Potential Medication Error Risks with Investigational Drug Container Labels Public Meeting
Day 1 Meeting Transcript (May 18, 2021)

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

Susan Winckler:

Hello. My name is Susan Winckler, and I am pleased to welcome you to this meeting. We are joined here, that you have joined the exploring Potential Medication Error Risks with Investigational Drug Container Labels, a public meeting of the US Food and Drug Administration and the Reagan-Udall Foundation for the FDA. If you're not familiar with the foundation, we're a non-profit, non-government organization created by Congress with the sole purpose of advancing FDA's mission. Now, a few logistics, you'll note that we are starting a few moments late, because that is what happens in virtual land when we have some audio-visual challenges, but you are indeed gathered for a public meeting of the FDA and the Foundation. Consistent with other FDA meetings, we will be taping this event.

Susan Winckler:

We have a number of speakers and a full agenda, which I will review. And we welcome you to pose potential questions in the Q&A portion of the event navigation. Because of the pace and content of the meeting however, we may not get to those questions. We will endeavor to do so, but also stick to our timeframe. I'll note that I'm particularly interested in this topic as I was a member of the National Coordinating Council for Medication Error Reporting and Prevention a long time ago, and certainly the Council's, FDA's and others' focus on medication errors continues to improve the safety of our medication use system. But we have additional work to do. We are gathered here for day one, and you will see in our agenda that we have a number of items that we will cover here in day one.

Susan Winckler:

So we will hear opening remarks from FDA. We'll then hear from the clinical trial sites, the on the ground users of these products and viewers of many investigational drug containers. We will then step up to the suppliers and the contract or clinical research organization. And finally, to round out today, we'll hear from regulatory, regulated industry rather, and the product sponsor perspective. We'll sign off for today and we will join again tomorrow. And tomorrow, we will open with some FDA remarks and we'll hear from other regulators about their approach to investigational drug container labels. We'll hear from the institutional review boards and close out the official planned portion of our meeting with a panel of FDA staff in providing their perspective of the regulator.

Susan Winckler:

We'll close with a public comment period where we invite you to contribute your thoughts about the discussion that we have had today. We welcome your engagement in that component. With that, I'm going to turn the virtual microphone over to an individual who with his team, has helped FDA strengthen its drug oversight and medication safety efforts significantly. Dr. Gerald Dal Pan is Director of the Office of Surveillance and Epidemiology at the Center for Drug Evaluation and Research at FDA. And with that Dr. Dal Pan, I'm going to turn it over to you.

Opening Remarks

Gerald Dal Pan, MD, MHS, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, FDA

Gerald Dal Pan:

Great. Well, thank you very much, Susan. Thanks to all of you for joining us today to discuss potential medication error risks with investigational drug products, a very important topic. If I could have the next slide. So clinical investigations, as everyone knows, are the cornerstone of the global drug approval

process. And these investigations include clinical trials, comparative clinical studies and bioavailability and bioequivalent studies. And approved drug applications contain data from both US clinical trials, as well as trial sites outside the United States. In fact, in fiscal year 2008, 80% of approved marketing applications for drugs and biologics at FDA contained data from outside the United States, and over half of clinical trials subjects and sites were located outside the United States. FDA requires sponsors to ensure protection of human subjects, proper conduct of investigation, and to promptly inform FDA and investigators of suspected adverse drug reactions that are both serious and unexpected.

Gerald Dal Pan:

So, where do medication errors fit in this? Well, medication error risks may threaten the integrity of clinical investigations and importantly impact the safety and protection of subjects who participate in investigations. And FDA has in fact received medication error reports associated with investigational drugs. And these reports have included things such as wrong drug and wrong dose errors, some of which have resulted in serious adverse events. However, the incidence and nature of medication errors associated with investigational drugs is largely unknown. But published literature has pointed to the investigational drug container labels as a contributing factor for medication errors. So, we at FDA are aware of two published studies in the last five years that have pointed to missing or confusing information on investigational drug labels as a contributing factor for medication errors. And both these studies recommended global harmonization of the information on the investigational drug container labels.

Gerald Dal Pan:

A 2019 study found almost half of investigational drug container labels were missing important information such as expiration date and storage information. They concluded that detailed and harmonized international guidelines are needed. A 2016 simulation study found an error rate of

approximately 12% with most errors related to dosage unit, trial code, drug confusion, or expiration date issues. And they concluded that to reduce medication error risk, a global approach is necessary including label harmonization. So, if we could go to the next slide, okay. So, we want to hear from you today and tomorrow about the risk of medication errors with investigational drugs.

Gerald Dal Pan:

The focus is on the information on investigational drug container labels and the format of that information. We want to hear about the prevalence and nature of medication errors and practices that minimize the potential for medication errors, especially those errors that may result in serious adverse events or threaten the integrity of a clinical investigation. We have received medication error reports associated with investigational drugs, and we are aware of global regulatory differences for labeling investigational drugs and medication errors. And we understand that the situation can be improved. We want to hear specifics so we can determine if regulatory action is needed. That's why we're here today.

Gerald Dal Pan:

And so if we go to the next slide, here are the discussion topics for this meeting. The speakers and participants will cover a wide range of issues related to investigational drugs and medication errors. And the specific topics of interest to FDA are listed here on the slide. The first is the prevalence and types of medication errors attributed to container labels and the impact of these errors on clinical investigations. We at FDA are interested to hear more about the prevalence and types of these errors and how they may threaten clinical investigations. And when we talk about medication errors, it's important to realize that we're referring to preventable events, let me underscore that, preventable events that may cause or lead to inappropriate medication use or patient harm. This includes near misses because these scenarios inform the potential for a medication error to occur and the need for mitigation.

Gerald Dal Pan:

Some medication errors may result in adverse events, some may not, but they're all important to us. The errors may threaten the investigation of the clinical trial success. For example, when a subject received the wrong drug, the active drug is confused with the placebo, or the subject receives an incorrect or delayed dose, or in some cases a missed dose. The next topic is that FDA is interested to hear if there's information that should always be on the investigational drug label. I think as you all know, for products approved and on the market, FDA has comprehensive requirements and best practices. Should the same be true for investigational drugs? Is there stakeholder consensus on what should be on the container label? Next, we want to learn about the entities responsible for labeling containers. We want to understand who's responsible for labeling investigational drug containers as the drug moves through the clinical trials supply line. We also want to understand what typically happens when a container label is identified by a clinical trial site or CRO, and how and when the container labels are revised and other sites are notified.

Gerald Dal Pan:

Next, we're interested in hearing about existing practices for reporting and analyzing medication error reports. Sponsors are required to report to FDA any suspected adverse drug reaction that is both serious and unexpected, the so-called SUSAR. For serious adverse events caused by a medication error, what's the usual process for analysis and risk mitigation? And what are medication errors, including those that are considered unanticipated problems, reports to sponsors, investigators, and FDA? And finally, we want to talk about global convergence and differences in the information on container labels. Are there opportunities for global harmonization on labeling and reporting medication errors with investigational drugs? As we previously mentioned, we're aware that globally other regulatory agencies have varying requirements relating to medication error reporting and investigational drug labeling. And we also want

to hear about any potential burden for applying different label requirements for each country and the benefits and obstacles of global harmonization.

