Potential Medication Error Risks with Investigational Drug Container Labels Public Meeting
Day 2 Meeting Transcript (May 19, 2021)

Welcome
Susan C. Winckler, RPh, Reagan-Udall Foundation for the FDA

Susan Winckler:

Hello and welcome to day two of our public meeting on potential medication error risks with investigational drug container labels. My name is Susan Winckler and I am Chief Executive Officer for the Reagan-Udall Foundation for the FDA. And I'm pleased to be moderating today's meeting. If you had the opportunity to join us yesterday, you know that we are deep in a discussion and I'm going to just cover a few logistics before we jump into today's programming. So note that we are recording this meeting and following the meeting, a transcript will be made available. The slides will not be shared. If we think through what we have on our agenda today, we are going to open with some remarks from the FDA. We're then going to hear some international regulatory perspective.

Susan Winckler:

So yesterday we were focused more internally on the United States and we'll expand our view this morning. We'll then hear from folks in the Institutional Review Board and then close out our official presentations with a discussion among FDA staff to provide the FDA regulatory perspective. The final component of our meeting is a public comment period, and to participate in the public comment period, we'll need you to use your Q and A function. What we request that you do is you put in that Q and A function your name, your professional affiliation, and then a phone number at which you can be reached at about 12:30 Eastern time. When we will go to the public comment period to provide public comment. You will be called from the meeting. And then that will be your opportunity to present up to two minutes of public comment.

Susan Winckler:

So I'll just note if you sign up early, remember to be available when we get to that part of the meeting and we will trek through all of those who choose to participate in the public comment section. If you have a Q and A prior to the public comment section, feel free to submit a question in that same area. We do have quite a few people attending today's session, and we will attempt to address the questions that you submit there. But because of the size of the meeting, we simply may not get to all of those questions. Regardless, I hope you'll find that the presentations and discussions illuminating With that I'm going to open and turn to our key FDA colleague for this two-day meeting. Dr. Jo Wyeth is at the Office of Surveillance and Epidemiology within The Center for Drug Evaluation and Research at FDA. And Jo, I'm going to turn the microphone over to you.

FDA Remarks

Jo Wyeth, Center for Drug Evaluation and Research, FDA

Jo Wyeth:

Sounds good. Thank you Susan, and welcome to each of you. The purpose of this meeting is for FDA to learn more about the risks of medication errors associated with the use of investigational drugs. In the next five minutes, I will summarize messages that we heard yesterday from the panelists and then provide additional details for today's agenda, so everyone understands what FDA would like to discuss today to round out the meeting. We are aware, as it was noted yesterday, that medication errors can result in patient harm. We are also aware that in the course of an investigational study, medication errors can threaten the integrity of a trial. Yesterday, there were three panels that included representation from clinical trial sites, contract research organizations, and sponsors.

Jo Wyeth:

We saw specific examples of how container labels that have limited or confusing information, and in some cases no labels at all, can contribute to medication errors. It was realized that some sites, but not

all, may have proactive risk assessment processes or work arounds to mitigate those risks. We also heard that continued development of novel products, global expansion of trials sites, costs, diversity initiatives, and speed will further the complexity of the clinical trial environment of the future. Yesterday's panelists discussed several ways to potentially mitigate medication error risks, including require minimum content, use of symbology or specific formats on container lists, leverage lessons learned post-market for approved products, share knowledge throughout the entire investigational drug use process, which would include reporting and sharing information, making sure that IRB sponsors and other trials sites are aware and sharing that information, harmonizing, creating communities of interest for best practices, standards, engaging patients. We agree. They are the hearts of clinical trials and drug use and their voices should be heard.

Jo Wyeth:

And the importance of facilitating innovation and applying advances in technology. Today then, we will return to the discussion to hear from our first panel, regulators from Health Canada and MHRA. We are aware globally of the regulators' have varying requirements related to labeling and safety reporting. So we want to hear their perspectives, especially in light of what we heard yesterday about the need for flexibility and facilitating innovation and harmonization. Our second panel will take us back to the clinical trial frontline with perspectives from IRB and an investigational drug pharmacist, who will provide more specifics about their roles and in mitigating potential medication errors. The last panel will consist of my FDA colleagues who will share their expertise in medication error prevention, medical policy, good clinical practice, and compliance related to investigational drugs I echo what Dr. Dal Pan, Director of the Office of Surveillance and Epidemiology said yesterday in his opening remarks, FDA is committed to ensuring the integrity of clinical investigations and protecting human subjects. As part of that commitment, the information gathered from this meeting will help us evaluate the risk of

medication errors and inform any actions to minimize those risks. I'd like to thank each of our presenters for participating today. I'd also like to personally recognize Susan Winckler, Lea Ann McNee, and Bizzy Fain from the Reagan Udall Foundation for FDA, for organizing and working to put this meeting together. Thank you.

Susan Winckler:

Jo, thank you so much for kicking us off this morning and for setting the stage for day two of our discussions. We are going to, as you noted, pivot to hear from the international, from regulators from other countries. Certainly that we know that regulatory agencies around the world are dealing with the issue of labeling investigational new drugs. And we're going to hear from two different regulators this morning. From Health Canada, and then from the Medicines and Health Products Regulatory Agency in the United Kingdom. So we're going to open, we will first hear presentations from each and then we'll have a brief discussion after that. So if I may, I'm going to turn the microphone over to Dr. Kasina, who is a Senior Regulatory Advisor for Clinical Trials Compliance Program in Health Canada. First, thank you so much for joining us. And we are looking forward to learning from your experiences in this space. I'll turn the microphone over to you.

Panel 4: International Regulatory Perspectives

Alicja Kasina, Health Canada

Jason Wakelin-Smith, Medicines and Healthcare Products Regulatory Agency (UK)

Alicja Kasina:

Thank you very much for this introduction, and hello everyone. It is my pleasure to be here at this meeting and present Health Canada clinical trial compliance program and our label requirements. So thank you very much for inviting us to this important meeting. I am going to talk today about some examples of our common inspection findings and inquiries related to label deficiencies. I will also touch on the Canadian regulatory framework and provide you with some links to a useful Health Canada guidance documents. Our national program is a small program. We usually have less than 20 people, and we are spread all across the country. Our biggest group is located in Ontario with the national manager, the supervisor for inspectors and two advisors. The second biggest group is in Montreal with two inspectors and one advisor. And then we have staff located in all the bigger cities. One inspector, in BC one in Alberta, one in Manitoba. And one in Newfoundland and myself.

Alicja Kasina:

I am located in beautiful Halifax, Nova Scotia, and I work there as a program advisor. Moving promptly to our Canadian regulatory framework. In Canada, we have a clear framework with the main legislation being a Food and Drugs Act, which gives us authority to inspect under Section 23. We have Division 5 regulations, drugs for clinical trials involving human subjects, which came enforced in 2001 and the regulations include the requirements of good clinical practices as described in ICH E6 (R2). And they do not apply to natural health products or investigational testing of medical devices. There is another set of regulations for those. Division 5 applies to drugs, which of course covers also biologics. Let's move into some of the details of Part C of Division 5 Regulations for Clinical Trials. This slide is mostly for your information. I'm not going to get into too many details. I will just concentrate on sections relevant to the labeling. As you can see half of Division 5 applies to the application process.

Alicja Kasina:

And it's important to note here that Health Canada does not review labels during the application stage. The review directorates, they can ask for a label if they have any particular reason, but they do not do it routinely. Also, you may notice in Section 7 and 8, we have notifications and amendments, and if there are any changes related to a protocol that could be linked to medication errors, they would be covered by these sections and amendments cover all the changes to the protocol that may involve risk to participants and notifications are much more administrative. But we do review labels during our inspections. We have reviewed the labels as you can see under Section 11. And we also look at the sponsor obligations, good clinical practices, as well as records during our inspection process. So you can see the three Sections that we concentrate on during our GCP inspections involved on this slide.

Alicja Kasina:

Let's move to the main points in our legislation related to labeling. In Canada, the sponsors are ultimately responsible for the conduct of clinical trials. And Division 5 is written for the sponsors. Of course the sponsors can delegate study related responsibilities to other third parties. For example, the investigators or CROs, but they still keep the overall responsibility. Another point to make is that because we have two official languages, the labels are required to be bilingual, both English and French. Also, I need to bring your attention to our broad definition of a label, which gives the sponsor flexibility in fulfilling the labeling requirements. The broad definition of the label covers not only the primary label and the secondary label, but also any material that would be attached to a drug. For example, a brochure, a, pamphlet, information sheet or anything else that is affixed to the secondary container. Finally, what Health Canada wants to see on the primary container would be a lot number, the barcode because the traceability has to be assured. Of course it would be also good to see the expiry date or a retest date on the primary container.

Alicja Kasina:

But we understand that sometimes the vial is too small. So the lot number or anything that would assure identification is the name [inaudible 00:14:48] that has to go on the primary label. Then of course,] blinding has to be protected whenever required. Moving to the next slide on which I provided for you a full definition of the label from the Food and Drugs Act. As I mentioned, it can include any material, any legend, any word, any mark, which is attached to a drug. And of course there may be some additional requirements from the sponsors. Sponsors may add to Health Canada requirements. And as I said, they are responsible for the overall conduct of a trial, including labeling. Local or research boards may have some additional requirements as well, also institutions or some additional provincial requirements that would need to be considered. Let's look now at details of Health Canada requirements regarding the labeling.

Alicja Kasina:

So again, everything has to be in both official languages, English and French, starting with a statement indicating that the drug is an investigational drug to be used only by a qualified investigator. But we also accept a similar wording, for example, for clinical trial use only. Then the name, number or identifying mark of the drug has to be present on the label and the expiration date. And we also accept a retest date, manufacturing date. We also would accept use of IDRS or some other electronic means of controlling the expiry date. Of course, all the electronic systems use must be fully validated. We understand that drugs in clinical trials are often in narrowly development stage. So the expiry date is not available and this is why the other options like retest is also acceptable to us. The recommended storage conditions for the drug needs to be present as well.

Alicja Kasina:

The log number, as I mentioned before, this is what we expect to see on the primary label for the flexibility. The name and address of the sponsor, the protocol code or identification. And if the drugs

that are radiopharmaceuticals, there are some additional requirements on the other sets of regulations and the same would apply to narcotics and control drugs, including the symbols that are required by the other regulations outside of [inaudible]. Moving promptly to some examples of observations, which our inspector would cite under the labeling section of the regulation.

Alicja Kasina:

We don't see too many issues with the label. Maybe because we have clear requirements and clear regulations in place for over the last 20 years and sponsors are educated and aware of the requirements. But of course from time to time, there is something missing on the label. So the inspector would make an observation that the label of the investigational drug did not contain the required information providing what exactly was missing. As I said, we don't see many observations regarding the label, especially with potential medication errors issues. But we get a lot of inquiries regarding labeling. I would say that the inquiries on labeling are the most common inquiries coming to our offices. Luckily, almost every inquiry can be answered by the broad definition of the label and we still provide information to the sponsor. And we share this definition, but some sponsors are still not aware.

Alicja Kasina:

So they keep asking us about small vials. How can I put] all the information on the label in French and English? So then we would provide some guidance. We also get inquiries about the expiry date. As I explained, we accept retest manufacturing date as well as a IDRS system or any other electronic systems. And we also get inquiries in regards to labels of marketed drugs used as comparators. We accept marketed labeling in some situations. In Health Canada, probably other agencies are doing the same. If we receive a lot of questions on a specific issue, we usually issue a notice or some guidance to stakeholders to provide some education and also to decrease number of inquiries coming to our offices. So because we had a lot of questions on marketed drugs used as comparators and in general marketed

drugs used in clinical trials, there was a notice to stakeholders, regarding this topic posted on the internet.

