by FDA.

Having similar methodologies between the pilot program and the current FDA process will also help assess the final analysis of the effectiveness of the pilot at the end of the day.

The agency has also requested input on OTC name assessments, and because some OTCs are routinely prescribed and used in inpatient settings, and have also been seen in post-marketing reports, as part of outpatient written orders and prescriptions, we recommend that OTC names be reviewed like prescription drug products for that particular environment.

With that being said, we recognize that OTC product names should have more latitude with regard to the positive associations or connotations with those names, since consumers are the principal users of these products.

We look forward to working with the agency and the pharmaceutical industry in reducing medication errors due to sound alike

and look alike proprietary names.

Thank you very much.

MS. PAULS: Does anybody on the panel have a clarifying question for Mr. Phillips?

DR. PHILLIPS: Jerry, you said you would take issue with the 20 different scenarios, that we are working on under the concept paper. And it sounded like when you did I think four different options and variations of the above, were pretty much contemplating something similar.

Could you tell me exactly where you differ from the approach that is proposed in the concept paper?

MR. PHILLIPS: And maybe it's just confusing the way it's presented in the draft concept paper, and maybe what I suggested would fit the guidance document. But I think the - to construct the survey methodology in a way that works is, you would have to take under the proposal a prescription that if I'm

the physician and you are the ward clerk I would have to have this order; you would have to listen to it; and then you would have to write that order down into the chart, or give it to a nurse, who would then also have to participate in that to the pharmacy all the way down.

In the case that I am describing the methodology is that what we are trying to test, the overall objective in a simulation study from a prescription point of view is to make sure that one, you can read the prescription or hear the prescription or select the right product when you write it or when you hear it.

The actual scenario of who reads it and who writes it, it's important to consider the process, the process and the FMEA on how an error can occur, but the mechanics of writing a prescription, whether I write it as a physician or if I write it as a pharmacist, the handwriting is the tool in which it is

being communicated.

So as you interpret it, it really doesn't matter who writes that prescription in certain respects; that's what I'm trying to say. So the survey methodology is quite complicated by doing it in a 20-scenario versus the methodology that I just outlined where you make sure that no one sees the name any more than one time, so you maintain that. You maintain the marketed drug products, and the prescription sample; and you segment it, in patient orders, outpatient orders, computer orders, and verbal orders. And then you have those different respondents who represent different users in the health care chain, interpret, order those products.

So the concept I think is the same; it's just the survey methodology may be more complicated under the scenarios that were proposed under the draft concept paper.

DR. HARTMAN: Just one clarifying question. You said you attached an FMEA one,

I assume RPM score, to name rejections that the FDA has done; is that right?

MR. PHILLIPS: That's correct.

DR. HARTMAN: And that would also include a score attached to the likelihood of harm; is that right?

MR. PHILLIPS: The likelihood of harm is also considered in that.

DR. HARTMAN: If I understand what you said earlier, Carol, as far as the FDA is concerned, likelihood of harm should not be a factor?

MS. HOLQUIST: We consider it, but it's not the overall overriding theme. If we think that something is going to be confused, we are looking at this from a preventive mode. So just because today one error doesn't kill somebody, tomorrow it might. It just depends on the scenario that is set up.

And so I think what we are looking at it from is, are these preventable events? And if they are, let's fix them before

approval.

MS. PAULS: Any other questions from the panel?

Okay, thank you, Mr. Phillips.

MR. PHILLIPS: Thank you.

MS. PAULS: Our next registered speaker is John Breen, the research director from Interbrand Wood Healthcare.

MR. BREEN: Thank you all. Again, I'm John Breen. I have been working at Interbrand Wood Healthcare for about nine years now conducting main validation studies on pretty much a daily basis.

And again, we want to applaud the efforts of everyone in this room to collaborate on this issue that has challenged many of us for a number of years.

I prepared some remarks in advance of this meeting, some of which have been touched upon already today. However, after nearly 20 years of conducting brand name evaluations, Interbrand Wood has learned many

significant lessons.

As such I'd like to briefly discuss some key issues that we believe should be considered regarding the FDA's proposed plan to conduct a safety review of proposed proprietary names.

Just a little background. For the past 30 years Interbrand Wood Healthcare has developed specialized services to address the brand challenges faced by the health care industry.

We have consistently encouraged health care clients to use trademark creation as a core component of global brand and communication strategies.

In 1990 rxmark was created as a distinct division of Interbrand Wood to address the growing importance of brand-related research and safety research in health care.

Today we are widely recognized as a leader in the global assessment of proposed

trademarks that minimize the potential for harmful medication errors using our proprietary 10-10 trademark evaluation model and other methods.

To date, over 135 trademarks that are either FDA or EMEA approved have gone through 10-10, and we have literally conducted thousands of 10-10 studies to assess proposed pharmaceutical nomenclature.

So in terms of the concept paper and the pilot program, we strongly agree that there is no fail-safe method or gold standard to evaluate proprietary name candidates, and that it is necessary for sponsors to employ multiple methods to identify potentially unsafe names.

From a macro view, the proposed approach mirrors and builds upon best practices historically employed within the 10-10 model.