Gerald Dal Pan:

So in closing, FDA is committed to ensuring the integrity of clinical investigations and the protection of subjects who participate in those investigations. And I'd like to thank each of you for participating today. I'd also like to thank Susan Winckler and her colleagues at the Reagan-Udall Foundation for FDA, for organizing and working to put this meeting together. So my FDA colleagues and I look forward to hearing from you and considering your perspectives as we evaluate Potential Medication Error Risks with Investigational Drug Container Labels to determine if regulatory action is needed. So once again, thank you for your participation and I wish you a good meeting.

Susan Winckler:

Great. Thank you so much, Dr. Dal Pan. Thank you so much for taking the time to open our discussion. And with that, we are going to turn to our program and what led to our conversation today were stories from clinical trial sites. And so we are going to have a great discussion from a number of different clinical trial sites. And I am going to turn the moderating duties for that panel over to Dr. Michael Cohen, who is known. I will say when this meeting was being set up and we knew the topic I asked first, whether Dr. Cohen would be involved and indeed he is. So I want to confirm Dr. Cohen, could you turn on your camera and your microphone and begin our next section?

Panel 1: Clinical Trial Site Perspectives

Moderator:

Michael Cohen, RPh, Institute for Safe Medication Practices (ISMP)

Presenters:

Sapna R. Amin, PharmD, MD Anderson Cancer Center

Jamie N. Brown, PharmD, Durham VA Medical Center

Han X. Feng, PharmD, National Institutes for Health

Raymond J. Muller, RPh, Memorial Sloan Kettering Cancer Center

Richard Needleman, RPh, Fox Chase Cancer Center

Michael Cohen:

Okay. Thank you very much, Susan. Can you hear me okay?

Susan Winckler:

Yes, I can.

Michael Cohen:

Okay, great. So I'll take the next slide then. Well, first of all, welcome everyone and thanks very much for being with us today. And I'm very happy to be working with my colleagues working in the investigation of drug services in several locations around the country. That includes Sapna Amin from MD Anderson in Houston, Texas, Richard Needleman from Fox Chase Cancer Center in Philadelphia, Jamie Brown, who is at the Durham VA Health Care Center System rather in North Carolina, and Han Feng who's with the NIH in Bethesda, and my colleague Ray Muller who's at Memorial Sloan Kettering. All these folks work in Investigational Drug Services.

Michael Cohen:

And my name is Mike Cohen. I'm president of the Institute for Safe Medication Practices and we run several different national error reporting programs. We're a non-profit organization and our entire focus is on medication safety. Like I say, we operate these different programs for medication errors. And everything that we receive, we have a memorandum of understanding with the FDA so that all the reports we get go into the FDA Adverse Event Reporting System. And we have a Vaccination or Vaccine Error Reporting Program as well. The same thing, we pass that on to FDA. We also have a Consumer Error Reporting Program. And I think-

Susan Winckler:

Mike, I'm going to pause you there. We can't see you. Could you turn on your webcam?

Michael Cohen:

Oh, it is on here. I'm sorry. How's that?

Susan Winckler:

There we go. Well, it's a little.

Michael Cohen:

Thank you. And I'm sorry about that. I was saying that the reports that we get are driven by providers and consumers, and they're really acting altruistically. The whole idea for them reporting is not because they're forced to, not filling out an incident report where they work. It's really because they want people to learn from mistakes that they made or potentially hazardous situations. And that has come up again and again with investigational drug container labels. So we're going to be looking at that with my panel, panel number one. First of all, I should mention that, let me get the next slide up, we do have the reporting program and we have several publications, newsletters that reach different areas of the

healthcare community to turn this information around that we get through the reporting program and put it to use. We have a presence in international, nationwide or I'm sorry, issuing nationwide hazard alerts and press releases.

Michael Cohen:

The program is about learning and dissemination of information and tools. And then obviously product nomenclature issues, labeling, packaging, device design. We've learned a lot from people's ability and willingness to report altruistically to this program and FDA then receiving this information and being able to interact with FDA. It's had a real advantage nationwide and even internationally as well and helped with guidance statements, and also with standards from the United States Pharmacopeia and even provider organizations like the accreditors, the Joint Commission, CMS another one, and the pharma and bio industry. I have to tell you that many changes have occurred with labeling and packaging and other product related issues over the years, thanks to the reporting program and the influence, obviously of the FDA with a lot of this as well.

Michael Cohen:

Let me see the next slide. Back, I guess it was four or five, well, three years ago, four years ago, we've been talking to our colleagues in the Investigational Drug Services. I visited some of their hospitals. I spoke with researchers, physicians, nurses, pharmacists, about a problem that they were having with occasional errors that they were aware of. And we decided to try to do something about it. And we published the ISMP two-part article in May, in April rather and May 2018 and that is depicted on this slide. It's available on our website, investigational drugs, product related issues, and then also some recommendations that we had as well. So, the medical products industry has a long history of making improvements with product labels.

Michael Cohen:

I think we have some of the best in the world actually, but we have a lot of problems as well with these container labels. And I list some of them, just some of them you're going to hear about today, like having used license plate numbers, rather than the names of the medications, even though an INN might exist for example. Changing product names not reflected on labels and protocols that lead to confusion. You are going to see containers of investigational drugs that have no label whatsoever, similar to the carton that I have here, but also in the immediate container as well. And lots of other problems that you will hear about from our participants on panel number one today. And like I was saying, industry really has responded- I would say it's truly in hundreds and hundreds and perhaps thousands of cases over the years to reports of medication errors with their products.

Michael Cohen:

This is one that goes way back and it had to be, it was a mix up between carboplatin and cisplatin. These have a major dose difference, and unfortunately they were often referred to as a platinum compounds. And unfortunately we occasionally would see these mix-ups. The sponsor of this product, the cisplatin product or Platinol, called together a group of practitioners from medicine, nursing and pharmacy to look and do what we call a failure mode and effects analysis, to look for potential problems and real problems that we saw and then make recommendations for improvement. And I think you can see from the time of the error report, and we've had several of these in the past, this goes back well, 15, 20 years ago. Look at the difference in the container, in the carton and also the vial . And that's required now, this is now non-proprietary. And so many manufacturers have cisplatin, but you can see colored tall man letters, a stop sign that wants to check out the dose, the maximum dose that you usually see.

Michael Cohen:

This is carried through to all of the companies that make this drug right now. And I think we learned a lot from that episode. So I'm going to turn this over to the folks. I do want to make on the panel, I do want to make one more comment, all the images and drug names that you're going to see are for illustration purposes only. Please understand that in no way are we intending to single out any company, even though it's container label may be theirs. In fact, this is a global problem. It's not one that any single company is theirs. So with that, I'd like to turn this over now to Dr. Sapna. Thank you.

Susan Winckler:

And Mike, just as we go to Dr. Amin, if I could get you to turn off your webcam, that may help us with the visual when you come back on. With that, Dr. Amin, would you pick up the microphone?

Sapna Amin:

Can you hear me?

Susan Winckler:

Yes, we can.

Sapna Amin:

Okay, wonderful. So thank you so much for this opportunity to discuss this important issue that was brought forth by investigational pharmacists around the country. And we look forward to sharing the information that has been correlated. My name is Sapna Amin and I am the Investigational Pharmacy Services manager at MD Anderson Cancer Center. I've been given the task to go through the labeling overview in terms of labels and concerning examples. We'll go through the awareness and timeline related to pharmacy practice and how this issue was brought forth to the FDA. We will also go through in summary some pharmacy practice recommendations for harmonization that came about through

various standards and guidelines that will include a discussion of the Hematology/Oncology Pharmacy Association Best Practice Standards, the ISMP two-part article, the Association of Dedicated Cancer Centers Investigational Subgroup recommendations, and also the American Society of Health-System Pharmacists guidelines for investigational agent management. And in short, we will have a short summary at the end.