Alicja Kasina:

And I provided here a link for your information. Moving to another guidance document we are very proud of because it's an interpretation of entire Division 5 and it covers the most frequently asked questions, including labeling questions, is Guide 100 which hopefully helps everybody who is involved in the conduct of clinical trials. And it's not only that it promotes a stakeholder compliance with Division 5, but also it promotes consistency and quality in the conduct of our compliance activities. So it's a widely used by our inspectors and the entire industry. In this guide, there is a large section on labeling on C.05.011. And it basically covers everything that I am talking about today. So I would suggest if you need some more details and you would like to look at this guide, that's the section that is very informative. We also have some other useful guidances that are linked to the labeling requirements, starting with the clinical trial application guide.

Alicja Kasina:

There is a section on labeling that as well. All these guidelines are included in Guide 100. So if you have the Guide 100, you also have everything gathered in one place. Lots of questions are coming from US about the import requirements. So it's covered under a guidance document on this topic and finally Annex 13. Which also has a section on labeling and packaging and it's a helpful and useful guidance. Moving again to some other guidance documents that are not really related to labeling, but it seems we are all needing during the COVID-19 pandemic. For your information, we included these links. Of course, Health Canada is aware of the impact of the pandemic on the conduct of clinical trials. So we issued a notice helping the sponsors and decide to manage this studies and this notice is being updated quite

often. It was updated recently, beginning of May again, and we also issued an interim order, respecting clinical trials for medical devices and drugs, which is relating to this notice.

Alicja Kasina:

Again, this is not strictly related to labeling because it doesn't introduce any changes in labeling requirement, but we thought it would be beneficial to include this information for this presentation, and this would cover everything that we wanted to share with you today. I thank you very much for your attention and I am ready to answer all the questions you may have. And if there is no time, don't hesitate to send questions to our email address, GCP_BPC@hc-sc.gc.ca, it's listed on this slide. So thanks again for having me and I look forward to your questions and our further discussion.

Susan Winckler:

Excellent Dr. Kasina, thank you so much. It's always helpful just to gather the experience of regulators in other countries. So we are going to go to a second presentation, and then we will bring both of you back for a conversation.

Susan Winckler:

So our second presentation is Dr. Jason Wakelin-Smith who is the Lead Inspector of Good Clinical Practices for the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. Dr. Wakelin-Smith, thank you for joining us today. I am going to hand the virtual microphone over to you .

Jason Wakelin-Smith:

Thanks very much. So yeah, I'm Jason Wakelin-Smith. I'm a lead senior GCP and JLP inspector. Previously, I worked within the National Health Service in the UK, predominantly within either manufacturing and also the clinical trial environment. So within that, I spent several years on the

receiving end of what various sponsors tried to do to me in terms of giving me labels which weren't particularly compliant or weren't particularly helpful to give out to the various patients that we were serving. So what I'm hoping to do today is to walk you through the regulatory setup within the UK, in terms of labeling. Obviously with the UK's exit from the EU this only really applies to the UK, but we haven't changed our legislation to do anything different to Europe at the moment. So you can very much take the references, which sit within this and you'll be able to see pretty much what happens within Europe.

Susan Winckler:

And Dr. Wakelin-Smith, as you do that, would you turn on your webcam so that we could see you?

Jason Wakelin-Smith:

Sure. It wasn't behaving earlier so you might just need to use my photo like Alicja. I don't think it's behaving. So-

Susan Winckler:

That’s alright. Go ahead. We will make that accommodation. No problem.

Jason Wakelin-Smith:

Thank you. Sorry. So in the UK we have the medicines for human use regulations. These very much govern how clinical trials work within the UK. They stem off 2001/20/EC of the European Clinical Trials Directive and the various other changes to that, which happened over time. So within those regulations, they then can be defined as you can see on the screen. And within that, it also then defines what a label is and what that looks like. So as we work through that Regulation 46 of Medicines For Human Use

Regulations, basically says and refers back to Article 15 of the European Directive, 2003/94. So you'll see that on the right hand side of the screen. And as it says there, an IMP is labeled to ensure the protection of the subject and the traceability of the medication to that subject, to enable identification. The product enter the trial and facilitate proper use of investigation of medicinal product. So when we start to follow those through, that's really what we're looking for. Can you do those things?

Jason Wakelin-Smith:

So carrying on Regulation 46 then says when this doesn't apply. So if you think about clinical trials, not everything is brand new. Not everything is the first time it's been given to a patient or a volunteer. We have plenty of clinical trials which use marketed product, and then it's marketed delivery or are being used very much in terms of their marketing authorization and so on and so forth. So the regulations in the UK permit the labeling to be adjusted to take that into account. So on this line that says, Paragraph 1, what we've just talked through, doesn't apply to those who meet Article 14 of the directive. And so when we move forward, Article 14 basically says, if it doesn't require any particular manufacturing or packaging, so this will be marketed product.

Jason Wakelin-Smith:

And then it's marketing authorization. Same for the bullet point below. And in some respects the same for the one underneath that. So they're all slightly different, but in reality, if you're using it for marketed product, marketing under its authorization, coming directly from a physician. This kind of thing, then you can adapt that labeling. All we require from you is that you tell us that that's what you're going to do. And then equally what that looks like.

Jason Wakelin-Smith:

So let me then come back to that. The regulations then go on to say, if it's dispensed to subjects in accordance with a prescription given by healthcare professionals. So we have some trials where the clinical trial protocol clearly states that there's nothing different with the marketing authorization or the product with the marketing authorization. And that it's very much, we're giving it as part of a trial, but there's nothing different than if they turned up in my practice. What we're really looking for is not particularly specific to that clinical trial, whatever that might be. You can also make a claim that you're going to label it in accordance with some other aspects of our regulations. So this is very much how you would label your product if it was going to be given out in response to a normal doctor's order or prescription. So on the right hand side of the slide, there's a tiny little picture. Not that you'd be able to read any of that, but that starts to define what needs to be on your normal products. If it's being dispensed, if you're ill.

PART 1 OF 5 ENDS [00:31:04]

Jason Wakelin-Smith:

Let me then carry on through our regulations, so obviously labeling is dotted throughout for our legislation. Documents that accompany that request. You need to tell us when you submit, you need to provide a description or a sample of the labeling of the IMP. So, this is very different to Health Canada. Our assessors want to see what you propose to do and what that looks like. They want to see a mock-up or they want to see, really, what it's going to look like and how things are designed. Certainly in the past, we've rejected things, because either the label doesn't make sense or the writing's too small, this kind of thing.

Jason Wakelin-Smith:

So, we then move into Annex 13. So this is listed within EudraLex, Volume 4. And this has very much the contents of what that label looks like. This works really well, it gives a nice defined list of what's required. We see plenty of companies who use the checklist driven approach for making sure that the content is all there. So EudraLex Volume 4 works across Europe, so it has some things like it needs to be in the official language. In the UK, that would be English. You can use pictograms and symbols. They need to be obvious and clear and that's one of the things the assessors would look for. In reality, we don't tend to see too many of those. The obvious ones are things like expiry date, but often we don't see symbols. We tend to see clear written text.

Jason Wakelin-Smith:

You can start to justify as well why some aspects are not included. So certainly today with things like IRT and other systems like that, web pages, this kind of thing, we start to see some people say, well, they don't want to put information on a label for whatever that might be. So, you can start to justify why you might not do that. So particularly, if there are things like patient cards and this kind of thing in place. We're always interested in why you don't want to put it on there. Often, it's due to size or what that might look like. But one thing to bear in mind is, it's not just labeling for the investigator or the healthcare professional. It's there to sort of take compliance by the patient, but also to assist a paramedic or an emergency room, should they receive that patient and their medication, so it's all very well taking things off, but you're not going to be able to access that kind of information if the patient doesn't have their card with them, or can't remember what the webpage is.

Jason Wakelin-Smith:

We also were interested in terms of some of the packaging specifics. So, it's all very well having a label, but if it's buried within a booklet containing thousands of different languages, how easy is it for the

patient to access the label text, which is within it? And certainly we've looked at some of that in the past. We've had problems with that in the past as well, where particularly big booklet labels, we've seen sites who were perhaps a bit keen, where they've ripped off the booklet, that they've taken away the pages which aren't relevant in terms of all the other languages. Unfortunately they've also torn away things like the expiry date, which was on the front page.

Jason Wakelin-Smith:

So, Annex 13 then goes on to describe a whole load of things which are required. So they're fairly obvious things like name and address of the sponsor, the form, the route of administration, batch numbers, expiry dates, the trial subject number, this kind of thing, so you can work out who it's for, what it's going to be used for, what trial it relates to, things like directions for use and for clinical trial, certainly, as Alicia referred to earlier on. And then we also see the expiry dates, so we're also happy to accept use by dates, expiry dates, retest, depending on what's applicable. And we insist on keep out of reach of children to be placed on it, unless it's not going to leave the hospital. There needs to be a little bit of care with this, because we've had problems in the past where things haven't included that, and then the trial has changed partway through where patients are then allowed to take some of that home.

Jason Wakelin-Smith:

Something which has come for me on this is, I'm always as an inspector, particularly interested in any text which is vague. So, my big bugbear is take as directed, and I'll translate that to do what you want. If you tell a patient, "Take as directed", they will do all manner of weird and wonderful things and they're very, very unlikely to go back to things like a patient card or some specific instructions. They will truly do what they want. The patient needs to have a bottle in their hand and it clearly needs to say if you want them to take it after breakfast, after food in the morning, then you need to tell them that, so otherwise, query take us directed.

Jason Wakelin-Smith:

In preparation for this presentation, I had a discussion with a couple of our clinical trial unit assessors. So as I said, it's required to submit the labels for approval as part of your clinical trial authorization. And then if you update those labels on the way through, you also need to tell us. So, some of the things that they said they see, and some of it is from the conversation, but equally there's a link within the slide, which points you to a particular page on our website, which includes these as well.

Jason Wakelin-Smith:

So we commonly see a lack of justification for deviating from the Annex 13. We often see an absence of justification for using standard dispensing labels in place of specific trial labeling, particularly in things like hospitals, where they may be using the exemption in our regulations, which commit them to do particular assembly activities and manufacturing activities without the need for a license. Sometimes we see problems with that. Size of texts, particularly for things like tiny, little vials and things, the regulations allow for amended labeling, but sometimes in the battle to try and get everything on, we get teeny tiny text, which just can't be read by anybody.

Jason Wakelin-Smith:

We quite often have problems with campaign labeling, so your sponsor may have a large supply of medications to be used across the suite of trials. And one of the things they often want the site to do is to fill in the protocol it's going to be used for. That's often not very helpful and we have problems with this campaign labeling, because often, it's not just that, that's being asked to be completed. We want to know what trial it's for, we want to know how it's going to be managed. We've seen problems with all the trials looking the same, which potentially then leads to dosing errors going forward.

Jason Wakelin-Smith:

Our assessors will sit there with issues about substantiality of changes, so within the clinical trial requirements, you have substantial amendments, you have non-substantial amendments, so we quite often get changes to labels, which people have decided are non-substantial, but actually they are quite to things like changes in dosing and this kind of thing, so they would be required to be submitted. And then finally, we get lots of queries rather than necessarily authorization about relabeling frozen products, things like stick and[inaudible 00:38:22]. Stick, when you take it out, there's a big risk of defrosting the product, this kind of thing. So we take quite a pragmatic view about that, depending on what the actual change is for those.

Jason Wakelin-Smith:

Annex 13 permits some post certification labeling. Commonly, this is for things like changes to the expiry date, but equally it allows additional labeling to be applied for safety reasons. So [inaudible] if it says something like take as directed and the investigator site aren't happy with that, then they will be allowed to put on the actual instructions. Can put on things like the patient's name. You can put on the protocol number and you can put on other information to make sure it gets to the right patient at the right time. We spend a reasonable amount of inspection time looking at what's been added, because sometimes we see things which have been added, which perhaps we're not truly happy with, that it should have been there at the beginning, or the sponsor asking the site to make changes, which aren't really appropriate.