The 10-10 uses rigorous, multifaceted research methodologies to aid in

trademark selection, and to identify names that could increase the potential for medication errors, including quantitative prescription simulation studies, quantitative closed and open-ended surveying techniques, automated and human drug database searches, and evaluation and consultation by a multi-disciplinary team of dispensing experts.

However, there are also some considerations we feel we need to look at when we are reviewing the concept paper. Number one, the methods proposed in the concept paper have many practical and logistical implications for the industry. Name validation studies will become more complex and expensive to execute. For example, FDA has proposed a minimum requirement of 20 prescribing scenarios, as part of the prescription simulation exercises. After convening a group of our most serious statisticians within our analytics team, we confirm that the optimal sample size, defined

as one that balances a standard error rate of 5 percent with a reasonable market research budget, will be in the 400 - 500 respondent range, given the FDA's proposed requirements. With 20 prescription simulations, that would be approximately 20 respondents per individual simulation.

Our current best practice is to conduct the evaluation with fewer simulations, with approximately 150 to 200 U.S.-based health care professionals, again, depending on the specificity of the product, the specialization of it, et cetera.

Combined with other more stringent research requirements, such as conducting a promotional review separately from the safety review, pharmaceutical companies can expect to see large cost increases and increased resources put against conducting name assessment studies.

Additionally, because pharmaceutical companies face a number of

intellectual property challenges such as the maturation of the trademark from a legal perspective, and are often looking for global, not only U.S. trademarks, typically anywhere from 10 to 20 brand name candidates are evaluated in a single study, not just the one or two that are eventually submitted to FDA.

Given the requirement of 20 plus prescription simulations and separate promotional reviews, you can probably imagine how this will impact timing and costs. Again, from an execution standpoint, it will be very challenging.

Going forward, it's imperative to identify surveying techniques that do not detract from the guiding principle of designing a research model that will help us make an informed decision while also keeping some of these practical considerations in mind.

The other point I want to make is that in general, when conducting name safety

research, there is certainly a learning curve. For example there is a learning curve when searching similar joint names in online databases.

While the release of the POCA software provides another tool and standardized methodology to identify drug similarity issues, best practices for search strategies must be defined through other online drug database sources.

For example within the 10-10 model, Interbrand Wood conducts an automated search of the IMS database that employs an algorithm that implements over 900 search strategies to identify conflicts with similar prefixes, end-fixes and/or suffixes, visual or phonetic similarities; and similar letter placements or letter combinations.

In the spirit of the public meeting, we would be happy to participate or lead a best practices committee in this area.

As noted earlier Interbrand Wood

supports the recommendation that multidisciplinary teams of experts be included as part of the review process of FMEA analysis.

However, more guidance needs to be provided regarding criteria for selection and panelist qualifications. And also the criteria for judging names in this evaluation to remove some of the subjectivity.

For example, should we consider - should we as an industry consider a training and certification program in this area for experts?

Interbrand Wood has already gone to great lengths to develop an international panel of dispensing experts, that can also help define key criteria for selection.

As discussed today, and in the concept paper, medication use errors occur due to drug name similarity, unclear labels and/or poorly designed packaging.

However, the bigger issue that

still remains is that we are still not totally certain where the trademark itself falls within the medication error paradigm on a case-to-case basis.

As noted at the June 2003 public meeting, many participants offered views that prescription and order simulations should reflect actual situations wherever possible. We must ensure that the process we settle on takes into account the entire prescribing, dispensing and administration environment, and in some of the methods proposed, including the guidance for the FMEA analysis, I believe we are on track.

A specialized panel within our analytics group tasked with evaluating the proposed pilot program also recommends that we continue to look at new forward looking surveying techniques and technologies that will create, will help to create more of a real world environment for name safety studies.

So as stated earlier, we hope that standardized methods and endpoints eventually ratified by the FDA will lead to greater predictability and transparency in proprietary name reviews.

We also believe that the introduction of a concept paper and pilot program will heighten awareness and education on issues related to medication error within the industry.

Ultimately, though, the goal of the program must be to define consistent standards for acceptability, and to create a threshold for approvable names. Unfortunately, the processes outlined still requires that certain judgments be made which will impact our ability to predict a successful outcome. Perhaps it is impossible to take subjectivity totally out of the equation. However, as stated in the concept paper, it is critical to remain open to new approaches for evaluating trademarks, and for us to continue to identify

methods that can be replicated, and where key research endpoints can be clearly defined.

And what I wanted to do was just close with an example of a project we worked on, on behalf of a client, where a proprietary name was submitted and rejected by FDA.

It was rejected for visual similarity to two marketed product names. We conducted a very extensive evaluation employing multiple methods such as again looking at prescription simulations, conducting a script matching exercise. We looked at over 30 prescription scenarios. We had over 1,000 impressions. And at the end of the day saw a less than 1 percent error rate in those simulations.

Additionally, we conducted an audit of the products in question, actual prescriptions greater than 500, to understand whether or not the different prescribing characteristics would actually overlap, and we employed the expertise of dispensing experts

in the evaluation.