Sapna Amin:

With that being said, where did this start off? So when we talk about labeling, it's not just a concern of what the actual label is, but it's also a concern of the lack of labeling for investigational products. And as Mike mentioned, all images and drug names are for illustration purposes only. So here, this is an example of a drug product that was sent for clinical trial at our site. And as you can tell, there was a complete lack of identifying labeling on the medication itself, which could lead to patient safety issues, let alone using this product in the clinical trial. As we go through other examples, here is an example where the drug is just labeled study drug. So here it doesn't have any other pieces of information that may be relevant related to the name medication shrank yet it only provides information on how to take the blue capsule and how to take the beige capsule, also known as study drug.

Sapna Amin:

Whereas you see here, and you will see other examples presented by Mr. Needleman, is kind of the heart of what the issue is and what the sites face on a daily basis when they are undergoing clinical trials and as new clinical trials start up at organizations. With that, when we look at labeling and labeling requirement overviews, there is an excellent article on the literature from Smith and Gick that had a graph related to what are the requirements for labeling overviews. And what it did demonstrate was that the requirements were not consistent across the board from the US, Japan, Canada, or the European Union and India. There were no set requirements related to harmonization in relation to what

drug labeling should look like. And perhaps that may be one aspect of the source of the issue of what products and how they come to different sites and how the products are actually labeled.

Sapna Amin:

When we talk about labeling issues and awareness timeline, I'll speak from a pharmacy and a clinical site perspective. This is a short history of the timeline of how this issue kind of came about on a national level. In 2014, the Hematology/Oncology Pharmacy Association came out with their investigational best practice standards document. And in that document was the first time that it touched upon drug labeling as a topic. In the fall of 2017, the Alliance of Dedicated Cancer Centers, which were nine NCI Comprehensive Cancer Centers, came up with a standard operating procedure document. And while that document was maintained internally at those sites, that document served as the basis for some site-based policies related to labeling.

Sapna Amin:

In 2018, this issue was also looked at by the ASHP, in terms of their management for investigational drug products related to labeling recommendations for best practice. And with that, the Institute of Safe Medication Practices came out with a two-part newsletter in 2018. That was the result of the clinical sites and the ADCC escalating it to the ISMP and the FDA based on the examples that were encountered at all of the sites. And moving forward, looking into the future, the NCCN investigational pharmacy subgroup will also have standards and recommendations that will come out for labeling that are in progress at this time. When we look at what the HOPA IDS labeling recommendation was at the time, and this was the first document that was published related to very specific pharmacy standards, it recommended that clinical sites follow state and federal guidelines related to compounding, dispensing and labeling.

Sapna Amin:

And that included being in compliance with USP 797 and Joint Commission Standards. And it also stated that sites should follow their local state board of pharmacy procedures related to labeling. Now that applies to when the labeling is going to the patient. However, one of the practice gaps identified was that there was not a specific labeling example of what kind of products when you are receiving them at the site, what that could look like. Moving on from there, the Alliance of Dedicated Cancer Centers were the nine centers that took this issue up in relation to identifying practice steps in investigational pharmacy.

Sapna Amin:

So the document was drafted to provide guidance and standardization to those pharmacies related to gaps that were identified. And one of those gaps was investigational container labeling. And as you see here, the names of the Comprehensive Cancer Centers that were part of this investigational pharmacy subgroup. In the subgroup document, it was a document that made specific recommendations on what would be mandatory in relation to acceptance at a product to a site. For example, if a site received the product that did not have the drug name, dosage, concentration, formulation, quantity, lot batch and storage information, those products would not be accepted for clinical trial use. It would be quarantined and the sponsor would be contacted. So that was the first in terms of sites creating internal policies to help mitigate risks related to investigational products.

Sapna Amin:

In relation to the ISMP articles and publication, the two-part article resulted in a lot of visibility surrounding the issue and also FDA engagement around the issue. Part one of the publication discussed product related issues and challenges, and part two of the publication discussed recommendations and mitigation strategies for clinical sites and manufacturers related to this issue who are also key

stakeholders in this process. Last but not least, with the ASHP recommendations, ASHP's guidelines for management and investigational products made very specific recommendations on labels, which included having drug names, strength, concentration, quantity, product and lot number, expiration and retest date.

Sapna Amin:

And this is a critical piece of information that has resulted in errors across the country with bottles having a lack of expiration date or the retest date information, not being sent to clinical sites or being sent to clinical sites after the drug has officially reached its retest or expiration date. Also having the clinical research protocol number on the labels itself, and then also for all medication that they adhere to the federal Poison Prevention Packaging Act and packaged in child resistant containers. With that and the pharmacy practice recommendations, what we do know in summary is that there is a lack of standardization on immediate container labeling. And there is a risk related to nude bottles and vials and this was a patient safety risk and for drug handling.

Sapna Amin:

The labeling we know varies among sponsors for IND trials versus investigator-initiated trials. What we also know is that there has been recommendations issued from various pharmacy stakeholder groups for standardization of this issue. The mitigation strategies have also been implemented at sites related to this issue due to the lack of standardization. One of those mitigation strategies is the minimum standards for drug acceptance at their institution as a policy or procedure. Other sites have also had to implement workarounds due to risk of inadequate labeling and that poses an incredible personnel burden and also risks to the site. There's a lack of uniform approaches at sites to being able to receive a product. So one site may receive it, another site may reject it, but those sites may never know because there's not a forum where that information is shared related to the same study.

Sapna Amin:

And also the introduction of third party labeling vendors that have also come into play in relation to facilitating some of these issues. What we do know is that there is a need for pharmacy, sponsors and regulatory collaboration for the standardization of guidance and heightened awareness of the issue. And with that, I will turn it over to my colleague, Mr. Needleman, who will go through a correlated information of labels from across the various clinical sites. And Dr. Feng will do a literature review of the topic. Thank you so much for the opportunity to present.

Richard Needleman:

Thank you, Sapna. The pictures of this presentation will present the issues we face at the clinical site level involving the investigational drug labels of containers and secondary packaging. These pictures are examples from my site, and from my ADCC colleagues at all their major cancer centers. The pictures will illustrate the medication safety challenges faced at the site level. I'll only present a limited number of examples due to time constraints. I want you to understand that these examples are not one-offs. The issues I will present are found through the majority of investigational drugs. Additionally, this isn't unique to one or two sponsors, but it's common with most. So why is this important?

Richard Needleman:

As we learned from commercial package label requirements and guidances, including critical information, label formatting and the use of technology has decreased the risk of medication errors, including selection errors. Selection error is having the pharmacist choose the incorrect container from storage. Simply put, pulling the wrong drug off the shelf. Remember selection errors, you're going to hear this often during my presentation. Without similar regulations established for investigational drugs, a wide variance of labels is found in practice. We believe that the enactment of similar guidelines or regulations to sponsors will provide standards that will eliminate these variabilities. The next few slides-

Susan Winckler:

Dr. Needleman, could you turn on your mic? Could you turn on your web camera for us?