Jason Wakelin-Smith:

So, a classic example is, if you take something like a change of sponsor along the way, it's appropriate for the site to potentially change the name of the sponsor on the bottle for the packs they've got, because the risk of shipping it all back somewhere and impacting on the supply of the ongoing patients

is quite high, but we certainly wouldn't expect the warehouse to continue to ship out poorly labeled, wrongly labeled IMP, and request the site to keep updating it. We'd expect that the stuff out at the central depot is dealt with appropriately.

Jason Wakelin-Smith:

The next slide is about some labeling issues on inspection. We quite often find that labels that have actually been used don't actually match the approved labeling. And sometimes this comes back to the substantiality of amendments, so you've told our assessors one thing and then partway through changed your mind to do something completely different. We see quite a lot of issues leading to dispensing errors, which had to do with similar kit or trial numbers, which lead to the wrong product being picked. This is particularly the case where the delivery of the bottles or the appearance of the bottles is very similar as well. People are quite often number blind, if the numbers are very similar and they just don't see the difference. And you can look at it again and again and you may not pick it up. So we quite often see that and certainly we often ask what's in place to make sure, particularly where you have this idea of standard delivery for your products, what you have in place to try and help the poor person picking the pot off the shelf to make sure that they pick the right kit?

Jason Wakelin-Smith:

We quite often see problems with failing to ensure blinding is effective. Over the years, we've become quite adept at picking up potential issues and we'll always talk to the site about them. If you think about how labeling actually happens, you would label potentially all of your active in one batch, and then you would clear down and then you bring in your placebo and label that. That has the potential to give rise to changes and things like the color or the label stock that's used, potentially the containers that are used so we've seen those at different times. Changes in the font, things like the printing ink, where it's much, much more faded for the placebo or drug A versus drug B whichever way it is. We've also seen

problems with things like expiry dates, where each drug has been labeled with its own expiry date rather than the nearest one. So, if you look at the batch number or the expiry date you can work out which is which.

Jason Wakelin-Smith:

So there are real things to look at, and it can be really helpful when you're planning and running your trials to actually have some mock-ups to look at. And not just one, to have a few, and then see if you can work through whether there's anything on there that can give you away. Sites and patients are very adept at picking that up and I've certainly had it in the past where we've spoken to some patients and they talk to each other. And so, it's not long, if you've got a trial clinic of patients along the same trial, they start showing each other their containers and bottles and things, and they're smart. They will pick up that there are differences. And with that starts to come the discussion of, "Oh, I think I have this, because of these side effects." And you can start to see some of that play through.

Jason Wakelin-Smith:

Heading towards the end of my presentation now, the other thing which gives us power in the UK is that there's specific offenses within our regulations, which also sit with labeling. Now, to the best of my knowledge, we've never used them, but they are useful if we ever need them. And certainly, we've reminded people in the past that if they fail to do their labeling appropriately, then potentially they're committing an offense. And then obviously that can lead to potentially up to two years in prison or an unlimited time, so that certainly helps concentrate the mind when you're talking to people about making sure that their labeling is effective and appropriate.

Jason Wakelin-Smith:

The last part I was asked to mention a little bit was about, how do we manage sort of management of labeling issues? Well, it really depends on what it is. If it's sort of a one-off, if it's a single patient, we wouldn't expect to be notified of that. That's pretty much back to the trial sponsor. It's back into the local risk management processes, depending on what that is. But if it's a systematic effect and potentially affects either the safety of trial patients or the integrity of the data associated with that trial, so let's say there's been a mix up with the labeling and maybe you now can't tell for some of them, which ones contain active and which ones contain placebo, then that's when you are very much into serious breach territory.

Jason Wakelin-Smith:

So, serious breach in the UK is defined within our legislation, but it's something which affects the safety of the patient or the integrity of the data in the trial. And you're required to tell us of that, it's listed in our legislation. It then comes through to the inspectors and then we have a look at it. We normally work with you to determine what the impact of that might be and how to manage that moving forward. We've seen trials, essentially halted or suspended for a period of time while things like labeling issues are dealt with. Equally, if it's a relatively small issue, what allowed it to happen in the first place? So we would expect some kind of quality review and to feed back into your systems to make sure it doesn't happen again. Thank you very much for allowing me to talk to you today.

Susan Winckler:

Thank you Dr. Wakelin-Smith so much. That was helpful as we get a view from another regulator, I'm now going to invite the two of you, so we're going to say, Jason and Alicja, if you could return to the stage, although that's going to be an audio stage only, and I'm going to go back here so we have a listing of your names. So, to remind us, we're talking with experts from Health Canada and from the United

Kingdom. And I want to make sure I want to capture or repeat to you some things that I heard, and then ask a couple of questions with our remaining time. I want to first note, I think I heard that in Canada, there is not a requirement for pre-review of the drug label for the container but in the UK there is. Did I listen clearly, or did I miss that?

Jason Wakelin-Smith:

You're correct, or certainly in the UK there's a requirement to submit your labels.

Alicja Kasina:

And there is no requirement in Canada.

Susan Winckler:

Very helpful. Thank you. And so, then I think that leads to different experiences. Jason, you had shared some things that you see and some changes that are recommended and then clearly that would just be different in the approach from Health Canada. So, thinking about those differences, and there were some other places where there's differences, which we just know happens, it's an inherent part of the different regulatory structures of different countries.

Susan Winckler:

But there's also quite a lot of work particularly in drug regulation, in device regulation around the world to harmonize on certain elements. And this is a theme that we heard yesterday, that there may be some places where it would be helpful to have regulatory harmonization, as well as some places to have harmonization outside of the regulatory requirements. I just want to ask the two of you, clearly not in an official position, but rather as you think about harmonization in drug regulation, is harmonization related to the labeling for investigational drug containers, does that seem like a space where there may

be an opportunity for global regulatory harmonization perhaps through an organization like ICH. Jason, do you want to pick that up first?

Jason Wakelin-Smith:

In essence, I think the fact that we've managed to get Europe over the years working to a standard set up using Annex 13 as the basis, somewhat demonstrates that it can be done. The additional labeling bits and pieces which occur, are generally fairly minor and they're often the unique bits for that particular country, the extra bells and whistles, if you want to call it that. But the core things which need to be on the label, the core essence of how labeling should done, if you follow Annex 13, it's a fairly simple approach. It can be checklist driven if that's what you want. It's readily translated into what things look like. And certainly, we don't have too many problems with it, really.

Susan Winckler:

Excellent, thanks Jason. Alicja, any thoughts from your perspective on whether this is space, where there might be interest in regulatory harmonization?

Alicja Kasina:

Health Canada is always interested in harmonization and I think Jason's already covered all the main points. I also wanted to mention Annex 13, which we all are using as well as ICH E6 (R2), so these are great documents to start talking about harmonization. But again, as Jason mentioned, there will be always some additional requirements. For example, in our case, our label has to be bilingual, because it's a part of our legislation.

Susan Winckler:

Right, right, so looking at where are those places where there's harmonization that's possible for that perhaps foundation or baseline, and then have the country specific requirements beyond that. So, I want to follow a thread that we heard yesterday about the idea of some non-regulatory harmonization, but harmonization on things like symbols. And so, perhaps more of a best practices and a sharing among regulated industry that there might be alignment on common symbols.

Susan Winckler:

As regulators, how do you think about that? I know sometimes it's difficult, because it's outside your sphere, but the talk yesterday was that perhaps there would be some benefit in having a forum for the clinical research enterprise and regulated industry to think through and come up with some best practices or harmonization for things like symbols? Any reactions to that idea. And we'll go in opposite order. Alicja, I'll turn to you first.

Alicja Kasina:

For sure, a specific forum related to label issues will be very helpful, if we have any plans to harmonize the label requirements. And we already, as I mentioned and Jason as well, have documents that will help us all to start this process. At the same time, we have to remember that in our case at least, and probably for other countries, harmonization could bring some changes to our legislative documents, so this will bring the changes to policy issues and it will be a bit time consuming, because it would change the regulations. It has to go through several stages and it takes time and a lot of approval.

Susan Winckler:

Part of that regulatory and statutory change process, which takes time. And so, some of these are perhaps more slow moving than others might expect. Jason, any thoughts on the idea of collaboration and harmonization outside of core regulatory requirements?

Jason Wakelin-Smith:

MHRA is a very pragmatic regulator, or at least we try to be as much as we can and we always welcome opportunities for harmonization or development of non-regulatory guidance that's easily quite often input into that kind of guidance where we can. It's often useful to try and understand what industry is trying to do and their reasons for that. I think when you come to symbols, I think symbols can be really helpful, but equally they need to be widely adopted and widely understood. There's nothing worse than having a picture on a bottle that you have no idea what it means. And you can even see that with lots of food labeling where you look at it and go, "Well, it's obviously somebody's symbol for something, but I've actually no idea what it means," whether there's no genetically modified things in it or whatever it might be.

Jason Wakelin-Smith:

So, it would need to be really obvious in order to replace the text. I think also, it's worth saying that the pharma industry and non-commercial research as well, tends to be pretty adverse to doing different things, particularly when you're having to put that in front of a regulator. So, it would need to be something which was tried and tested and approved, I guess, by enough regulators that it would start to come into common practice. But we're always open to that. If there's a forum to start doing that, then we'd probably be quite interested in the output of that. But with that, you'd probably look to start to see sort of consumer testing and sort of interpretation about what different cultures and countries and whatever understand by that particular logo or symbol or whatever that might be.

Susan Winckler:

Definitely, and in fact that emerged in some of our discussions as well, that its not just the regulatory agency, regulated industry, the clinical or contract research organization, and then the clinical trial sites,

but ultimately the patient. So all of those kind of engaging and contributing to the dialogues so we understand how, for example, standard symbols might be understood

Susan Winckler:

Yes, go ahead.

Jason Wakelin-Smith:

The other thing to bear in mind is the age of the participant. As the ages vary across the trials in what you're trying to treat, then obviously their understanding of labeling will also differ as well and their level of comfort with pictograms and symbols and things.

Susan Winckler:

Indeed, indeed. Well we are approaching the last two minutes of our time, I want to provide each of you the opportunity, if there's anything specific from your presentation that you want to emphasize or something that you want to share, that you didn't have an opportunity, I want to give you a moment to do that. So, Dr. Kasina, what would you want to highlight as perhaps one of the most important items that you shared today or is there another thought that you want to share before we close out?

Alicja Kasina:

I wanted to thank you for inviting Health Canada to this forum, I think it was very productive. Again, we are open to harmonization and issuing any kind of international guidance and creation of any panel working on labeling. It's interesting to hear that EMA and MHRA are looking at the label during the application process and we don't. I think this is something that I will discuss with our review directorates. It's always good to see how different approaches can be used and to echo Jason, I also feel

that the patient involvement is very important here, but we need to pay more attention to the age of the participants and different groups, depending on the clinical trial they are participating in.

Jason Wakelin-Smith:

I think I would like to just remind everybody when you're compiling your labels, that there's a patient on the end of it. And that it's all very well being regulatory compliant and having a myriad of identifiers and dates and coded symbols for all sorts of things. But ultimately, there is somebody at the end of it, that's got to work their way through it and work out how you intend them to take their medication.

Jason Wakelin-Smith:

The key message here is that the labeling is there to, one, facilitate their safety, so they're taking the right thing, but equally, to tell them what to take and when to take it. So whatever you put on it needs to be clear and obvious and helpful. If it's not helpful, it's pointless, a patient won't do what you want. And finally, I think it's worth saying that the MHRA is equally open to future development of standard approaches across the [inaudible]. That's a great thing to be involved with, so thanks very much for the opportunity.

Susan Winckler:

Wonderful when we could speak with our global regulatory colleagues as we're facing similar challenges and opportunities throughout our activity, so thank you both for joining us today. Your conversation has really helped our discussion.