The challenge we face today is as a market researcher, when I saw a less than 1 percent error rate, the fact that the prescription audit yielded very favorable results, and our dispensing experts did not see a major issue, we felt it was a successful due diligence, and we had completed our due diligence. And as a result we will be able to demonstrate that there was not a significant risk for medication error.

The reality was, the arguments were not accepted. So the real challenge we face again is, what is that threshold? And how can we increase predictability and transparency into this process?

I thank everyone for your time, and happy to answer any questions.

MS. PAULS: Are there any questions from the panel?

DR. PHILLIPS: I'd just like a clarification. You were talking about the FDA

concept paper approach with the different scenarios requiring a much larger sample size. They actually estimated about 70 participants for the 20 scenarios, so what you are suggesting is that it would be necessary to do, or more beneficial to do fewer different scenarios, with larger samples each, than the approach that the FDA is recommending?

MR. BREEN: If we want to look at 20 scenarios for it, I think what we are recommending is that the total sample size would just need to be increased. Because what we want to do is make sure we look at enough individual respondents on a per scenario basis. So even with 400 we are still talking about a threshold of 20 per individual simulation. So that's why I think, when we looked at the analysis, we believed it was necessary to go to a higher number of respondents in an individual study if we are looking at 20 simulations.

MS. HOLQUIST: I think we tried to

clarify that this morning that you would be able to use more than one name in each scenario.

MR. BREEN: Oh, absolutely, and we have anticipated that in a single study, we can look at anywhere from 10 to 20 brand name candidates. But again what we would want to do is look at a reasonable number of interpretations for that individual scenario per name.

MS. PAULS: Sue.

DR. HARTMAN: One of the - usually I don't find myself on the side of the agency on matters like this. A 1 percent error rate for 1,000, that's 10. Doesn't it really depend on not - doesn't it really depend on the kinds of errors? I mean if they are one-off errors, the kinds of errors that are very unlikely to occur repeatedly, the kind of errors that I think Eric Glass talked about that I think could occur in the consumer health study that could also occur in

prescription setting.

Those are - then I can see that 10 might not mean anything. But sometimes a small number of errors, if the errors are of the kind that are representative of a class of errors that could repeatedly occur, then I can see that more weight should be given.

Which is just a long way of saying that number, 1 percent, doesn't do it for me. It's really - it's not a question of the number of errors; it's a question of the quality of the errors. And I would hope that the FDA takes that into consideration when they evaluate a concept paper, that it's not the number of errors that turn up, because you are going to churn out a lot of data in this name simulation study; it's not going to be the number of errors, it has to be the quality of the errors.

DR. PHILLIPS: But also, even a 1 percent when you are talking about hundreds of thousands of prescriptions over the course of

a year, and each consumer taking that medication one or more times a day, so depending again, that's an awful lot of opportunities for error with all of the use, so it could be extremely significant at 1 percent.

DR. HARTMAN: That might be true, that isn't my point. My point isn't to focus on a number. My point really is that the issue is the quality of the error. We had an earlier discussion about whether one mistake, one error, was enough to kill a name. And the point I'd like to make is that I suppose it depends I the abstract. It depends on whether it's a one-off event or it's not, and that's the point I'm really trying to convey.

MR. BREEN: Can I make one additional comment without giving away any proprietary information regarding study design with the 1 percent. We had set up a study, almost in a worst-case scenario, using a range of different handwriting scripts. Some of

them were pretty illegible, and also, we tried to limit the number of distinguishing factors, for example, in the script. So we had a mix of ordering instructions and non-ordering instructions.

The point of this again was to demonstrate what we believe would be the worst case scenario, without any other factors. And looking at multiple rounds of scripts for the three names in question.

So I agree, the 1 percent could be significant on a wider range scale, but it also did represent the absolute what we believe in the study design the worst case scenario, and the reality is, that is less likely to happen in the real world.

MS. PAULS: Sue.

DR. JOHNSON: We had a part of the discussion in the first panel was about shifting the burden to the industry to do this. I am just curious, again without giving away any proprietary information, are your

clients largely big pharma, or are your services accessible to a small company?

MR. BREEN: We service companies of all types, big pharma, biotech device companies. And we have a certain threshold for name safety studies, and if it's a very specialized product, typically it's in the 150 range, and that's where I was going with that, and it can range up to 200 and even higher given the specific scenario.

DR. BRASS: I continue to have some tension, and as I think about this, in terms of this error rate and what it means. I mean I agree completely with the comment. But the number to me is irrelevant. It's the context, it's the consequences, it's the scenarios under which it occurs, that allow any interpretation in terms of a risk for public health perspective.

Then I also hear since there is no offsetting benefit, any risk is intolerable.

Then I hear we are going to do 20

patients, or 20 scenarios, and worry about 1 percent risk rates.

I mean the various lines of discussion I have trouble resolving around a coherent forward looking plan, because even if the goals are worthy, there is no way the proposal can address them except as I say, generate noise, and unformed decision making under the guise of informed decision making.

MS. HOLQUIST: I think when we look at it, we don't just look at one particular study and base our decision making on that aspect of it. That's why in our proposal we did use a lot of different methodology. And it's the complete or the comprehensive look at all of this data and what does it exactly mean.