Richard Needleman:

So it is on - nope. Thank you.

Susan Winckler:

There you go. Thanks.

Richard Needleman:

Thank you. The next few slides present the issues and challenges at the clinical site. The clinical site may be a pharmacy with Investigational Drug Services, or it may be a physician's office that doesn't even include pharmacy services. Here are the issues I will show you. I will show you the pictures of examples of each. Key information is lacking such as drug name, strength, concentration, lot number and doses. This picture is an example of a naked container that was sent to the site unlabeled. Another issue is too much information on the label that is extraneous. It makes it difficult to find critical information.

Richard Needleman:

Sometimes the drug name is hard to find with all the other information on the label. Another information is that the font size is too small to be legible. Also, multinational labels with languages other than English are found in practice. The sources of label information such as the pharmacy manual, investigator brochure and the protocol do not harmonize with the label information. The use of license plate naming nomenclature, for instance, BMS-123456 presents site challenges. The drug name may be similar to another drug or the protocol title. This picture contains two drugs, PF-04518600 and PF-05082566, which could be used concurrently in the same study.

PART 1 OF 5 ENDS [00:34:04]

Richard Needleman:

Large multi-arm studies are becoming more prevalent. Many of these studies may they have over 10 arms, which combine investigational drugs. Additionally, the drug name may be similar to the protocol name, which increases confusion. Labeling deficiencies increase the risk of product selection errors. Another issue is a change to the drug name. During the course of a drug's life, from phase one to phase three and sometimes four, the drug name may change multiple times. This may be either to sponsor acquisitions or the change from license plate to generic name. For example, PT2977 became MK-6482 and then became Belzutifan. Having multiple drug names in pharmacy electronic systems is a challenge, especially when labels don't match the current drug name.

Richard Needleman:

Other issues include the use of the key or legend on the label that lacks critical information. I'll talk more about this in the next slide. This picture is an example of a commercial drug versus investigational drug variances. Commercial blinatummomab is labeled as 35 micrograms per vial. While the investigational product is labeled as 38.5 micrograms per vial. The pharmacist who sent me this explained that both products are being used in her pharmacy at the same time.

Richard Needleman:

This is an example of the use of a key or a legend format. Instead of simply including the drug name, strength, dosage form, amount and lot, the label is formatted like a roadmap. The pharmacist is expected to know the value of each field. What is the drug name, quantity, lot number, expiration? What do the values mean? Is a lot number value four, five or six? Is value seven the expiration or manufacture date? What is value one and two? Is the drug a tablet, capsule, lozenge, or something else?

I may sound like a broken record, but product selection is critical in preventing errors. Having to refer to a legend without the drug name clearly visible, may increase the chance that an incorrect bottle or vial is chosen.

Richard Needleman:

This container was shipped to my site last month. The drug name on the label is LEE 011. The drug in the container is Ribociclib, which received FDA approval on March 13th, 2017. Four years after approval, the license plate name hasn't been updated on the label. Having multiple drug names for the same drug, especially outdated names in this example, present challenges at the site level with our electronic systems, when the same product has different nomenclature. Also, there are multiple undefined numeric values on this label. How does this site know which is the lot number? This is an example of two different strengths on the label. Is the drug one milligram or five milligrams?

Richard Needleman:

These pictures represent labels missing critical information. The picture on the left, the drug name, strength, dosage form and quantity are not included on the label. In the picture on the right, the label includes the concentration only, 25 milligrams per mL. Not included is the volume and the total amount of drug in the vial. Without this information how does the site know how much drug is in the vial? During drug preparation, pharmacy safety checks are compromised without this information. This vial is labeled as daratumumab 1800 milligrams SC. Since the concentration isn't included, how do I know what volume to withdraw to prepare the prescribed dose ? Is 1800 milligrams the entire vial or a portion of the vial? Additionally, the FDA allows an acceptable overfill during production. Will withdrawing the entire contents of the vial be an overdose? Also, SC is an unapproved abbreviation. The language should be subcutaneous. There isn't a clearly defined lot number on this label. Also, notice that this label clearly doesn't even fit the container.

Richard Needleman:

The ultimate in labeled deficiency is the container with no label. The only information given to the site is on the secondary packaging in this example. As for current regulations required for sterile preparation, secondary packaging is discarded prior to preparation. Without a container label, all pharmacies safety verification processes are compromised. These are pictures of labels missing critical information. In the bottom picture vials don't include a strength or concentration. The site was informed by the sponsor that the strength was defined by the lot number and to check a separate document with a list of lot numbers, to determine the strength. As with the previous example, pharmacy safety verification processes are compromised during dose preparation. Multinational studies are becoming more common. So, these may be [inaudible 00:39:45] to accrue in multiple countries concurrently. Frequently sites are presented with containers with multiple labels, each in a different language. Often the English version could be anywhere amongst the multiple labels, making it difficult to locate the information required for product selection. Additionally, for all medications, this is the label that the patient is given for at-home administration.

Richard Needleman:

This is a picture of a multinational label for an intravenous drug. It's difficult to find the critical information for sterile drug preparation or for product selection from storage. Again, this may compromise pharmacy safety verification processes. These are more examples of bottles that utilize legends and multinational labels. Similar issues exist with secondary packaging. In this example is the element by the arrow the drug or the protocol? Multiple elements are missing, including drug name, strength and storage conditions. This label also uses a key. Is the lot B or C? Is D the expiration or manufacture date? Similar to the naked vial example presented earlier, without a label, how do I know what the drug and study is contained in this packaging or how to store the drug? At my site, I prepare a

label with information as a workaround to prevent an error. Since most sites participate in multiple trials, whether it's 10 or hundreds, like at my site, or thousands, like at MD Anderson and Memorial Sloan Kettering, it's critical to have the necessary elements on secondary packaging labels.

Richard Needleman:

These three examples show the difference between commercial drug labels and investigational drug labels. The investigational drug labels are on the left, the commercial drug is on the right. While the drug name, strength and dosage form is clearly visible on the commercial label, the investigational labels are difficult to read and lack the same information. I want to commend pharma for not only following FDA regulations with commercial labels, but also going beyond the regulations to work with safety organizations, such as ISMP, to format labels in an effort to promote medication safety. Next two slides represent the elements on the label that our panel recommends. The first label is for an oral medication. The font size should be a minimum of eight point, preferably larger. Information should include drug name, strength, formulation, quantity per container, lot or batch number, storage requirements, expiration or retest date, CFR statement pertaining to investigational drugs, and sponsor.

Michael Cohen:

Well, not sure what happened to Rich. Why don't we pick up with Han's presentation now, which had one more slide left. So, we can get to that maybe at the end of the day, if necessary. Han and Jamie?

Han Feng:

Thanks, Mike. So, good afternoon, everyone. And thank you for this opportunity to present. We'll go through, and just building upon the conversations and the information that was previously presented by

our other panel members, and look more in depth into the literature that Dr. Dal Pan introduced during the beginning of this presentation. But ultimately what we want to do is think about what did we see today and what can we actually do moving forward to help [inaudible 00:43:59] to prevent these events from reaching to our patients, to make our work environment the safest possible to prevent these errors from ever reaching to our pharmacies. So, to start, let's look at some of the studies that are available. And what we will find is that there's very limited information that is captured in our literature right now. This is not a widely studied phenomenon, even though medication errors and medical errors are something that we've known for years and years, decades.