Panel 5: Institutional Review Board (IRB) Perspectives

Nichelle Cobb, PhD, Smart IRB

Susan Winckler:

And with that, we will go to our next section where we're going to hear the perspectives from Institutional Review Boards. And IRBs or Institutional Review Boards came up a couple of times yesterday in speaking about where medication errors might be reported and we have a great panel this morning to help us think about this topic. And so, I'm first going to introduce the panel and then Dr. Gordon, I'm going to let you take over and talk through a couple of slides and then we'll come back for discussion.

Susan Winckler:

So joining us this morning, we have Dr. Bruce Gordon, who is Assistant Vice Chancellor for Regulatory Affairs and Executive Chair of the Institutional Review Board at the University of Nebraska Medical Center. Dr. Nichelle Cobb, Senior Advisor for Strategic Initiatives at the Association for the Accreditation for Human Research Protection Program and Senior Advisor at Smart IRB. And closing out, Dr. Johnston, Health Pharmacy Director at the University of Wisconsin Madison. So thanks to each of you for joining us, Dr. Gordon, I'm going to turn it over to you for a couple of slides here.

Bruce Gordon:

We're going to do this a little different from the last panel, we're going to all talk at the same time, maybe not literally the same time, but all share our thoughts. When Nichelle was asked to participate in this conference and spoke to me and to Susan, I have to admit, it wasn't entirely clear to us what we, as representatives of the IRB community, would necessarily have to say on this topic. And I think on closer

examination it's clearly an IRB issue, though perhaps it's not given the kind of attention that it ought to be.

Bruce Gordon:

So, the IRB obviously has regulatory responsibility to assure that the risks of subjects have been minimized. And so, to the extent that medication errors do occur or can occur as a consequence of absent or deficient labeling of investigational drug containers, it is relevant to the IRB. So with that, with those two statements of fact, we thought we could just go on and go through a series of questions that would look at how the IRB does and how the IRB ought to be involved in protecting subjects within this context.

Bruce Gordon:

So, the first question we have was, how often do these errors occurred actually reached the subject and are they in fact reported to the IRB? Are the errors in fact attributed to the labeling or to something else and how did the IRBs respond? So, Nichelle and Susan, please speak up as appropriate. So, Nichelle, go ahead, you start us off.

Nichelle Cobb:

I think this is something that Susan has a really interesting story to share with us about. So, Susan and I work together at the University of Wisconsin Madison and when I was first approached about this issue , as you said, Bruce, I thought, "Oh my gosh, there's a labeling issue? I had no idea." And as you said, Bruce, thinking it through, especially talking with you and Susan, there's definitely, and we'll get to that. There's definitely a place where there is an intersection with IRBs, because I think as Dr. Wakelin-Smith was saying, there is a person on the other end.

PART 2 OF 5 ENDS [01:02:04]

Nichelle Cobb:

I think as Dr. Wakelin-Smith was saying, there is a person on the other end of the recipient of these drugs and the job of IRBs is to protect these human participants. So there are, of course, time to time, IRBs will get unanticipated problem reports or adverse event reports saying somebody didn't get quite the right dose of medication or somebody got the wrong medication. And it occurred to me like, ", it's not until this discussion that maybe we aren't drilling down enough." So I'm not aware of this issue being prevalent. I could see how it could be, and we'll talk a little more later about why it might not be getting reported to the IRB, but Susan, you're the Investigational Drug Service and I would always rely on you to be the bulwark and I think you guys acted like that. So what are your thoughts on how often this occurs and what do you do when it happens?

Susan Johnston:

Yes. As a panel discussed yesterday and showed various examples of really not great labeling of investigational drugs and all who run services such as mine, we all have mitigation strategies to avoid potential mix ups. I think that medication errors do happen, and I think IRBs definitely will play a role in making sure we're protecting our research subjects. I think when we thought about what to present, our struggle is what type of information really should be presented to an IRB. Certainly when we are aware of a medication error and that is reported to an IRB, I think what we can do as investigational drug pharmacists is really encourage and help script the reporting, if we feel that the medication error is in response to substandard labeling.

Susan Johnston:

For example, a container mix up when you're dealing with very small type. I think that what we are charged would be and what we can do to ensure that the IRB is aware is to make sure that we are providing the details on not only the wrong product was chosen, but drilling down to why the wrong

product was chosen and what are the causal effects at that level. So I do think it's an IRB issue and I do think we have a role and we can play a strong role in making IRBs aware.

Nichelle Cobb:

How often did you see this at the University of Nebraska?

Bruce Gordon:

I don't think we have a good feel for how often it actually happens. This particular scenario where the error reaches the patient, or at least it occurs and is recognized by the pharmacy or the dispensing physician or the dispensing nurse, I think for that, we have a good handle on the fact that they occur. We don't know how often they're being reported to us, but these are the ones that are most likely to be reported to us, because I think investigators tend to think about adverse events and unanticipated problems as being something that happens next to the patient. So these are the ones that we are going to get reported in, and I'm confident that IRBs know how to handle these things because they are reporting and because they're concrete events that we can deal with. Different IRBs will deal with them in different manners.

Bruce Gordon:

In all cases, there's something on the order of a corrective action plan, perhaps that extends as far as root cause analysis when we consider why this patient almost got or got the wrong dose. So I'm actually confident that we're handling those well, whether we're attributing them appropriately to mislabeling or deficient labeling, or we're just attributing it to a pharmacy error or a dispensing error. I'm not quite so certain on that, and I really have no... Couldn't guess at how often they are actually being reported, but my guess would be that almost all of these, because they get close to the subject are reported. That leads us to the next question is then what about the ones that don't miss, which is certainly the ones

that are near misses? The one that a pharmacist looks at the [inaudible] of, "I have no idea what this is or what the dose is. I'm not going to draw this up. I'm going to query the investigator. I'm going to query the sponsor. I'm going to query somebody else on what I should do here."

Bruce Gordon:

And my assumption on that is that that is not routinely reported to the IRB because nothing happened. We don't think of that as an adverse event, but perhaps we ought to be involved in that process because it really is what falls into the next category, unanticipated problems involving risks of subject or others. Susan, or Nichelle, do you want to elaborate on that?

Susan Johnston:

I do think that deficient labeling alone constitutes an unanticipated problem. And I think there's an opportunity as well to engage the IRB in helping assess how to handle before we actually use a product. And an example I can cite is receiving a batch of a solution or an IV product that actually was devoid of any labeling. The vials were completely blank. And we did go round and round with the providers of the medication and finally really discussed it with the PI. And that would have been, I think, a good opportunity to leverage our IRB colleagues in the form of a consultation, whether it be formal, informal, and in addition to leveraging our IRB colleagues, I think that we have an obligation in a health system or hospital level to utilize the safety mechanisms that are in place. We're encouraged to report near misses. We're encouraged to report unsafe conditions. This would be one, that in my opinion, would warrant utilization of hospitals' reporting network to ensure that we are protecting all of our patients, some of whom happened to be human subjects.

Nichelle Cobb:

I appreciate what you're saying, Susan, and I do think this is a tough one because I'm thinking about... And I did some work on looking at the variations and interpretations of unanticipated problems, how they're defined. They're not defined in the regulations, although the FDA and OHRP have issued some guidance about what IRBs should consider to be unanticipated problems. So a lot of IRBs would not see these near misses as unanticipated problems and therefore, not reportable, but it is intrigued me, the idea... I mean, if this changes so that we now say, "Bad labeling that could pose risks to participants is something to be reported to the IRBs," it will open the door and redefine for many institutions what an unanticipated problem is. I'm not saying we shouldn't do that, but it will be a major shift. But if we do that just to catch these labeling errors, I agree with you, Susan, that when a situation occurred, like the one you described, involving the IRB, makes sense, especially if there is a reluctant sponsor, but it also suggests that where these things get caught can be before it even gets to a participant.

Nichelle Cobb:

And that's the hope, the preventing these errors. You also made me think about the fact that at many academic research centers, there's a really robust infrastructure there. There are investigational drug services with outstanding pharmacists like yourself and the staff there, and I know that's true of many institutions, but this is where it's of concern, where there are organizations that might not have that. And I'm arguing this mostly that I think that it needs to be a combination and I think that's what the FDA is probably looking at, that there are some things that if it comes to the attention of the IRB, certain actions should be taken to reinforce, "This is not okay. This does put people at risk and we should treat it as such." But we would hope to back up that so that these things aren't even happening. So they don't even need to get reported there because it's just not occurring. So, Bruce, what would you add or modify?

Bruce Gordon:

You guys both made a lot of good points there. I just want to make a comment on the definition of an unanticipated problem. Michelle, you're absolutely right. There is no regulatory definition. There is OHRP guidance, I think it's vintage 2007 that says it's going to be serious. It's going to be related or possibly related and would increase the risk rather than a direct harm would increase the risk of harm to a subject or to others, but then that's a pretty wide scope. To limit the scope, there is a codicil attached which suggests that these kinds of things usually require or lead to a change in protocol, a change in consent, a change in procedure that gives IRBs to a certain extent to have some leeway that can be a good or bad as to what they report.

Bruce Gordon:

If on one level you could report anything that's essentially a serious adverse event, on the other level, you could say, "Well, it was a serious adverse event, but it only happened once. So we're not going to change the protocol. Therefore, it's not a reportable unanticipated problem." So that's part of the definitional concern. The other thing in response to, I think what Susan said about leveraging the role of the IRB and the IRB acting in consultation is we have to remember that the scope both from a knowledge and from a regulatory point of view of the IRB is that we really can't fix the problem, partly because we don't have the authority to go into an investigational pharmacy, but also because, I can speak personally, I have no idea about what an investigational pharmacy does. It's all a black box to me, and I assume that you have policies and procedures and that you know what you're doing.

Bruce Gordon:

So the IRB can't necessarily say you investigator, or you investigational pharmacy have to do X, Y, or Z. Whether we can or can't, we shouldn't do that, I believe. But what we can do and what we should do is require that people who know how to repair it, repair it. So we can demand a corrective action plan

from the people who know how to do a corrective action plan in that particular setting, and that corrective action plan might be requiring appropriate labeling, or it might be something else that might be changing investigational pharmacy policies and procedures, or it might be a combination of things. Nichelle, Susan?

Nichelle Cobb:

I want to hear Susan's thoughts too, but I'm just thinking IRBs don't even drill down to the level necessarily, and some do, about who's preparing the medication and who's labeling it. Some certainly do and AAHRPP expects that organizations that are accredited have to have policies and procedures for controlling investigational drugs, as well as devices, which is another thing. So for institutions that are accredited, that there're some expectations there, which I think help with this. But I think otherwise, the IRBs are not reviewing like, "How good is that labeling on the investigational drug?" And as you said, Bruce, would we know? And even if it's not investigational drug, things happen, medication errors happen with prescription drugs and in some ways, it's partly what is the study team doing to educate people on how to take the drug and when to take it? Things come up otherwise.

Nichelle Cobb:

So it's a larger issue. So I find it really an intriguing space to be in where if the IRB is asked to look at these labeling errors and this doesn't stop at investigational drugs, and I'm not sure they have the expertise, but maybe the expectation is that any study, as you said, Bruce, you're expecting research teams to have certain expertise to conduct the study and conduct it appropriately. You're expecting an instance wherever the research is happening to have the right infrastructure to promote the protection of human subjects, and that would include pharmacy. So there's some presumptions made there that IRBs are operating at a certain little thing like, "Yep." We think the organization and study teams are

qualified to do it" - there's a lot built into there. I'm going to pause because I want to hear what Susan has to say.

Susan Johnston:

It is somewhat of a gray area to say the least. It is vitally important that from a research perspective, and we talk about accreditation. When you're dealing with pharmaceuticals, when you're dealing with medication, there are also other regulations that you do need to take into consideration obviously. You have state law, you have federal law, you have Joint Commission. It really is important that if you are in a role, whether you're an investigational drug pharmacist or a pharmacist handling any research medications, that you are engaged with at an institutional level to ensure that you are compliant from those perspectives as well. I go back to again, making sure that you leverage whatever RCAs, patient's safety data collection reporting. That you're leveraging that, so that any issues become a point of discussion at a system-wide level or at an institutional level to address some of these things that perhaps an IRB can't or shouldn't be correcting.