We often will run our own studies and might get a hit in our name testing studies, but we don't always say no to the name just because of that. I think we do look at, what did we see through our failure mode

effects? Do we see errors that will likely occur? And if we see that people have conducted studies and in fact the same things that we predicted in those analyses are actually occurring, in small simulated studies, that that represents a risk to us. ;

And that is sort of how we look at this data. We don't just look at each one and say, yes, okay, you had no confusion; your name is good to go. Or you had 20 hits on this, and you know, what does that mean?

MS. PAULS: Thank you, Mr. Breen.

MR. BREEN: Thank you very much.

MS. PAULS: We are going to move on with our third registered speaker. It's Mr. Maury Tepper, a partner with Womble Carlyle Sandridge & Rice.

Mr. Tepper.

MR. TEPPER: Thank you very much.

And I am very pleased to see that my firm's name was not the victim of name confusion, nor my name. Maury is often

mispronounced. I have a favorite list of those.

I do want to thank all the participants today. Many of you, it's amazing how quickly five years passed. You all still look good. I haven't gotten any taller. And here we are in many ways at the very same place that we left off after the June, 2003 meeting.

So I do want to underline and emphasize just a couple of points. Just as a matter of formality, I will mention to you, I am an attorney practicing in the trademark field. I work frequently on pharmaceutical naming projects. I also serve as a special government employee. I am on a public advisory committee for the Patent and Trademark Office. I serve on the Trademark Public Advisory Committee.

None of my remarks today relates to the work of the Patent and Trademark Office, but I did want to at least make you all aware

of that. I am not here in my capacity as a government employee, or on behalf of the PTL.

I just want to draw out a couple of comments. I see a lot of benefit in this pilot project. I think we have lots of interested groups in this room all working towards the same goal, and all continuing to reach different conclusions on occasion, which simply means this is a difficult task. There are no clear answers.

But any proposal that will increase predictability, reduce duplication of effort, and provide a measure of certainty, is certainly a welcome one. And in many ways I see great opportunity for that in the proposal.

I want to back up and just highlight a couple of things that bring us forward from the context of our 2003 meeting five years ago. Many of them are commented on in the draft position paper, but I think it's worth underscoring just a couple fo things.

There are some serious questions that do remain unanswered since 2003, and the paper does note some of the questions that were raised. You heard some comments today relating to the issue of causation. We know that names play a role; I think the correct view is, many many factors in the system play a role in every error.

We still don't know the degree to which the name contributes to that, is a cause, or is even a significant cause. And there are some statements even in teh8 draft position paper that continue to state, names are a significant cause of errors. I think we need to be very careful in our language about that, because that conclusion remains unproven, and I think we heard a lot of more informed information today. In fact I was very pleased with the notion that even within those errors that are attributed as name errors - and I apologize for tilting at windmills - that nine out of 10 of those are

attributable to confusion between established or non-proprietary names.

So we can all pat ourselves on the back at least a good bit to the extent to which trademarks are doing quite well, and these increased efforts and scrutiny are paying dividends.

We do have at its core, though, given all of these factors, a subjective field that we are dealing with. And the position paper uses the word, qualitative. I applaud FDA for recognizing that. What we need when we are dealing with subjectivity is human judgment. I would love for there to be a single test. I would love for there to be a predictive measure that would give us all the answer. If someone had found that, I think that person would be on a beach enjoying the royalties that the rest of us would be paying them for that answer, and we would all be very happy for it. We are striving for that, but unfortunately it is simply difficult to

identify any single measure.

And I endorse FDA's approach then of using multiple tests to try to get the relevant information to make an informed prediction. I think FDA's method has gone a long ways toward informing the way in which industry works to develop names, the way we all review names. You have heard from a number of representatives of companies today, and there are others in the room here. Many companies have developed systems that are based on the FDA system to try to help provide that certainty; to try to help those kinds of reviews. And I think we all benefit from that.

The fact that we still come to different conclusions says a lot about the degree to which this is a subjective field. We are not comfortable with, we would love to have a zero error rate. We need to be honest and say, that is not a possibility.

I'll come to the focus on FMEA, and

then I'd like to make two significant points.

FMEA is a useful tool. If you look at its origins, it was designed to detect weak points in the system; to consider the effects or the significance of those weak points. And that is all it does. The "e" needs to be stressed. And I again welcome your comments about understanding whether it is an important error, or an error likely to recur, or understanding what the contributing causes are in that error.

FMEA is well suited for that. FMEA is not well suited for establishing similarity likelihood of an overall error. It is really better applied to the entire system.

Dr. Cohen has written very eloquently and very correctly about the many factors that can contribute to an error. And typically an error is not caused by one thing. Lots of things need to go wrong. FMEA helps us find out those weak points, and trace through the overall system.

I recognize we don't have the luxury of regulating the entire system; it'd be great if we had all of the authoritative members assembled today. Nonetheless, we need to focus on the role which names play in the overall system, and be realistic about the extent to which we can ask the name or the trademark to make up for all of those other failings rather than addressing those other root causes as a part of the overall solution.

Once - one area I would encourage FDA to focus on in this process, I think that the pilot program and the system that has been developed by FDA is excellent at data gathering and data generation. We have lots of places to look now to gain information about potential problems, about potentially similar names, about measures of similarity.