Han Feng:

So, the first study that we'll go over is from 2015. That was a national survey that was conducted looking specifically in one health system, which is the VA Healthcare System. The authors of the study, Cruz and Brown, looked to assess what is the perceived safety risk when it comes to managing, dispensing and handling of [inaudible 00:44:46] medications. The survey found that four out of five participants, 81%, indicated that they have a distinct concern with medication safety risks associated with just handling of investigational drugs. And to further compound that, 42% indicated that they felt that the sponsors may not be as receptive to reports of safety concerns by the pharmacist that are dealing and working through these events on a daily basis. Now what's notable about this particular study is that the authors characterize what are the actual specific concerns that not only their surveyors responded to, but also a common theme by which many of the various healthcare systems within the VA across the United States found to be common themes of concerns.

Han Feng:

Those include things like lack of differentiation between products, very common look-a-like, sound-a-like packaging, that contributes to potential mix-up and errors. A lack of expiration dating, which is a

very common thing that as a pharmacist we may be looking for as part of the complete medication process. And also things that are more towards the human factors component of looking at the font sizes and colors, to help make sure that it's as easy as possible to identify products that we have in our hands, as we've seen with some of the pictures that Dr. Needleman presented and also with modern healthcare processes in pharmacy, in particular, the availability of barcodes to help augment and facilitate a really streamlined process to identify and make sure errors do not happen. Next study a year later in 2016, looked at specifically a simulation-based learning program to see that if we were to place various pharmacy personnel within a training session, to see how prone were errors going to occur, looking specifically at investigational medications. Simulations, as you may know, is not very common in pharmacy practice as far as our training, our orientation processes.

Han Feng:

So, it's very unique to look specifically at a one set of medications. In this case, investigational agents. The authors found that a 12.5% error rate occurred within the simulation-based tools that are prone and within that actual simulation themselves, they conducted a 10 point risk scale for 10 items to determine which items are the most potential for risk. They stratified that based upon high-risk labeling concerns as well as low risk. And what the authors found was 17.1%. So, higher than that overall percentage with the high-risk labels found errors associated with the identification and dispensing ultimately of medications. The most common errors in the simulation were related to the dose, the trial name, which for lack of better description is essentially the identity of the medication itself and also confusion risks associated with mixing up various types of medication. Within those three components, this is a very core fundamental of what we do within pharmacy to make sure that the medication that we do dispense ultimately to the patient is the correct medication at the correct dose for the correct patient. In this case of study, ultimately this error would potentially propagate to a patient.

Han Feng:

The error rates, however, were not significantly affected by the occupational category of the actual individuals themselves or experience in clinical trials. So, when the simulation involved not only pharmacists, but pharmacy technicians with a variety of different years of experiences working not only as pharmacy staff members [inaudible 00:48:08], as well as new practitioners [inaudible 00:48:13], as well as incoming new pharmacists to students, the high-risk labels themselves found in the study resulted in significant, also longer response times, or basically identification of what the actual potential error is, or if there was an error to begin with. This leads to also a potential fatigue built into that workflow, where especially if a pharmacy is going through a lot of different medications at very quick pace, this lag unfortunately adds to some of that stress factor that we think with working in a pharmacy setting environment.

Han Feng:

And then lastly, most recently in 2019, there was a study that looked at evaluating the variability itself of drug labels, knowing that there is some commonalities as well as some differences in how we as pharmacy staff members interpret and review medication labels as a whole. We, as practitioners, would think mostly build upon our experiences in checking commercial products. So, how does that relate to when we have a variety of different investigational agents, but from varieties of sponsors, and as you saw in the previous pictures,, a variety of different ways in which the medications are labeled. 27 protocols or essentially 58 different labels were included in this 2019 study. The authors utilized an 87 item checklist to try to assess the content, the formatting, the readability, essentially what it defined as the labels themselves. What the authors found that for a median of 14, with a range of one to 69 pages, the medications themselves, the labels can vary greatly in terms of how much detail is in the label itself.

Han Feng:

We do not necessarily just be a single label with information that's readily available. There may be multiple pages of analysis that's necessary to go to one product. What the authors also found that there's a high discrepancy between the labeled information contained in an outer packaging when comparing to the individual bottles and labels. And we'll go into some details as to how that may happen, particularly as we move through some of the studies themselves. And also that approximately half of the labels, if we look back, this is the version 58 labels, so roughly 25 to 30 labels themselves had [inaudible 00:50:21] numbers that were determined to be difficult to find by a variety of different pharmacists, with a variety of experiences, meaning that not even with particular years of practice or years experienced working in the pharmacy and investigational pharmacy, would this information become a readily norm for our practices.

Han Feng:

More so within the study, they looked at the expiration dates that when they were presented within the labeling itself, they would use the different format. And this ties into the fact that we're now seeing a lot more international based studies in which the different countries may have different ways by which they present expiration dates or dates in general. The two most common format being the date first, the month and then the year. Whereas in the United States we very commonly see days presented as the month as a preceding value with the date and the year. Now, if we add into the complexity of different ways by which the manufacturers and sponsors may display this information, we can see that there's a very wide variety of different ways by which these numbers may be presented to us. And also without a standard, it can be very hard to interpret is this medication itself expired? Is this an actual date that's further down the line or is there additional information that's necessary for me to determine as a pharmacist, if this is something that we can indeed use?

Han Feng:

So, those are three studies that we have available to us to try to build the foundation by which we're looking at the challenges that we face. So, what can we actually do about it? But in order to really understand what is available to us in terms of tools and next steps, we have to look at the stages of clinical research as a whole, but we know to be a four phase approach in which the first three phases one, two and three are what we think of as the investigational portion of the medications lifecycle. Phase four comes after the drug approval process. And that's actually where we're going to start.

Han Feng:

Within phase four, we have something referred to as post-marketing surveillance that allows us to learn more about the medications in the real-life scenarios, in which they're being used out in the commercial setting. Information regarding adverse events, errors, potential errors, safety concerns can all be gathered and collated back into not only the manufacturer's information, but also for various sites through multiple different venues. The two that we're prominently aware of is the FDA's MedWatch program, as well as the Institute for Safe Medication Practices. What's most important about these post-marketing surveillance is that we have a shared learning opportunity. So, that information that one site experiences can be shared and learned by other institutions through these two venues. For instance, two years after FDA's safety communications, or ISMP's routine medication safety alerts, which encompasses not only the events that occur within acute care settings, but also in ambulatory and nursing.

Han Feng:

What's important about the shared learning opportunity is it gives us the opportunity to going back to Dr. Dal Pan’s presentation introduction. How do we prevent any potential errors from happening not only in one specific location, but throughout the country where patients may be impacted by the same type of event itself. Now, when we look at the investigational agents and going back to those first three

phases, what's important to consider is that the core of the information that we share throughout any of these phases involves not only the sponsors, but the primary or principal investigators associated with those specific studies, those specific protocols and that those specific sites. Information that is shared however can actually be diluted or mixed in a sense, because there's multiple phases involved in the site. Now, where there's multiple phases, there's actually potentially multiple different sponsors involved and multiple stakeholders when it comes to the management of the investigational agents itself.