Nichelle Cobb:

You intrigued me too, because when you talked about getting the shipment and how badly labeled it was, you actually took action and said, "Not acceptable." And how often is that happening? And though there are some major research institutions that can do that pushback and also recognize the consequences because that's the latest study and you at least had a researcher who was on board and saying, "I can see your point. We don't want this." But you can imagine other situations where an institution doesn't feel like they have that, [inaudible 01:17:48] is not quite the right word, but that position status to do that and a researcher saying, "But we need to get going. This is really important research. I only have money for a short amount of time."

Nichelle Cobb:

I can just see some confluence of factors coming about to make this without some sort of regulation that lays out, say, "Here's the expectations of what needs to be there." That I can absolutely see that providing some hook for somebody to say, "Wait a second, this is not compliant." And aside from the argument that this could harm participants and give you lousy data too if people aren't taking it. So what do you all think about that? About how institutional status and researchers being able to push back?

Susan Johnston:

I agree. That's a risk. On that particular situation, it's based on judgments and given the authority to make the decisions that you feel are in the best interest of our patients. I would hope that that's the case, but I know that it's probably not the case. You don't necessarily have institutions that handle a lot of research products and maybe wouldn't question it. If a packing slip says, "This is what's in that vial," even though the vial is devoid of labeling, I would hope somebody would sound the alarm bells, but I also understand investigator pressure and time and grants and funding, and there are other pressures. So additional labeling requirements would help in those particular situations.

Bruce Gordon:

I think it's important here also to remember that the IRB is a piece of the Human Research Protection Program as is investigational pharmacy, and we have to be very careful to understand our interactions and understand where our areas of expertise are. And I mean, IRBs wouldn't get down to a level of asking the nurse dispensing an intravenous product what rate is he or she going to run the fluid at, or how are they going to flush the tubing? Likewise, perhaps we ought to be asking the investigational pharmacy, what is the packaging look like? What the labeling look like? We ought to be saying to the

investigational pharmacy, "As a piece of the Human Research Protection Program, we expect you to protect subjects in this manner by dispensing the right drug, the right dose, the right time."

Nichelle Cobb:

I think that is a really important point that human subject protection is multifactorial and it takes more than an IRB to protect human subjects. And I think that's an important awareness for institutions to have. The other part too, with clinical trials and Susan knows this very well too, is that there's that overlap between clinical care and research. So some of these systems that have worked together so that it's sometimes indistinguishable between the clinical care expectations. So IRBs usually don't get into what the clinical care, what's behind that, what's the processes and infrastructure? You're making some assumptions that they're abiding by certain standards. I think it's a similar analogy for research that you are expecting as an IRB that there's that expertise there. But I think your point Bruce too made me think that it needs to be very explicit. And the other part was a multi-site study. I can just imagine how complicated this get with a single IRB situation. You have one IRB overseeing a bunch of sites.

Nichelle Cobb:

And then is that IRB thinking about the management of the drug at all these different institutions, and is it appropriate? Does that need to be in protocol? Something more specific about labeling. So that's another area where you could say if that's missing from actually being written into the protocol we are using, we have these expectations for our sites and how this drug is managed, how it gets to participants, and how they're instructed to use it. So that in some ways would be great, because then at least the IRB could say, "Yes, the sponsor, whoever's written the protocol has thought about it, and there's some standards and expectations set for how this is going to be executed."

Bruce Gordon:

Let's see if there's any comments or any questions in the queue. I have no idea which of these boxes to look for questions.

Susan Winckler:

My job. Because we've got just a few minutes left, I want to do three things. I want to first confirm something I think I heard, so confirm an understanding. I want to share an observation and then ask a question. So first, to confirm an understanding, there's been a lot of conversation before this panel and then on this panel about unanticipated problem and whether a medication error due to a labeling issue that results in harm or subjects to others. Would an IRB generally consider that to be an unanticipated problem? Is that a head nod yes?

Bruce Gordon:

What an IRB would consider, that definitely would be an adverse event. If there's actually a harm occurred, the question I think that's more relevant to this group would be whether is a poorly labeled vial without any harm [inaudible 01:24:09] an unanticipated problem involving risk, risk being the possibility of harm occurring. And there, I think we agree that it should be, although not all IRBs will because of the definition.

Nichelle Cobb:

[inaudible 01:24:24], it sounds like if this is as ubiquitous problem, maybe it isn't an unanticipated problem, which is a sad thing to say.

Susan Winckler:

I think we saw and heard yesterday that there are distinctively some challenges to be addressed. And Susan, I heard your naked vial. We heard about naked boxes yesterday. It might be the FDA public

meeting with the naked observation more common than any other. Just happens to be a reality in describing the problem. So the observation I wanted to share, it seemed like a lot of the discussion here is that you were posing that certain IRBs could be a resource for the pharmacies who are dealing with this, particularly, the example where perhaps you need to talk through something or the gravitas in working with a researcher or a product sponsor that the IRB could be a resource. Is that a fair observation?

Susan Winckler:

Yep. Okay. Then my final one is a question. One of the ideas that's been emerging throughout this public meeting is some sort of a forum where all those involved in the clinical research enterprise could talk more about these challenges and identify opportunities for improvement. And it seems like the IRB experience would be a helpful contributor to that type of a forum. Am I thinking about the IRB role in the right way? That if there were to be a forum to look at these types of things, that the IRB experience could indeed be helpful?

Nichelle Cobb:

I think so. Partly, awareness raising for IRBs for one thing, and I think that was an important, but IRBs are very good at saying where they can be helpful and where they can't and I think it could start the conversation amongst the IRBs that I don't think these conversations are happening otherwise and given what I know about the landscape. So Bruce, what do you think?

Bruce Gordon:

I agree completely. I was just remembering back to your previous comment is that I think that IRBs don't necessarily have a competence to fix this problem. The FDA investigational pharmacists certainly do, but the IRBs don't. What the IRBs can bring to this is a certain amount of authority. Ultimately, we can say,

"You investigator have not protected human subjects. Therefore, this research will not be approved here until you work with the pharmacy to fix this problem." The IRB can't tell you how to fix the problem, but what we can say is, "You got to fix it. Otherwise, we won't approve it."

Susan Winckler:

Excellent. Doctors Cobb, Gordon, and Johnston, thank you so much for bringing us into your conversation about the IRBs' role here and then the opportunity for additional role. We so appreciate you joining us today and sharing your insights. Let's go to panel six. Panel six is where we are going to hear the perspective from colleagues at the Food and Drug Administration. So for this discussion, we are going to have two presentations and then we will invite three other folks to the stage and we will have a conversation and explore some different observations here. And I know the team has been listening to the meeting yesterday and today, and we want to turn to you to share FDA's concerns and observations in this space and how what we know about improved products might inform our decisions made for investigational drugs. So I'm going to turn first to Dr. Janine Stewart, who is a safety evaluator in the Division of Medication Error Prevention and Analysis within FDA Center for Drug Evaluation and Research. Dr. Stewart, I'm going to turn the microphone over to you.

Panel 6: FDA Regulatory Perspectives

Janine Stewart, Division of Medication Error Prevention and Analysis, Center for Drug Evaluation and Research, FDA

Lubna Merchant, Office of Medication Error Prevention and Risk Mitigation, Center for Drug Evaluation and Research, FDA

Janet Donnelly, Office of Clinical Policy and Programs, Office of Good Clinical Practice, FDA

Paul Gouge, Division of Clinical Trial Quality, Office of Medical Policy, Center for Drug Evaluation and

Research, FDA

Ryan Raffaelli, Office of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, FDA

Janine Stewart:

Hi, thank you. Good morning. Good morning, yeah. Hi, my name is Janine Stewart. I am a safety evaluator in the Division of Medication Error Prevention and Analysis here at the FDA. In the presentations shared yesterday and earlier today, we've heard from clinical trial sites, suppliers, regulatory agencies, and institutional review boards. So today my objective is to provide the FDA's perspective on medication errors involving investigational drugs. Okay. To do this, I will provide a background on the role of the Division of Medication Error Prevention and Analysis, or DMEPA for short, and also a background on medication error. I will outline what we know about the prevalence and impact of medication errors and summarize the data from published literature, which identified the factors that contribute to medication errors involving investigational drugs. Then I will review the requirements for investigational drug container labels, and finally, I will discuss current practices and limitations of reporting medication errors, which involve investigational drugs.

Janine Stewart:

Medication errors are a public health burden. The Institute of Medicine in their report presenting medication errors, stated labeling and packaging as the cause of 33% of medication errors, including 30% of fatalities. Among other recommendations, the report advised that product naming, labeling and packaging should be designed with the end-user in mind. This report was pivotal and it was the impetus for much of the work we do today in DMEPA. DMEPA is considered lead for medication error prevention and analysis for drug and therapeutic biologic products. The division is composed of scientists and healthcare professionals with various backgrounds, including pharmacists, nurses, engineers, and social

scientists. DMEPA's mission is to increase the safe use of drug products by minimizing the use error that's related to naming, labeling, packaging or design of drug products. Because we're focused on prevention, we take a proactive approach to address the risk of medication errors before the product is in the hands of the end user.

Janine Stewart:

DMEPA's involved in many different review activities in the pre-market and post-market arena. However, we currently do not review container labels for investigational drugs. We review proprietary names, non-proprietary names, suffixes, product labeling, product packaging, product design and human factors, and we conduct post-market surveillance and medication error reports submitted to the FDA MedWatch program. DMEPA has signatory authority to review proprietary names and human factors protocols. All of our reviews take into account current federal regulations, applicable guidance to industry, USP standards and relevant post-market experience. This graphic illustrates the drug product life cycle from discovery and development to clinical research trials, to FDA review, to market approval.

Janine Stewart:

And after a product is marketed, FDA continues post-market safety monitoring to ensure safe use in the healthcare system. As part of the FDA review, DMEPA may be involved as early as the end of phase two, prior to the filing of the investigational new drug application. Pre-market clinical research trial data is the cornerstone of the drug approval process. Strategies that help to mitigate the risk of medication errors occurring during clinical trials help to protect the research participants from harm and protect the integrity of trial data

PART 3 OF 5 ENDS [01:33:04]

Janine Stewart:

upon which approval decisions are made. For clinical investigations, we are very interested in minimizing medication errors in these results in serious adverse events or threaten the integrity of a clinical trial.

Janine Stewart:

A lot of what we know is from the very limited public literature that exists. Recent literature highlight medication error concerns related to unlabeled and poorly labeled investigations on containers. For example, a 2015 VA Health System study looked at safety risks with investigational drugs and concluded that labels can impact the ability of health care providers to really locate and understand critical information for product use. A 2019 Canadian study that included labels from blinded protocols provided by the European and American sponsors found almost half the labels affixed to investigational drug containers were missing important information such as the expiration date, the sponsor's address or storage conditions.

Janine Stewart:

Error rate estimates vary between studies and range from about 0.35% to 5.4%, depending on the type of error and the use environment, to 12%, as estimated in our French simulation study using IMB container labels in which most errors were related to dosage unit, protocol identifier, drug confusion, or expiration date. And as you heard yesterday, The Institute of Safe Medication Practices published a two part series in 2018 of which the first part of the report reported risks with investigational drug nomenclature, labeling and packaging. And the second part recommended error mitigation strategies for FDA sponsors, investigators, and the clinical trial sites.

Janine Stewart:

The additional factors that may contribute to medication errors include the use of small font sizes, less than eight points, the presence of error-prone abbreviations, limited use of color or other differentiation techniques and how many similar products or protocols identification numbers.