What we need, and what I encourage you to consider incorporating into the pilot project, is some analytical framework for all of us to apply in order to evaluate that data.

I do not believe FMEA provides that framework and I believe that we are all making subjective determinations without a common language, and without articulating the basis for those determinations, which adds uncertainty and difficulty to the process.

I have proposed, goodness, more than five years ago, one test; I don't think it is the only one, but a starting place to look. Since I am an attorney, I look to the legal test. But we have a very well established body of law in the Lanham Act and in trademark law called the likelihood of confusion test. It has the benefit of having sets of factors that are weighed, and yes, in every subjective determination different factors may get different weights depending on the situation. But the test recognizes the reality of the marketplace, thinks about the way in which the mark will be encountered, and in our situation who may be prescribing or dispensing or receiving the medication; what

the dosage forms or strengths may be; and gives appropriate weight, which again requires human judgment to those factors, to arrive at an appropriate decision.

In any subjective situation, people do not always agree. But having a test gives us the benefit of sharing a common analytical framework; having a basis for discussing any disagreements; and for resolving them in a rational way; and adds predictability to the system.

I encourage FDA to look at this test or any other test to provide some framework for analyzing the data that, again, it has done such a fabulous job of encouraging us to all look at and generate and collect.

The next step to help us would be for us all to have a common system for analyzing that data.

I also encourage FDA to consider the parties who are reviewing that data. We heard a bit this morning about expert panels.

Expert panels are not mentioned in the pilot program, but we did hear about FDA's use of expert panels. We've heard a little bit about external.

As far as I can understand at the moment, our experts, and they are laudable, they are volunteers at FDA who are willing to give up their time and who have an interest in this, but the expertise so far seems to be they have been doing this for a good long time.

I wish that that worked with my golf game. It doesn't. FDA has a great track record with turning to advisory committees, having recommendations provided by those advisory committees, with having them analyze information.

That is an outstanding model that should be considered as part of this review process. If we could establish the appropriate criterion for expertise in predicting and understanding the medication

dispensing and prescribing system, naming, similarity analysis, expert panels could be assembled in the form of an advisory committee who could, in a public fashion, analyze and discuss and provide recommendations on all of the data that has been submitted.

The final point I'll make with regard to the paper as published, I think the pilot program is a laudable effort, and FDA acknowledges correctly that there does not exist a gold standard currently. We are using lots of different approaches.

The draft, or the proposed method for assessing the data from this pilot program appears to be a comparison to FDA's existing approach and conclusions which de facto makes FDA's existing standard look old standard.

I think we need to find a different framework for discussing and analyzing how useful the project was.

I understand that it will be extra work for FDA to duplicate the analysis during

this pilot program; I appreciate that effort. I think it would be ill advised, however, to judge the success or failure of the pilot program based on whether or not external reviews reached the same conclusion in what is at the core a subjective analysis.

So the words qualitative comes to mind again. I think that it will require some careful consideration and discussion of the outcomes. I think there will be great benefit to all of us to having a standard set of data to consider.

I think we could benefit further from having some system for analyzing and appropriately weighing that data so that we can have rational discussions about that.

And I'll be happy to take any questions. Thank you for your time.

MS. PAULS: Thank you.

Any questions for Mr. Tepper?

MR. TEPPER: Thank you very much.

MS. PAULS: Sure, go ahead.

DR. JOHNSON: I'm sorry to bring you back up.

MR. TEPPER: It's not that far, actually.

DR. JOHNSON: In regard to creating a framework for the analysis of the data, I think we have heard a lot of discussion today about various parameters that could go into that - what are the number of errors, what are the type of errors, do they suggest a systematic problem, or are they just very serious adverse events.

Are you thinking about different parameters in your analysis framework, or along the same lines?

MR. TEPPER: I think there is an element there. I mean when we talk about the number of errors, and you have heard several comments, that may or may not be relevant. What type of errors are they? What parts of the system are causing those errors? To what extent does the name play into that?

And if it is, again, preventable, and likely to recur, that is important and relevant to know, and should be given a lot of weight. If it truly is an unpredictable error, or something more likely caused by another part of the system, it should probably be considered, but be given less weight in terms of what is really going to address the root cause of that.

The test, the legal test at least, gives some factors that you can weigh that would actually look at and this mimics again the proposal for simulations, we tried to approximate real world conditions. We would look at who is the relevant class of consumers. Are they specialists? Are they nurse practitioners? Is this a hospital product? Is this going to be a product that is promoted and has a lot of consumer recognition?

That will inform our understanding of how close are people paying attention; what

orientation do they have; what panelists should be considering that.

It certainly plays a role, and I'd love to give you the exhaustive list of all those factors, but I think the most important thing is for us to have a common language. And some agreement about what are we looking at, so we can discuss the appropriate weights of that information.

DR. JOHNSON: I think it would be helpful, and just to remind everybody in the room, the docket is open to get additional comments on this in addition to the meeting, and whatever specifics you would like to add, I think that would be very useful.