Han Feng:

So as example, phase one may involve one specific manufacturer that is smaller in size, potentially with a chemical name associated with their actual investigational agent. As that moves forward into phase two there may be a different sponsor associated with the actual management of the investigations and the protocols, which may also impact not only a potential name change as the compound moves from one sponsor to another, but also additional information provided that will add to the complexity of information on not only the label, but also the agent itself. As we move into phase three now we may have either the same sponsors from a previous two phases or a whole different sponsor, a whole different stakeholder group that may have additional information, additional labeling. And also, when you look at the examples of medication names as Dr. Needleman presented, that name can actually change through all three phases. For now we have one agent that has three different names across three different phases and maybe all, but in one single label.

Han Feng:

So, what do we do about this information? For an Institute like ourselves as the National Institute of Health, we actually see all three phases. We have medications that we started with phase one, moved into phase two, and then ultimately into phase three. And for us and many other organizations, when

we do face these potential challenges or improvements and safety scenarios, we'll communicate with the sponsors, the PI, try to resolve the issue for that specific protocol for that specific medication within that specific instance in which may occur. Ideally this information will be carried forward throughout not only the various phases, very similar to phase four post-marketing surveillance through knowledge sharing opportunity. However, what we find is that that information often doesn't happen due to some of the complexity with changing sponsors, changing stakeholders, and as medications move through these various processes, the number of hands that may be involved in making sure that the medications get to where they need to go.

Han Feng:

What's important here is that as a result of this, the errors that we may have seen in one phase, may be propagated or repeated in other phases, particularly phase two. And then also when it goes to phase three, the things that we may have addressed in the previous two phases may be replicated again because we haven't fully addressed it as the medication moves into phase three. So, what can we actually do about it? What is the ultimate goal of something to prevent these events from happening? That is really looking back at the post-marketing surveillance and the idea of knowledge sharing. The idea that we can try to prevent errors from happening by learning from the events as they happen, sharing our information, sharing the preventative measures that we may take as any organization and allowing other institutes, other clinical study sites to learn what the scenarios were that propagated and resulted in a potential error or near miss or any adverse event so that we can prevent it from happening at the site.

Han Feng:

What this would entail is essentially a wave so that other investigators and study sites will be aware of the situation. A real-time manner in which we can have that information shared amongst a multitude of

different individuals, especially as we look at as the phase three studies in which there's a lot of different sites that are maybe participating in a lot of different pharmacies with individual workflows, and a variety of different amount of investigational agents at any particular pharmacy may have to manage, so that they can learn from us and learn from each other.

Han Feng:

This is all great information and a lot of details, but what is ultimately the key points of this presentation? Really investigation drug labeling needs to be something that's consistent. Now we talked about some kind of standardization, not only across the sponsors protocols and formulations, so that it's something we as pharmacists and pharmacy staff can easily interpret from one to another. The inconsistencies that we've seen through the examples that we've seen earlier today contribute to unsafe conditions and potential errors that may potentially compromise research integrity, and ultimately cause patient harm, which are both aspects that we do not want to happen when it comes to investigational agents.

Han Feng:

Individual sites should have the ability to collaborate with not only its sponsors to address the safety concerns, but that information while individuals who are at a site can actually serve as lessons learned for other areas, so that not only can we share it with different institutes, study sites and organizations, but also share across phases from one to three so that we can actually help prevent them from happening as we learn, not only about the medications themselves within the patient populations that we're trying to treat, but ultimately the modern aspect of how we get medications from the manufacturers to the dispensing processes when pharmacy, but ultimately to the patients themselves. There's a need ultimately to report medications in ways that ensures learning, but everyone that's involved in the medication process, not only for us within pharmacy, but also for physician colleagues,

primary investigators, but also ultimately in the nursing staff who may be administering these medications as well as the variety of sites that may be involved in this process.

Han Feng:

And with that, I'm going to turn it over back to Mike, concluding my part of the presentation. Mike?

Michael Cohen:

Thanks very much, Han, that was great. And thank you to all of the participants on panel number one. You know what? We do have time for some questions or a panel discussion at the end, but I'm wondering if we could get Rich Needleman slides back on the last two so he can complete his talk. Susan, are we able to do that? Oh, there we go. Great. Thank you.

Richard Needleman:

Thanks. I want to make sure there's adequate time for discussion. So I'll be brief. Had some technical difficulties. So this is our recommendation for the oral label. As you can see, the font size should be a minimum of eight point and bold lettering is preferred. There should be standard information included as mandatory on this label. The drug name, strength, formulation, quantity per container, lot or batch number, expiration or retest date, storage requirements and the CFR statement pertaining to investigational drugs and the sponsor.

Richard Needleman:

Another important issue is the utilization of technology. Barcoding is becoming more prevalent on commercial labels. The same FDA guidance language should be implemented with investigational drugs. The next slide shows what would be our recommendation for vial labels. The information is similar to the oral label except the strength and concentration should be included.

Richard Needleman:

So, to summarize my presentation, medication error prevention and patient safety is a shared responsibility. All participates involved with clinical trials have a role in this process, including industry, CRO's, regulatory agencies, and clinical sites. Currently site pharmacies are taking the primary responsibility in preventing untoward events by using various workarounds to prevent errors. Patient safety must not rely on workarounds. There needs to be uniform labeling regulation and guidances, so that clinical sites aren't the gatekeeper. Thank you.

Michael Cohen:

Thank you very much, Rich. Panelists for panel number one, can you unmute yourself? And I do have a couple of questions that I want to ask. First of all, in fact, let me start with Jamie. You're on the panel and you're one of the speakers. So, let's start with you. How do sites currently deal with the situation when you have deficient labels?

Jamie Brown:

Thank you, Mike. My name is Jamie Brown. I'm from the Durham VA Healthcare System. I think the first thing that our site does for every investigational drug study is to conduct a proactive risk assessment. And that includes a number of factors, including reviewing labeling and storage, [inaudible 01:02:18]. If we identify a deficiency, our site will develop a medication safety risk mitigation plan, and that can include a lot of different strategies, such as creating and adding auxiliary labeling for packaging and

critical information we see as[inaudible 01:02:39]. We have storage adjustments, we develop protocol specific training. We also report any safety concerns to the study sponsor. Typically we do that through the clinical research associates. That's a [inaudible 01:02:44].

Jamie Brown:

However, I think it's important to point out that the process that we use to mitigate risks are site specific and other sites might have different processes, or they might have no process at all. As an example, Dr. Amin spoke to quarantining medications that are missing specific information. And so I think you have to keep in mind that there are many clinical research sites out there that do not have a dedicated investigational pharmacy. There are also many out there that don't conduct a proactive risk assessment. So, the importance of investigational drug labeling standardization is that it removes the burden of mitigating the risks from the pharmacy and pharmacists and it improves medication safety universally, for all practice sites.

Michael Cohen:

Thanks Jamie. Anybody else want to respond to that?

Raymond Muller:

Yes, Mike, this is Ray. How are you?

Michael Cohen:

Good. I have a question for you. Go ahead.

Raymond Muller:

Yeah. So, just to add to what Jamie had said. I'd like to add a little bit of context from Memorial Sloan Kettering. So, there are about 175 FDA approved drugs for the treatment of cancer. At our site we have

triple that for investigational drugs for the treatment of cancer. And when you think about an investigational agent as Sapna and Rich has highlighted could be referred to by five or 10 or more names. It makes it an enormous challenge to mine medication-related events, such as adverse drug reactions. And we want to continually improve our process. So, for example, all of the panelists here all have electronic order entry and prescribing and drug administration.