Janine Stewart:

Another contributor is variable formats for expiration dates and lot numbers. The format for how dates are expressed varies between different countries, and sometimes expiration date and lot numbers are confused.

Janine Stewart:

Additional known factors include nomenclature inconsistencies and the use of non-standard symbols and keys to identify product information that is presented on multiple languages for international trials. From this information we know that investigational drug pharmacists and other providers in this area and practice would need to be vigilant to identify and prevent medication errors from occurring.

Janine Stewart:

Now let's look at a few examples based on real container labels, which all have been de-identified and are provided here for illustrative purposes only. These images show a large container label that illustrate how cluttered product information and small font size affect the readability of important information, which can lead to medication errors.

Janine Stewart:

Here we have examples of investigational drug labels that are missing a strength statement or have confusing strength statements. In the image on the left and the image in the center, the strength is lot number specific, meaning the provider must check a list of lot numbers in order to identify the product

strengths. Note the lot number is clearly labeled on the bottle on the left. However, it's not so clear which number is the lot number in the center image. In this instance, the provider will have to consult a legend to determine which of the numbers in the center image correspond to the lot number then check a list of lot numbers in order to confirm the product strength. The image on the right shows a container label that has two strength statements, one at the top, which reads five milligrams, and one at the lower right side, which reads one milligram. This confusion can lead to a medication error.

Janine Stewart:

Next we show examples, modified for illustrative purposes, of confusing product identifiers and protocol numbers. In comparing the protocol numbers, which begin with H2W on these two container labels, you will note that they are quite similar. Likewise, when you compare the product identifiers which begin with KY12, you will note that they are also very similar. These represent very common lookalike scenarios which require a great deal of effort by investigational drug service staff to avoid mixups.

Janine Stewart:

Another contributing factor is related to nomenclature and how a product identifier may change during drug development. Nomenclature changes in this example are shown clockwise. The drug entity starts under development as ABC-010. Then this identifier is switched to ABC-101. Later the product becomes XYZ-437016, before it becomes known under its established name. And finally, the drug is granted a proprietary name.

Janine Stewart:

Many sites often have hundreds of active clinical trials and investigational new drugs, thus investigational drug pharmacies might need to devise tracking methods and reference sheets to keep

track of these changes. Further, the written protocol may not always be updated so that the product name is consistent across all the clinical trial labeling.

Janine Stewart:

FDA's draft guidance titled "Safety Considerations for Container Labels and Carton Labeling to Minimize Medication Errors," which was published in 2013, focuses on safety aspects of the container label and carton labeling design, and provides a set of recommendations for industry to ensure that marketed product container labels and carton labeling are designed to promote the safe use of the product during initial prescribing, procurement, preparation, dispensing and administration. However, these concepts can also apply to investigational drugs. FDA recommends sponsors to develop drug products using analytical methods to investigate, understand, and correct identified risks. These methods should be a part early in drug development to build safety into the product design and throughout the drug product life cycle. The goal is the design of drug product that enables safe and correct use, and eliminates or reduces design elements, which could lead to use related hazards.

Janine Stewart:

You will hear more about FDA's draft guidance from the Office of Medication Error Prevention and Risk Mitigation. Deputy Director, Dr. Lubna Merchant, in the next presentation.

Janine Stewart:

Under 21 CFR 312.6, the requirements for labeling an investigational new drug include the following. The immediate package of an investigational new drug intended for human use shall bear the label with the statement, "Caution new drug, limited by federal law for investigational use;" and the label or labeling of an investigational new drug shall not bear any statement that is false and misleading in any particular way, and shall not represent that the investigational new drug is safe or effective for the

purposes for which it is being investigated. While not a regulatory requirement, investigational drug container labels may also include additional information such as the protocol or the clinical trial number, the concentration and/or strength, dosage form, quantity per container and storage requirements and lot number.

Janine Stewart:

The FDA has received case reports associated with investigational drugs, and here are two examples. Example one is a case where a drug recipient had to be hospitalized with grade IV anaphylaxis and febrile neutropenia secondary to an accidental overdose. Errors can result in serious adverse events as is in this case. But an error can also threaten the integrity of the clinical trial data.

Janine Stewart:

In example two, a patient was randomized to receive drug A, but inadvertently received drug B. Although there was no adverse event associated with this report, this type of error will be considered a protocol deviation, which could skew the results and impact the integrity of trial data upon which approval decisions are made.

Janine Stewart:

Using the same two sample reports from the previous slide, we see the error reports from investigational drugs may contain limited information. Neither of these two reports provided information regarding the factors that contributed to the error. These errors could be related to the container label, or maybe not. Those details are needed to determine the root cause, and having that information would help efforts to prevent the error from reoccurring.

Janine Stewart:

From post market experience, we know that errors often go unreported, thus the reports that we receive are often just the tip of the iceberg. And furthermore, for multicenter trials, it's not clear if error report information is shared with other sites to inform strategies to mitigate known risks.

Janine Stewart:

Under the current recommendation outlined in these guidance documents, reporting of medication errors involving investigational drugs may be inconsistent. FDA requires sponsors of investigational new drug applications to report any suspected adverse reaction that is both serious and unexpected to FDA and all participating investigators in an IND safety report. Adverse reactions that are not serious or unexpected or medication errors that do not result in an adverse action, may be reported by the investigator as unanticipated problems or in the annual report.

Janine Stewart:

So in summary, we know that medication errors involving investigational drugs occur, but we need to understand the prevalence and the impact of these errors. Poorly labeled investigational drug containers appear to be contributing to medication errors because they impact the ability of healthcare providers to readily locate and understand critical information for safe product use. Therefore, a proactive approach is ideal to address the risk of medication errors early in drug development.

Janine Stewart:

Unclear processes for reporting and analyzing medication errors related to investigational drugs is another aspect of this issue. But because ultimately we know that strategies that help to mitigate the risk of medication errors which occur during clinical trials help to protect research participants from harm and protect the integrity or trial data upon which approval decisions are made.

Janine Stewart:

Thank you. That's all I had. But next you will hear from our Deputy Director of CDER's Office of Medication Error Prevention and Risk Mitigation, Dr. Lubna Merchant.

Susan Winckler:

There you go. I see you're coming on the stage and we will turn the microphone over to you, although we're not seeing your webcam right now.

Susan Winckler:

Dr. Merchant, it looks like there's still something over your webcam, but if you want to go ahead and present that's okay.

Lubna Merchant:

Maybe I turn it? All right. I'm not sure why my webcam is not working.

Susan Winckler:

It might be covering it, but if you want to just go ahead and present, I think that will work well and we'll continue to work on the webcam.

Lubna Merchant:

I don't have anything covering here. That's interesting. Okay. Why don't I go ahead and get started and we'll figure out the webcam in a minute?

Lubna Merchant:

That was a very informative presentation from Dr. Stewart. She walked us through several examples of investigational drug labels and areas of vulnerability. We saw very similar examples in the presentation from panel one yesterday. In the next 10 minutes, I want to focus on how to proactively address these

errors and make recommendations for the marketed product label and labeling that we review prior to approval in order to mitigate some of these risks.

Lubna Merchant:

Before I get into the specific recommendations, I wanted to provide this visual to give a perspective on how drugs are stored in a typical pharmacy setting, be it retail, hospital, in the refrigerator on the floor or in the automated dispensing cabinet.

Lubna Merchant:

We also know lookalike labels have frequently contributed to product selection errors, leading to dispensing and administration of the wrong drug, wrong strength, wrong dose, as seen when similar labels are stored side by side or near one another as illustrated in this slide.

Lubna Merchant:

Before I get into the recommendations, I just want to clarify what we mean by container label and our term labeling. So any display of written, printed or graphic matter on the immediate container of any drug product, that is the vial, bottle, cube, pouch, syringe, are all examples of container labels. And all are printed with some graphic matter that is present on the outer packaging are examples of carton labeling.

Lubna Merchant:

Dr. Stewart mentioned this guidance, the guidance that we have for marketed products to provide, the guidance focuses on safety aspects of the container label and carton labeling design and provides a set of principles and recommendations to the sponsors for ensuring that critical elements of the product container label and carton labeling are designed to promote safe dispensing, administration and use of

the product. And this is applicated to approved labeling, but certainly the principles here can apply in investigational drugs as well.

Lubna Merchant:

The guidance covers multiple recommendations and best practices, but I will focus on those aspects that were covered in the last presentation, as well as in the presentation yesterday. We generally recommend that container labels are large enough to accommodate all critical information on the immediate product container label required for the safe administration of the product. However, we do know that that is not always possible and there is a lot of smaller containers, such as vials [inaudible 01:48:31] are smaller. And we do have the small label exemption for these smaller containers. But even in those instances, the following required information has to be present on these small labels or the small container labels, and that includes the proprietary name, the established name, the product strength, the lot number, the name of the manufacturer, packer or distributor. And for these small labels, USP also requires them to bear an expiration date.

Lubna Merchant:

Here is an example of a principle display panel that you typically see in marketed drug products. Again, product container labels should communicate information that is critical for the safe administration of the medication. The information, such as the product name, product strength, dosage form, route of administration, any warnings, et cetera, should be prominently located in the same field of vision. We also recommend that this information is presented with a minimum font size and adequate color contrast to maximize readability.

Lubna Merchant:

Now, there is a lot of information or a lot of important pieces of product information. However, the placement of all that information within the PDP may lead to decreased readability. In the previous presentation, you saw an example of an investigational container label that illustrated how cluttered product information and small font size affects the readability of important information, which can lead to medication errors. When labels are crowded, text size and prominence is generally decreased and important information may be difficult to read or easily overlooked. We generally recommend that lines or blocks of texts are separated by sufficient white space to avoid crowding and clutter, and less important information can be located on the side or the back panels.

Lubna Merchant:

You also heard about how the product strength is sometimes missing or confusing with other information that's presented on the investigational drug labels. A product's strength or concentration is critically important information for the end-users. What we recommend for sponsors to use in marketed products is techniques such as boxing, prominent typeface or color differentiation, as illustrated in the example on this slide where the two strengths are adequately differentiated using color differentiation.

Lubna Merchant:

Now, I talk about the placement of strength and net quantity. They should be placed such that their proximity to each other should not be confused with each other. In the example on the left, you'll see the 20 capsules, but that quantity of 20 capsules and the strength of a hundred milligram is located right next to each other. And this may be confused, especially if the product is also available in that strength. In this case, the product is also available as a 20 milligram capsule.

Lubna Merchant:

On the right-hand side, you'll see the strength and the net quantity is displayed away from each other, or placed away from each other, and that is less confusing. And in this instance, this product is also available in the 30 milligram tablets, but the chances of confusion are minimized.

Lubna Merchant:

The route of administration must always be present on the principle display panel for all [inaudible] products per federal regulations for a marketed product. You also want to ensure that the route of administration is not abbreviated, as certain abbreviations are dangerous. For example, the symbol and abbreviation for microgram can be mistaken as milligram. IU, which is an abbreviation for international unit, has been confused with IV, intravenous route of administration. We've also seen mistakes occur with non-standardized or unfamiliar abbreviations.

Lubna Merchant:

Additionally, we always recommend using positive statements for the route of administration. In the examples below you'll see the route of administration is noted as going to be misused only, fatal if by given by other routes. Affirmative statements help potential readers understand the intended route of administration, even if they do not read every word.

Lubna Merchant:

Sometimes healthcare providers may overlook the word, 'not,' depending on how the container or the vial is positioned. Here are some examples of confusion with lot numbers. We always ensure for our marketed products, that there are no other numbers located in close proximity to the lot number, where it can be mistaken as the lot number as you can see in figure one. In figure two, also the lot number could be confused as an expiration date.