DR. HARTMAN: I would like to ask Maury, with regard to your suggestion about advisory committees or expert committees, who would be - what qualifications are there for such an expert to be on a panel? Because it is not something you get a degree in, I assume. You don't get a degree in medication

error safety. And certainly not in name safety. So how would - do you have any thoughts about that?

Let me put it a different way: would an experienced pharmacist automatically qualify as an expert? Or are we talking about someone having some more experience than that?

MR. TEPPER: Thank you, Steve.

First of all, I've known for years that Steve asks the best and hardest questions, and I knew I was at risk in coming up here. And having a blank sheet of paper is a good thing.

The truth is there are no preset qualifications right now. However, I would submit at least as a starting point that we look at relevant practice. It needs to be not just relevant but current by the way. Those who are out there in the market understand the pressures and the conditions under which products are actually dispensed, so they can make an informed judgment about how risky

would this be, and when I have 10 seconds to reach for this on the shelf, how careful am I going to be? And who can understand and interpret that?

I think certainly it involves those who have a background in name analysis. We've mentioned the similarity is only one measure, but it is a measure that should be involved. Those who understand and analyze the similarity of names, we haven't spoken about handwriting science, and it's not in the paper. It's certainly something that needs to be further explored, and I certainly welcome as I trust the agency would any new information on understanding handwriting patterns, how we can better predict them, how we can look at them.

A panel discussing that, who can apply that knowledge and understand, is this an aberrant set of pen strokes? Or is this really a common pattern that we are going to see in the marketplace? How can we apply some

reasonable level of predictability to trying to guess what people scribble like, to the extent we are going to be asked to factor in and try to prevent or protect against handwriting errors.

Certainly people who have appropriate market experience in understanding the way in which drugs are promoted, perceived by, and remembered by their customers, be they practitioners, consumers, those in hospitals. And I will be glad to think further on this and submit perhaps some written comments and suggestions.

MS. PAULS: Thank you, Mr. Tepper. Oh, Diane.

DR. COUSINS: Sorry, just a follow up to that. Do you believe that having these people that are too expert could introduce bias as well? Don't you really want people who are reflective of practice which can be very variable?

MR. TEPPER: That's an excellent

observation. I agree with that. And it comes back to my notion of current expertise and practical experience. But having a large enough panel that consists of multiple viewpoints helps with that somewhat, but there is a real danger, particularly being too academic, or being - it's not unlike, since we are talking about a group of probably 12 people, you think about a jury. Is there someone who will dominate it simply by intimidating everyone else with their apparent knowledge. And that is a danger that should be considered.

MS. PAULS: Dr. Cohen, one last comment?

DR. COHEN: Yes, I was just going to say, I can't agree with that, actually I don't agree with that. I think you really do need expertise in this particular field, knowing that history of the kinds of things that have gone wrong is very important. Many times we are able to see something almost immediately

when a new product is launched, with a label, a design for example of how the concentration is expressed, that we are able to pick something up immediately. And I don't know that that would be the case if you just had a panel of practitioners looking at it, or looking at data that was collected. I think that is very important to have the expertise. And I think that is available in some of the consultant organizations for example, certainly amongst my colleagues at ISMP. We see these things all the time, day after day, and that does bring a certain level to these reviews that is very important I think.

MR. TEPPER: By the way as a closing comment, although I don't have a list of expertise, I know for sure that Mike will qualify.

(Laughter.)

DR. LEONARD SEGAL: Lana, can I just ask one question?

I'm wondering what the threshold to

taking the naming reviews to the committees would be? Would it be every name? What would be the triggers that you would be recommending would be the - or the doubts that you would recommend trigger the assembly of an expert committee?

MR. TEPPER: Well, that's a difficult question to answer, since again the paper as drafted does not really incorporate any form of expert review, and I suppose there is a lot of discussion about the degree to which FDA would want to trust an initial expert review that is conducted externally and submitted to FDA.

But certainly cases where FDA has a real disagreement with the conclusions in a submission, or perhaps in the qualifications of the experts or the analyzers who reviewed in a submission, having an advisory committee available to refer the issue to or seek guidance from would be a benefit.

MS. PAULS: Thank you.

Okay, we have one last registered speaker for today, and that is Susan Proulx, the president of Med-ERRS.

Susan.

DR. PROULX: Thank you. It's really hard being the last speaker in a day like this, because everybody said a lot of the things that I was going to say.

But what I'm planning on doing briefly is to - our task force at Med-ERRS who looked over this concept paper put together a little bit more specific thought, so we are not going to go through what our MedERRS process is in name safety testing. What we plan doing is giving a few more comments on what we agree with specifically in the paper; what we disagree with; and then raise a few questions that don't necessarily need to be answered at this time of day, but that will - you can put forth with the - at the end during the rest of the comments.

By the way, Med-ERRS is a wholly

owned subsidiary of the Institute for Safe Medication Practices, for those of you that aren't aware. We consider ourselves a safety company. We work specifically with the pharmaceutical industry on safety issues related to the things that the pharmaceutical industry has control over, such as labeling, packaging, and nomenclature.

We have been in existence 10 years. This is our 10 year anniversary, and I am a former clinical pharmacist. All my staff is professional pharmacists, and I've worked with Mike for over 13 C almost 13 years now.