Raymond Muller:

But I think a key point is that over 70% of all antineoplastic drugs are actually given in a physician private practice or community practice. And although there are certainly some really good ones, I'm not so sure they have a sophisticated redundant checks that we have here. So, I think the bottom line is that we need to standardize our practice. We really want investigational drug labeling to be as close as possible to what the FDA approved package looks like here. It has to have a drug name. It needs to have a strength. It needs to have a concentration and lot numbers. That should be the absolute bare minimum that we need. And then that will allow us to compare our event reporting among colleagues and peers. Now, what occurs is that, as Han says, it typically goes through the sponsors. And one drug could be evaluated by multiple sponsors.

Raymond Muller:

So, there's not this status sharing so that we can improve our patient's safety. Thank you.

Michael Cohen:

Great. Thank you too. And Ray, you can answer this, or any of the panelists. I'd like to clarify. I know you guys speak together with colleagues from around the country, through your organizations. You, what have the clinical trial sites been doing when an error is recognized? In other words, who is notified? Are

your IRB members made aware? Do you get back to the companies? It doesn't seem to be a standard way from what I'm hearing. So, I'd like you to answer that. Ray, you could start.

Richard Needleman:

But I could talk.

Michael Cohen:

Okay then.

Raymond Muller:

Go ahead, Rich.

Richard Needleman:

Yeah. I can speak to that. Cause we just had an example a couple of months ago of an outdated use of an expired product because there wasn't an expiration date on the label. So, we basically, because there isn’t a site [inaudible 01:07:20] process, or I don't know what's going on at other institutions, we kind of go by the seat of our pants. So, we reported it to the sponsor. We reported it to the IRB and then we informed the patient at the same time. But that was just intuitive. There isn't a good guidance out there for how to report these events.

Michael Cohen:

Somebody else want to respond to that? Han?

PART 2 OF 5 ENDS [01:08:04]

Han Feng:

Sure. And to kind of add to and building upon what we looked at, when we think of reporting we often think of something has happened and in some cases it's not necessarily an actual error may have occurred. But take an example of those unlabeled naked files that Rich really highlighted. Those are scenarios and necessarily may not be in a sense easily reported and recommended as to what can we do about it. So oftentimes at least for us here at the NIH, what we do is try to make adjustments work around the fence to try to prevent errors internally to us in a way that is trying to standardize our processes. I think what is the most challenging aspect of it is we may have multiple different medications, multiple institutes with a common theme related to medications that come to us, our investigation with that may not be labeled or the information is very difficult to discern for a variety of different reasons like we've seen in the Brown study.

Han Feng:

But then where does that go? Individual sponsors may not necessarily make some of the changes that will be ideal for us as an individual site, however, globally, that may be something that would benefit not only us, but a variety of different other sites as well.

Michael Cohen:

Thanks for that Han, any other responses there? Okay. Han, at the very end of your talk, you had some bullet points there and one of them was about learning from medication errors and that's something that we've certainly seen with reporting to FDA adverse event reporting system or reporting to ISMP or whatever patient safety organization is out there. They try to turn that information around. What kind of vision do you have for better communication about these issues that crop up during clinical trials and are related to a container label. Anybody have thoughts on that, how that might be done better than,

than what we're doing now, which is not really learning much and sharing that information, unfortunately, which is what we're all about. Anyone?

Raymond Muller:

Yes, Mike, well, most of us have very robust electronic reporting systems so that we can dissect what has gone wrong in which specific phase of the medication management process. I can tell you exactly my near miss event rate and an actual event rate for any class of drugs by day, by quarter, going back years. But with investigational drugs, we can't do that because the requirements are very unique per sponsor, so that it really is a major patient safety challenge that we can't grasp. And certainly I can't then share our lessons learned with our colleagues across the country. So again, we need to harmonize and standardize the labeling of investigational drugs to be as close as possible to current FDA approved labels.

Sapna Amin:

[crosstalk 01:11:13] I was going to say, as Ray mentioned, what that is a perfect example of what sites have done is sites have internal processes of how they track it, but there's not one way for site pharmacies to share this information in a transparent manner with everybody. And as one part out of this meeting, or a process could be some sort of standardization of reporting such that now that this issue is on a national platform, sites I believe will also be more comfortable to report this issue in that manner, rather than accepting the products active sites. There may be more of a stop the line at those institutions rather than forcing the workarounds to start a clinical study, and to ensure that those studies do start safely without the workarounds in place. So possibly having some sort of structured reporting system will be a benefit to this issue.

Michael Cohen:

Thank you Sapna. I'd say something does need to be done we can't keep going on like this, without communicating with one. And I have to tell you when you talk to people that are out there in clinical research, they're not really aware of the situation, as they should be. Well, anyway, we're just about out of time right now, and I am going to turn it over to the next panel. I'd like to thank each of you for great presentations and responses during the panel discussion.

Raymond Muller:

Thank you.

Sapna Amin:

Thank you

Han Feng:

Thank you.

Jamie Brown:

Thank you.

Susan Winckler:

And I echo that Mike. That was so helpful to ground us in what is happening in the clinical sites and what it is that we, that, that you are dealing with in navigating a number of different investigational drug label formats, and the reality of then sharing those and getting the right medication to patients.

Panel 2: Supplier/CRO Perspectives

Neil McCullough, PhD, IQVIA

Tony Heeley, BPharm, Parexel International

Our next panel, we are going to take it up a level. So we were just at the clinical sites, and now we are going to take it up a level and talk to folks who are in the clinical or contract research organization perspective. So I'm going to ask Tony Healy and Neil McCullough to come and put their webcams and their microphones on. And I'm going to turn to each of you for some opening remarks. And then we're going to have about a 45 minute conversation about your perspective. So Tony, if you would show your webcam, there we go. So Tony, you are coming to us as an Associate Director of Production Services for Parexel International and, and you bring a different perspective.

Susan Winckler:

So Tony open with a few remarks, as you think about the challenges, and we'll say opportunities for improvement in the container that goes on an investigation, the label, rather that goes on an investigational drug container. Tony, I can't quite hear you yet.

Susan Winckler:

You see the little green microphone at the top. Is it green there? We're still not hearing you, Tony. While, we address that, could I go to Neil first while we figure out your audio, Would that work? Great. Neil, are you ready to elevate? Excellent.

Neil McCullough:

Susan can you hear me?

Susan Winckler:

Yes, I can and let's give you a tiny bit of a proper introduction. So going first now, Dr. Neil McCullough, who is Senior Vice President for enterprise quality assurance at IQVIA. So everyone is internalized, Neil's going to go first and then we'll go to Tony, Neil.

Neil McCullough:

Ah, fantastic. Thank you very much, Susan, for the opportunity to talk today. The richness of the content of the first session made me realize I'm very pleased I'm not giving slides as most of them would be redundant. I have a lot of points I need to agree with on that. This really is a topic that's near and dear to my heart and then in fact, in many ways has shaped my career. I tend to get involved with companies quite often when they're experiencing difficulties in quality and compliance and certainly in the 2000s, I was involved with a major industry company, a sponsor company that I was working with that ran into difficulties where. because of the packaging, we overdosed vulnerable population, juveniles for many consecutive days, fortunately the investigational product was safe and the adverse events were very, very minor, but nonetheless, it was not something that you wanted to be in.