Lubna Merchant:

Talking about expiration dates, we know that expression of expiration date has varied on the label. The use of abbreviations, such as two letter month and two digits years has led to confusion and misinterpretation. For example, MA could be March or May. And the number 12 could represent the day, month, or year. We generally recommend a minimum of three letter texts for months, two digits numerals for day, month, and four digit numbers for the year. Listed below are some examples of how we like the expiration date expressed when all numeric dates are used over an alphanumeric date are used.

Lubna Merchant:

We do require barcodes for our marketed products. Barcodes have become cornerstones of safe dispensing and administration in [inaudible 01:54:34] drug patient safety. The review can show that its barcode on the container label and carton labeling and product identifier whenever applicable, and that there is enough blank space surrounding the barcode to allow for barcode scanning. We also recommend that barcodes are not placed in an area that can be easily damaged, such as the example on the bottom where it could be damaged because it's at the point of operation for blister packaging.

Lubna Merchant:

In the next couple of slides, I want to provide an example of an investigational drug label as compared to the approved labeling. So here's an example of a label for remdesivir. On the left-hand side, you'll see the IND labeled product. And this is very similar to the example provided by Janine in the last presentation. There's a lot of information [inaudible 01:55:32]. On the example on the right-hand side, you'll see the label for the approved product. And key information is very prominently displayed, easy to locate and identify the product name, the product strength, important information, that it must be diluted before you use, it has to be given by intravenous infusion, is all prominently located. Here is another example. Similarly for the casirivimab/imdevimab (Regen-Cov). On the left-hand side, the IND

labeled product, on the right hand side, you'll see the emergency use authorization labels. Again, the product strengths are very clearly differentiated on the right-hand side. Also key information is prominently displayed. The most important information, that this product has to be administered with the other component is very easy to locate and prominently displayed here.

Lubna Merchant:

The last topic I want to talk about before I close, as you've heard throughout the day in the presentations today, as well as the common theme in the presentations yesterday as well, about interest in global harmonization. We know that regulatory agencies have varied requirements related to medication error reporting and investigational drug labeling. Published literature also has recommended global harmonization of the information on container labels. Perhaps a creation of minimum best practices for the investigational drug labels, aimed at reducing medication errors could help address this at a global scale. Regulatory authorities can ensure product labels and packages are designed to minimize medication error. This would certainly benefit our patients and protect our research participants, and also benefit the pharmaceutical industry by decreasing the regulatory burden on manufacturers that produce drugs for the global market. And the recommendations could be very similar to those best [inaudible] and guidances from various regulators.

Lubna Merchant:

Again, the common theme that we've heard in the last two days is pre-market clinical research trial data is the cornerstone of the drug approval process. Strategies that help mitigate the risk of medication errors occurring in clinical trials help to protect people and participants from harm and protect the integrity of trial data upon which approval decisions are made. We are, here at FDA, very interested in minimizing medication errors that may result in serious adverse events, affecting the integrity of a

clinical trials and want to explore opportunities for global harmonization on labeling and reporting errors seen with investigational drugs.

Lubna Merchant:

And that's all I have. Thank you for your time and attention. I turn it over to you, Susan.

Jo Wyeth:

[inaudible 01:58:58} …and also Ryan Raffaelli. We would just like you to introduce yourself and maybe just give a little bit of background or your perspective as it pertains to medication errors and investigational drugs. Janet, can we start with you?

Janet Donnelly:

Sure. Jo, can you hear me okay?

Jo Wyeth:

Yeah, we can hear you great. Thanks, Janet.

Janet Donnelly:

Thank you. Thank you, Jo, and my other FDA colleagues, as well as the Reagan Udall Foundation for FDA, for the opportunity to listen into this meeting and to participate. My name is Janet Donnelly. I'm a policy analyst in FDA's Office of Good Clinical Practice, often referred to as OGCP. And OGCP reports into the Office of Clinical Policy and Programs, under the Office of the Commissioner. And we sort of serve as a focal point within the FDA for good clinical practice and human subject protection issues, or GCP and HSP issues that arise in FDA regulated clinical trials.

Janet Donnelly:

OGCP is often involved in discussions and conversations about interpretation of GCP issues, human subject protection issues. We also are involved in developing and revising new regulations and policy guidance documents for the protection of human subjects who volunteer for FDA regulated clinical trials.

Janet Donnelly:

I would like to also thank the panelists, actually, for all of the very valuable information that we've heard both yesterday and today, for sharing your experiences, and as Dr. Dal Pan said yesterday, understanding existing practices essentially, but also for the opportunity to engage with our stakeholders, to hear about some ideas about how do we move forward to address this issue. And I appreciated hearing yesterday about ideas of harmonization, standardization and data sharing and information.

Janet Donnelly:

I listened sort of today as we all do with an ear towards human subject protection. And I look forward to an opportunity to collaborate some more on how we might address this issue. I've learned a lot. I honestly can say in my role in OGCP, I wasn't very well aware of this issue, but certainly I do appreciate the opportunity to be here and to listen in from that perspective. And let me finish by just saying one of our panelists commented yesterday that patient safety should not rely on workarounds that might be needed. And I thought that that was really something that I've been thinking a lot about since I heard him say that yesterday. Let me close by saying, I think we all have a shared responsibility for human subject protection. So again, I think this is a great opportunity, and I'm happy to be a part of it. Thanks.

Jo Wyeth:

Great. Thank you, Janet. I'm just going to ask you to go ahead and turn on your webcam for those of you who may not have heard me, since I was muted. The Reagan Udall Foundation just ran into a little bit of a technical issue, no surprise with all the virtual world we work in. So I'm going a little bit for Susan until she can rejoin us. So thank you, Janet, for that introduction and your perspective. Ryan, would you mind going next introducing yourself?

Ryan Raffaelli:

Sure. Can you hear me okay?

Jo Wyeth:

Yeah, we can hear you great.

Ryan Raffaelli:

Great. I'm Ryan Raffaelli. I'm a medical officer in the Office of Compliance and the Office of Scientific Investigation. We're the ones who work with our ORA colleagues to conduct inspections of clinical sites, sponsors, contract research organizations, investigators, sponsor investigators. I'll just point out I appreciated that Janine Stewart from FDA showed a slide of the current regulations that we have for labeling. And as you may recall, it's very spare.

PART 4 OF 5 ENDS [02:04:04]

Ryan Raffaelli:

So with regard to what we do in my role in compliance is essentially that there's not a whole lot that we do regulatory-wise as far as GCP compliance goes relevant to labeling specifically. What ends up

happening is, for example, a medication or dosing error may occur, whether corrective or preventive action plan identifies that it was due to maybe some labeling concerns or a root cause analysis comes to that conclusion, we would proceed with sort of the downstream effect of any labeling issue. So say it's a dosing error, and dosing is laid out very specifically, often in study protocols, we would investigate that as potentially a protocol violation, not necessarily violation of the labeling, whatever the error ends up being, be it an overdose, an accidental overdose, or a wrong drug used in a study something along those lines.

Ryan Raffaelli:

We proceed to investigate that as a potential protocol violation because often that's where that information is described. And so I've been listening in for the last two days, and I've been really interested to hear the perspectives of all the stakeholders. It's been a really interesting conversation and I think I'll stop there and let other folks talk and then happy to answer questions later.

Jo Wyeth:

Thank you, Ryan. Yes, we do have a couple of questions that'll be coming up. So Paul, how about you? Could you go ahead and introduce yourself and provide a perspective?

Paul Gouge:

Well, hopefully everybody can hear me. It looks like they can. I am happy to join everyone here for this important discussion. I really appreciate all the inputs that we've heard from industry, I sounded very engaging. As a brief introduction for myself and how I might be related to this topic: my name is Paul Gouge and I'm a regulatory counsel for the Division of Clinical Trial Quality. And that's housed within the Office of Medical Policy. In that capacity, I don't work specifically on medication errors and labeling, but

I have found that it is an interesting topic because one area that I am heavily involved in is our IND safety reporting regulations and just how those work related to the various responsibilities that investigators may have and sponsors may have with our IND safety reporting regulations.

Paul Gouge:

Recently, we've been working to publish guidance that details both those sponsor and the investigator's responsibilities for IND safety reporting, and both of those guidances have actually been made part of FDA's unified agenda for 2021. So that's an area where we're continuing to build momentum and thought and get word out to stakeholders regarding our recommendations. So with that brief introduction, I just want to say that I really look forward to hearing any questions or any input that's related to how that IND safety guidance relates to these medication errors that we've been discussing. Thanks.

Jo Wyeth:

Susan just joined us and as she's kind of getting reconnected, Paul, I'd like to just start out by [inaudible] we've heard from the IRB regarding unanticipated problems. Could you just maybe talk to that a little bit more so that we kind of understand unanticipated problem as it pertains to medication errors in reporting?

Paul Gouge:

I think as we were talking internally before this, and as I've heard discussion throughout this public meeting, that it really is an area where maybe not everybody is aware of how there might be an interplay with medication errors and unanticipated problems. However, I think when you really think through it, and I know that we heard this a bit on the IRB panel, we can certainly envision scenarios where investigators must report medication errors as unanticipated problems to the IRB. Investigators

have a duty, a responsibility under 21 CFR 312.66 to report all unanticipated problems involving risks to human subjects or others to the IRB.

Paul Gouge:

Excuse me, prior [inaudible 02:09:02] could be triggered if a medication error occurs in the trials, for instance, maybe a patient receives the wrong dose. Unanticipated problems could be identified as rising from an adverse event, but an unanticipated problem could also occur even if there is no adverse event; therefore, the investigator could determine that the medication error is an unanticipated problem, even if they don't observe a resulting adverse event in the patient. Also, if the investigator does identify unanticipated problems related to medication errors, they must report those to the IRB.

Paul Gouge:

The IRB would then of course, need to follow its protocol to ensure that the unanticipated problem is reported to the FDA, to the IRB, and to the appropriate institutional officials. And I think it's under 21 CFR 56.108 that the IRB is required to have in place and to follow written procedures for ensuring prompt reporting to the FDA of any of these unanticipated problems that are forwarded to them. So, I think that's something that our IRBs are definitely working through and it sounded like it ... that panel, that they would agree that these medication errors in fact, many times maybe an unanticipated problem that the investigator must then course report to them.

Susan Winckler:

So do you want me to pick up? It's Susan. All right!

Jo Wyeth:

Thank you.

Susan Winckler:

So thank you so much for stepping in there. And I'm going to come in with a question that we got in the Q&A, and this one is for Ryan. So Ryan, are you ready?

Ryan Raffaelli:

I am.

Susan Winckler:

All right. So Ryan, the question is that many clinical research protocols refer to pharmacy manual. And so in with that, does it make sense, or would you think ... would your perspective be our pharmacy manual's then subject to IRB review or input?

Ryan Raffaelli:

I'll also ask Janet to respond to this question as well, but I won't speak directly to the IRB review, but I will say from a compliance standpoint, if a protocol is explicit that a pharmacy manual must be adhered to, and if, for example, that manual describes labeling practices that are required for conduct of a study by an investigator, then that manual could be subject to a review for consideration of any GCP noncompliance or violations of the regulations. Generally, we would probably consider those to be possible protocol violations because the details would have been within the protocol and the protocol would have explicitly referred to a pharmacy manual. So in that situation, I think that's how we'd probably approach it, but I'll defer to Janet to comment on the IRB review.

Janet Donnelly:

Thanks, Ryan. I really think it depends on what the pharmacy manual contains: does that pharmacy manual just address specifics for reconstitution, let's say of an investigational product? Or how does that pharmacy manual have an interplay with the protocol? So in general, I'm not familiar with IRB reviewing pharmacy manuals. However, I will say that the IRB can certainly determine what type of study information that they would like to have submitted to them to review. So again, I believe that there might be such variation across pharmaceutical sponsor companies as to how they create their pharmacy manual. So I don't think it's a yes, no answer, and a lot of it will depend on the interplay of that manual with the protocol and other sponsor documents that go to the IRB.