And we also participated in the two 2003 meetings; we were able to do that.

So I'm going to go into Section 4, which is what we have been discussing today, and I will have some other comments tomorrow for Sections 3 and 5 related to the logistics.

And Steve, by the way, there is a medication safety certificate program at Temple University School of Pharmacy, so there

are pharmacists being trained specifically in medication safety, and my comment on that is, you wouldn't want someone, just an expert in name safety, since we realize that medication errors are multifactorial, so you would want to understand the full range of medication safety.

And also one of the things for those of you that participated in the naming summit that ISMP and FDA ran last fall, one of the recommendations has been, by Mike and that group, that a medication safety officer should be part of the pharmaceutical industry, so that is something that has been raised as well.

So those may be two people that would be good to be on some sort fo expert group or an advisory committee, just as an aside.

Now I will start my comment. We agree that multiple tests and best practices is the way to go; that we understand there is

no gold standard.

We also agree that safety and promotional aspects should be taken into consideration, and tomorrow one of my colleagues will talk briefly about the fact that the promotional aspect of a name can impact on the safety of a product as well.

We also agree that both the name as well as the product characteristics impact on the potential for confusion, based on the hundreds of medication errors that we have seen reported over the years, as well as the near misses.

We also agree that other factors related to the name, but not specifically related to look and sound alike confusion, can also lead to potential confusion and errors with the product, such as the medical terms, abbreviations, laboratory tests, shortened names of products, for example, vanco for vancomycin, and also what we call at Med-ERRS name pair similarity, where if you were

actually looking at two handwriting samples, the up strokes and the down strokes wouldn't necessarily be the same, but that there is some - there is enough similarities in the letters that you would - you could potentially confuse them.

For example, Cozaar and Zocor, and Trilpetal and Atripla, we have had situations where there has been medication confusion, or medication errors reported, or near misses, with names that are similar, but we wouldn't call them look and sound alike products.

We believe that there are certain product characteristics, depending on the product, should have a different weight. So when you are looking at product characteristics depending on the product, whether it be a unique characteristic of that product, for example, if it's a new dosage formulation, that may help create a dissimilarity with other products on the market, and that my be required to hold a

different weight when you are comparing it with the products for which it is being tested, and that should be taken into consideration as well.

We also have a disagreement with this concept paper related to the use of dosage or root in the name. Now with new molecular entities we believe that to be reasonable, and that that should not contain caps, tabs or oral, et cetera, as it is stated in I believe it's in box one.

However, what we are finding, because more and more lines - we talked about lines of products with over-the-counter products, but we are seeing more and more lines of products even within the prescription realm.

And what we are finding is, it's becoming more and more difficult to come up with a way to differentiate that new product in a line of other products. The way people are doing it is either adding suffixes, which

we know create many medication errors, or somehow coming up with a totally new name, which then will not relate it to the original product.

So what we believe is that it may be useful in certain situations on a case by case scenario, to look at a way to identify a new product in a line with its original product, yet somehow make it different enough so that it wouldn't have look and sound like similarity.

It's just something to consider.

The neighborhoods are getting very crowded with these names, so I think we have to start thinking a little differently sometimes.

I think this has been discussed, but I'll just reiterate, so I go on the record as saying, as far as the USAN stems, I know Bob talked about it and Jerry also. We agree that in general you should not include USAN stems as obviously, especially the ones that

are not appropriate to that particular product's class. However, we know that with two letter stems, that it's becoming more and more difficult not to somehow have it be there in the listed products.

So we believe that again that should be looked at on a case-by-case basis, and not necessarily and unequivocally have a name rejected right up front just because it may contain a two-letter stem. Again, case-by-case basis.

Med-ERRS agrees it's important to review the name from the scripted, printed and the verbal standpoint. We think it's important to look at letter types. We have a very long list that we have been compiling for many years. One of my staff, Marci Lee, who actually is a former FDA employee, has been compiling this look alike letter list for many years. Examples of things like uppercase A looking like an uppercase C and a lower case L. We know those, and when we are doing our

evaluation, we take those things into consideration when we are looking at the prescription.

We also agree that the use of a computer generated list for generating names is reasonable to consider, and again, agree with the FDA statement that it should not be used for hypothesis testing. But we believe that you should set up a standard for setting its threshold. We know that that is not the case right now, so I believe there should be an agreement up front as to what the threshold should be when we start using these on a regular basis, and when FDA makes this public at the end of 2009 - or is it - either end of this year, or end of next year.

We also believe that it is important to understand and review medication errors to understand their causation, so when we are looking at trademarks and certain products attached to those trademarks, you can see where the potential errors can occur.

When it relates to a product that is being submitted, though, I think that it is more important when you are looking at it, if it's the same trademark. Again it goes back to the fact where, are you looking at the name, or are you looking at every other factor that could be involved in that particular medication error?

The problem is that the type of data you are looking for, the medication error data outside the U.S., is even scarcer than it is here. The causation of that error would need to be determined, and just because errors have occurred, it doesn't mean it had to do with the trademark.

And also, is it relevant first of all. And then if it's not the same trademark, I'm not really sure what the point is related to this particular conversation that we are having today.

I understand it may be related to approvability of the product in the U.S., but

not necessarily approvability of the name. The lexicon of drugs outside the U.S. is not the same as here, so you can't really do a comparison.

One of the things that we had questions about was Appendix B on pages 29 and 30. How important are all these methods? I think this has been alluded to. Do we really need all of these methods to work? I think we are just dumping everything in there. Is more better? Do we really need all of those? How are you going to determine whether each part of the safety review is important? Are you going to determine one or the other? Will you be trying to determine which part has influence on the outcome? There may be a lot of redundancy in the results that you get in each of those. How is the FDA going to determine that in their evaluation?

Will you plan on throwing out any of those along the way if you are finding that there is no influence on the outcome? I think

that has to do with Marjorie called rapid cycle improvements, where you want - we don't want to wait until the end of the two years to get any feedback if we are going to be working on these pilots. So throughout the whole process we would like to get feedback.

And if we are finding that parts of these A through G recommendations are not working, perhaps we wouldn't need to do them, because there is a lot of time, burden, energy, resources and costs for everyone involved.

As far as the name simulation studies, I'm not sure how you are going to be evaluating them, and I think John just alluded to that. If you are not - or I guess Maury. If you are not doing them, I'm not sure how you are going to be able to evaluate them, and I don't know how you are going to be determining the process, their value, over what we are doing now.

Statistically reliable data was the

comment that was used, or the phrase that was used, and they are not going to be statistically significant, because you are not going to get the large numbers, the 26,000 that Kelly Taylor mentioned.

So again, John mentioned in his previous discussion, we have talked to some human factors engineers, and it was suggested that perhaps error-prone situations should be used, not just do it in the daily activity, but if you want to create error potential, that you should use an error-prone situation. And that's what human factors engineers do.

As far as the questions related to what do you think this says, test, we are not really sure how worthwhile that is, because people have really never seen the name before.

So they could be guessing. If I was pharmacist for the first time, I'm not sure, if I say I don't know what it says, or if I say it says nothing that relates to any other product on the market, I'm really not

sure how worthwhile that is.

The issue to us is that if it's confused with something already marketed, or if it's confused with a lab test, et cetera, that's where we believe the value to be in these studies.

Also alluded to by John, and again, I'm not a human factors engineer, and I'm not a statistician, and also Jerry as well said that, you have got all these different scenarios, and you do them once or twice, and I am not sure what the value is, because again, human factors engineers show that there are certain tasks that different people do, and ti may not be that important that you get every single type of person to do that task.

For example, picking up a prescription and going to the shelf and getting the bottle correctly. You don't necessarily need a pharmacy technician to do it, and a nurse to do it, and a pharmacist to do it, as long as you are doing the same

tasks, and you do it multiple ways, you could use the same types of people. It's not really important to use a variety necessarily.

MS. PAULS: Sue, in the interests of allowing each person the same amount of time, I'm going to ask you to wrap up please.

DR. PROULX: Okay. I will have one more section on the FMEA, and then I won't say too much about the non-prescription, because that was really Gary's talk this afternoon.

We believe FMEA is a good way to evaluate the data. We believe that it is important, however, to look at the risks of confusion as well as the risk of harm, and I think just in the past few minutes we have talked about that. We believe the risk of harm is significant when determining this, since there is no such thing as zero errors.

Looking at the features of the trademark other than just look alike and sound alike is important, and we believe that companies should be allowed to offer risk

reduction strategies at the time of submission if there would be a way to mitigate the error, as opposed to just up front saying the name should not necessarily be rejected.

And the last thing I'll say is, as far as the team goes, the FMEA team, we believe that just using practitioners as recommended in section 4.8.6.c, should not be used, that you should use experts who are well versed in medication safety and error prevention, who understand how errors occur with labeling, packaging and nomenclature.

And I know it was alluded to this morning, I wasn't in the concept paper, but an expert panel I think is very valuable.

I'll stop there, and I'd be happy to take any questions.

Thank you.

MS. PAULS: Great. Any questions from the panel or clarifying comments for Sue?

Okay, thank you very much.

DR. PROULX: Everyone has had

enough. Thank you.

MS. PAULS: Carol, did you want to make any final comments?

MS. HOLQUIST: No, I'd just like to thank everyone for their participation today. I think we've had a good discussion. We have a lot to take back and consider when we are relooking at this concept paper. And we look forward to tomorrow's discussion.

So thank you all.

WRAP UP AND ADJOURN

DR. DAL PAN: That would make life a lot easier. There is also no clear way from an epidemiologic point of view, or a public health point of view, to actually go out in the real world and see what errors are really happening, why they are happening, quantify their frequency and their impact, that would really help us a lot.

But we don't have that, and we are not going to get it by December of this year, next year, or the year after.

So we have to do the best we can in the interim, and hearing new approaches, Ruth thank you for a lot of them today, and for all the others who brought them up to the table, it's important for us to hear.

So we look forward to more fo this discussion tomorrow.

MS. PAULS: Thank you. The meeting is officially adjourned for the day.

(Whereupon, at 4:34 p.m., the proceedings were adjourned.)