Susan Winckler:

For jumping in on, on that question. I'll direct the next one to Dr. Merchant, and this is a bit of an obvious one, but what's your view on the significance of medication errors associated with investigational drugs?

Lubna Merchant:

[inaudible] in the presentations before that FDA has received medication error reports associated with investigational drugs. Often we don't see their entire breadth or the scope of these issues because medication errors generally are under-reported. We know that from, from our other experiences as well for the postmarketing of marketed products that medication errors are under-reported. So what we know about this is that we have from published literature from other stakeholders have had reports of medication errors that included wrong drug, wrong dose, some of which have resulted in serious adverse events. We know incidence and nature of these errors is with investigational drugs is still unknown. We know from the published studies in the last five years or so, they have pointed to a lot of missing, confusing information on the investigational drug container labels as a contributing factor for these medication errors.

Lubna Merchant:

So having said all that, I think we certainly, and it's not a reflection of FDA's view, I'll give my personal view. It's certainly ... there is a lot of concern we certainly want to provide ... We want to see what we can do to address these medication errors. We heard a lot of information from a stakeholder in the last two days. And I think it's time for us to go back think about this, have some internal discussions and come up with certain requirements, or guidance, or what have you some steps to better understand and address the medication errors for investigational drug products.

Susan Winckler:

Consistent with what we might have expected, but also illustrative of how much we've learned in the last two days of the meetings. Let me toss a question ... Janet, I'm going to come back to you. If this is related, we talked about pharmacy manuals. Now let's talk about reviewing labels and labeling. Would you have an expectation for ... does the FDA or do IRBs have expectations for investigators to review the labels and labeling?

Janet Donnelly:

Thanks, Susan. I think the answer to that is yes, and the answer is sort of rooted in the IND regulations as well as guidance documents from FDA. So thinking through the sponsor responsibilities to choose qualified investigators, and then investigators are responsible for ensuring that the investigation is conducted in accordance with the 1572 and the protocol, and certainly regulation for protecting the rights, safety and welfare of human subjects. Investigators also have IND responsibilities for controlling the disposition of the drug in record keeping and record retention responsibilities. But I think the ICH GCP E6 guidance kind of sums it up well, when I think about one of the investigative responsibilities that essentially says: investigators should be thoroughly familiar with the appropriate use of the

investigational product as described in the protocol, the investigator brochure, and other sources of information provided by the sponsor.

Janet Donnelly:

So again there, I think that there's definitely an expectation. And then when I think through the IRB's responsibility, if there are certain approval criteria that the IRB must find and document in order to approve research, of which one of them is that risks to subjects are minimized by the use of procedures that don't unnecessarily expose subjects to harm, and that those risks to subjects are reasonable in relationship to anticipated benefits if there are any. And then I think as we heard from our IRB panel ... certainly IRBs are considering qualifications of investigators when they review information, as well as the adequacy of the site to conduct the study. So I think I can't argue that the answer at least in my opinion, there is yes.

Susan Winckler:

Can you hear me?

Janet Donnelly:

Now I can.

Susan Winckler:

[crosstalk 02:19:24] They're great. At some level logical, right? Our clinical research enterprise is about understanding and learning more about the performance of these products and the human subject protection is making sure that those who participate are protected and medication errors are counter to that protection of the human subjects, as well as to developing the data that we would evaluate in assessing the performance of the product. So, thanks so much. Ryan, let's talk inspections. Is that ... I

know that's your bailiwick. So if we think about inspections, how do you assess compliance with labels, labeling, and resulting medication errors when you're inspecting related to investigational drugs?

Ryan Raffaelli:

So thanks for the question, Susan. So we rely on our colleagues in the Office of Regulatory Affairs to conduct the inspection, and those inspections, they may result from an application that a sponsor submits. So following our user fee programs, we'll send out an investigators to conduct an inspection as part of a review. Or we may get a referral, maybe a referral for a medication error as an unanticipated problem that an IRB or a sponsor submits to FDA in a required report and the investigations that are then undertaken, I'll be very clear, it's minimal, what's looked at when it comes to labeling. I mean, I'll even read them. So there are our compliance program guidance manuals that our colleagues follow there are manuals for investigators specifically and manuals for sponsors and CROs.

Ryan Raffaelli:

And in both instances, I'll read it right here. It says, inspect unused supplies and verify that the test article was appropriately labeled. So Janine Stewart showed a slide earlier about what appropriately labeled means when it comes to the FDA regulations. And it essentially is a one-liner and the rest is up to the sponsor or a delegate, be it a CRO and, maybe some guidance in a pharmacy manual or a protocol for a specific investigator, but when it comes to the regulations when we're doing our inspections, it's ... there's not a lot of information to go on. So it's a very minor part of an overall inspection.

Susan Winckler:

Well, and certainly we know, in those inspections, there is, as you indicated a lot going on. And, and yet I might imagine that if an inspector came across the naked vial, or the naked box that we heard about that that would be on its face insufficient. Potentially.

Ryan Raffaelli:

Yes. But again, like I said, in my intro piece, it's the downstream effect, it's, what was the result of the labeling issue? Overdose, some other sort of errors, some safety concern. I mean, obviously it's, everyone has already ... I'll repeat it again, obviously subject safety and data integrity are vital to any conduct of a clinical investigation. So anything that impacts those specific factors where we'll pursue. But if we saw a naked vial, a naked bottle, that would raise some concern, but again, what was the result? Can we link it to a regulation? And then what's our consideration when it comes to a violation of that.

Susan Winckler:

Excellent. Thanks, Ryan. Paul, I'm going to come back to you. So are there circumstances in the current regulations where a sponsor would be required to report a medication error involving an investigational drug, would they be required to report that to FDA and to all participating investigators?

Paul Gouge:

That question, Susan, I know that we've touched a bit on this subject throughout the meeting, but I can hopefully expound on that a bit. The short answer is yes, absolutely. A sponsor has an obligation to submit IND safety reports for any suspected adverse reaction that is both serious and unexpected. Quite simply that means that if there is a reasonable possibility that the drug caused an adverse event

and that adverse event is both serious and not listed in the investigator's brochure, then the sponsor must submit an IND safety report.

Paul Gouge:

And certainly medication errors in a study could meet this criteria for mandatory safety reporting. In fact, our FDA's 2012 safety reporting requirements for INDs and BABE studies guidance actually explains that an adverse event could occur as a result of an overdose. In all cases, if a medication error results in a serious suspected, unexpected, adverse reaction, the regulations do require that the sponsors submit an IND safety report and provide that report both to the FDA and to all participating investigators. Not all medication errors will rise to this level of being a serious adverse event that requires an IND safety report; however, the sponsor would still of course, need to document any medication error as deviations in the protocol. So hopefully that helps add a little bit of information to that subject.

Susan Winckler:

It ties back to what we heard yesterday, more from the research enterprise saying, "it's so helpful to share the information." That's an example where it has to be ... should be going back out to all of those entities that are involved in that trial. Great. We are closing out here, and so I'm going to do two more questions. So actually, Paul, Ryan, and Janet, you can relax a little bit. Janine and Lubna I'm coming for you with the last two questions. Lubna what evidence is there that requiring certain information on container labels, including for approved products may mitigate medication errors, and how is information on near misses helpful to that medication error mitigation.

Lubna Merchant:

So we can draw a lot of experience from our review of post-marketing errors that we've seen with the marketed products. Here in DMEPA, and I think you've heard it in Janine's presentation, as well as mine.

We kind of take a proactive approach, right? So we are looking at what errors occurring with the marketed products, learning from those experiences, taking it back, applying to a review of new products so that we can address that, we can mitigate that right from the beginning. That's the results because of these lessons learned because of what we are seeing with the recommendations, because forward, the changes that we make in label that labeling, we are seeing those risks mitigated, that's the impetus, that's the background for having the guidance on the label and labeling design, where we put forth recommendations that we think are sort of best practices and are aligned, or are for addressing or mitigating the risk for medication errors.

Lubna Merchant:

And, you know, it's interesting. And the example that I showed the IND labeling and with the approved labeling the last couple of slides that I showed with remdesivir and Regen-Cov, and both of those labels are coming in from the same sponsor, right? But because we have specific guidelines, regulations, requirements for approved labeling, you see there is a lot more clear guidelines for the sponsor and what to do with that labeling, what information to emphasize, what critical information should be present, how to present that as opposed to the IND labeling. It's coming in from the same sponsor, but you can see the difference in the type of labeling, and that's the result of all those guidelines or regulations or the requirements that we put forth for marketed products. It's also interesting to see in the investigational drug labeling side, you heard from MHRA and Health Canada and I think in Panel 1[inaudible 02:28:17]

Lubna Merchant:

If you pick up a guidance from Health, Canada, or EMA on the marketed labeling products, you'll see that is very common theme, right? Similar recommendations that is coming from FDA, Health Canada, EMA, MHRA multiple other regulatory agencies. We are providing very similar recommendations on the

marketed products. So there is a wealth of information that we can learn and use from the marketed product label and labeling here that has shown us that applying these principles have addressed and mitigated medication errors.

Susan Winckler:

Really helpful. And I am going to get an award for [inaudible] computer to stay connected to our meetings today. I'm going to give myself that and go take the last question here for Janine and Lubna ... how does FDA envision your role in partnering with clinical investigators to support minimizing medication errors, as well as decreasing the burden, even spoken to some of this throughout the panel, but could you capture that for us?

Lubna Merchant:

I can stop and ... Did you say [crosstalk 02:29:52]?

Janine Stewart:

[inaudible 02:29:52] How we envision our role? Well, we were really looking forward to the information we will receive today, and then we would take it back and kind of discuss what the next steps would be, but we do see ourselves as a partner and with the IRB, with industry, with the clinical trial sites. So with the information that we gathered through this meeting, we'll likely have more information and we'll be able to go forward and make some changes or hopefully help to ultimately make an impact in this space.

Susan Winckler:

[inaudible 02:30:32] Were there any last words? [inaudible 02:30:45].

Janine Stewart:

I think she's frozen.

Susan Winckler:

Can you hear me?

Janine Stewart:

Looks like she's frozen. [crosstalk 02:31:00]

Susan Winckler:

And close out this panel. Thank you all so much for joining. And I will try and take us through, and I will say, we're going to close out here. We do have a public comment period available, if folks have the opportunity, if you want to do that, recall that you need to put your name, professional affiliation, and your phone number in the Q&A function, and then we will place an outbound call to you. While we watch for that, as we do not have any current public summit participants, I will just note, if we think about yesterday's discussion, taking us through the research enterprise from the clinical trial sites and their reality to the contract's clinical research organizations and what they say in working with many sponsors and many trial sites, and then from the sponsor piece, we got that great landscape of what it is that's happening in medication errors and got to some ideas of what might be excellent approaches for addressing those.

Susan Winckler:

Today, we turned to hear from the experience of other regulators. So what is it that's happening around the world, in the drug labeling space for investigational drugs and heard that there's some difference in that as well as perhaps an opportunity for harmonization. We then had a great dialogue with IRB and their potential opportunity to help us improve the connection in the pharmacies who are dealing with these products and seeing the challenges, and then assuring that we have good subject protection and an opportunity to contribute to those discussions. And finally, we closed out with hearing from our FDA

experts who work in this space and who every day are thinking about how might we do a better job to assure the protection of those who choose to volunteer in clinical trials as well as the integrity of the data that's generated in that research. So I will say with that, I'm going to want to confirm with my technical folks that we do not have any public comments.

Susan Winckler:

If I could confirm that. I don't see any requests to make a public comment. With that, we will close this meeting a bit early. Thank you all so much for joining us for this public meeting. It's been illustrative. I think we've had a lot of good engagement and have some fodder to consider what are those efforts that we can collaborate on to improve the protection of human subjects, certainly to decrease the risk of medication errors that are affiliated with the labeling on investigational drugs. With that, I'm going to go ahead and close the meeting and thank you all so much for joining us today.

PART 5 OF 5 ENDS [02:34:57]