Neil McCullough:

And I remember sitting in front of FDA in front of the medical officer, expertly appointed who after several weeks of an ongoing investigation, asked me if I thought it was good enough. And it's one of those moments where the room goes silent. And I responded I just don't think it is. What's disappointing was that was almost a decade and a half ago. And looking at all of the examples that came up on panel one, we're still challenged in this area. And from a CRO perspective, we get to see an awful lot of volume in the middle. So we get to see the sites and the pharmacy side, as well as the sponsor side. Now challenges are compounded by the variety in which we deal with. I saw the sites really to that degree.

Neil McCullough:

I see errors still on secondary packaging causing problems in supply chain, not to mention the primary packaging at us that we've all seen. And it's interesting as in the global trials that I'm associated with, and then the hundreds, the variety of standards that we try to manage and harmonize to. And so one of the questions that was asked of me for this session was is there an ask here? And I think there was an ask, that was clearly articulated by the previous speakers, that there is a need to harmonize here. Some of the literature that was referenced, I've reviewed myself and to say that it's really likely that a third of the mistakes that come from not being able to read the packaging correctly will be passed on to the patients, regardless of the effect of experience of the investigative site.

Neil McCullough:

It makes little difference in these scenarios other than with speed, it's a scary, it's a scary thought. And as I surveyed my internal teams here in IQVIA, we have the same asks come up. Can FDA help us come together here, and issue some harmonized guidance. I did get a strong feedback that Annex 13 was very helpful in most cases. Certainly the latest guidance in Singapore, which came out I think only in... I think it was March from NHSA. That was very helpful with giving examples and generally well interpreted and then being put together with a lot of input and so I come here with the same asks that were on the previous panel, can we harmonize? Can we get those better standards in. And for me, I really feel this is a place where the use of technology has to advance us with the best intentions over

Neil McCullough:

The last decade, we haven't really improved the scenario. In fact, the complexity of clinical trials is probably making this harder for everyone involved, as a CRO sitting in the middle of particularly of one like IQVIA which also works closely in the hands of affiliate investigative sites. Not only would you see it sometimes a challenge in interpreting standards from given to us from the sponsor companies we work

with. Sometimes requiring pushback, for instance, as trials move from local to global status, often requiring only local language and not understanding perhaps the complexity of needing more languages involved. Right away through to passing the safely on to the sites. And then the last year the rise of virtual trials, which I see to be a continuing force in the future. Where we have home dosing by subjects themselves, in some cases. This presents an enormous challenge to oversee the complexity and reduce the areas, puts a strain on the monitoring,

Neil McCullough:

, CRO's involved in this for every trial, as well as the site staff, the nurses, in fact, the patients themselves. So for me I have had an internal ask come through me and that is can we also consider collectively the force of pushing technology forward which I have to say seems to tend to suffer from a bias of extremely low risk tolerance compared to the errors we culturally accept as ourselves as human beings. The technology almost has to be perfect before we feel comfortable with it being validated and put into clinical trials scenarios. So those are the key points I really wanted to raise today in that that technology it's not just about, I love the knowledge sharing platforms, but it's also about the investment in whether labels can be used electronically to provide more detailed information through the use of mobile apps, whether we can use smart or a pill technology on the dosing containers themselves. And while these seem possible, they also come with a cost, and sometimes with the speed to get them through a huge barrier to get over in terms of technology validation.

Neil McCullough:

With our regulatory partners around the world. And I think we're in a situation here where there's a clear need, and I think we have an opportunity to address it.

Susan Winckler:

Neil, thank you so much. And you teed up a couple of threads that we're going to come back to with both of you and Tony thinking about that sense of standardization or harmonization, the technology piece. And then I would love to talk about one of the things that we know is happening as a result of COVID-19 is more of the democratization of clinical trials, whether it be the virtual trials that you mentioned, or the need to take to expand the clinical research enterprise so that we're taking clinical trials to the communities that we know we need to reach in order to increase the diversity of trials. So I want us to come, come back to that. But Tony, I think we have resolved the audio visual issues. I'm sorry that you were the one who got challenged with them. We know there will always be something like that in one of these meetings. So Tony, may I ask you to put your camera and microphone back on let's test that audio.

Tony Heeley:

Hopefully its now working.

Susan Winckler:

It is, go ahead, Tony. We'd love to hear some opening remarks from you.

Tony Heeley:

Yeah. Similar to Neil, I would echo a lot of the things that we heard in panel 1. Some of the things that Richard said though go against. where we're coming from this from the industry because of the constraints that we are under. And so I think we want to start by saying what is the process that [inaudible 01:24:35]. There's a great regulatory input to the label design, maybe from an international perspective, the QPS wants to get involved as well because they will be releasing the material. So we got this drive from regulatory to apply all the requirements of Annex 13 as it currently is, and India in

particular [inaudible 01:25:02] even more information on that. We then have the CNC team who is developing the product, getting involved. And it's important that we have those two groups communicating so that as the product is developed through its life cycle, we don't hit the problems where the label says capsules because that's what regulatory is probably using.

Tony Heeley:

But formulation moved on to tablets and that's what we're going to be using on a late phase study. We didn't bring in the clinical supply group that was trying to implement all the things that has been collected, and come up with the packaging the patients can actually use at the end of the day. The communication between those three groups, and then there is the CRO bringing in the sponsors. It's very important to make sure that we get things right the first time. So the things that Richard was saying in terms of 8 points font is [inaudible 01:26:03].

Tony Heeley:

Today in fact one of my team comes to me and says we need so much information on this label and the container is so small we may need to go down to 5 points, and we know that that is very small, especially with some of the technology, it's impossible with some of the technologies that we have. The commercial products tend to deliver the printing using lithography whereas in clinical supplies, it tends to be filled faster. You cannot get small font sizes with that technology. And we really look to stay within seven points, maybe six points, if we can manage it. But obviously there is a disconnect between ourselves and the regulators, and decide as to what they would really like to see. But I do appreciate the regulatory precedent that we are on the clinical supplies, can lead to poor label design. Fonts are too small generally, hard to find information, and patients will struggle to figure out the information.

Tony Heeley:

And then all throughout the supply chain, the issue with font size has come into play. My team who were assembling the product in our [inaudible 01:27:27] if they can't read the information on the label, they cannot be certain that they've assembled the material correctly. If the numbers are too low, too small then we cannot pick and pack and ship the materials correctly and the last thing that we want to do is have a patient two days away from treatment, and we ship the wrong container. And then finally at the site, I appreciate that, if you can't read those pick numbers, you can't dispense correctly.

Tony Heeley:

So we have to really think and again my team will be looking at how can we design the labels appropriately. And poor label design, and poor positioning of information can make it impossible to utilize.. So I'd like to see the label text grouped in three sections. So we have the information that what I will call [inaudible 01:28:20] what managers need access to. Can you see the protocol number, can you see the kit number, can you see the batch number and third, the use. That's important information for them. Then we have the information that the patient needs. There's a block of directions, any processes that we need to follow and then the storage conditions.. And then everything else is really a regular true requirement, and it's there because we're told to put it on the label. So keep out of reach of children, the clinical problems, like the product information to a certain extent, and the name and address of the sponsor too. If you think about grouping that information, then we can have labels that are much more easy to utilize by the supply chain and by the patient.

Tony Heeley:

One of the aspects that Richard mentioned was the use of code numbers and legends and that's something that because of the regulations we actively look at within the supply chain. If we have a very small container and it goes to many countries, then creating the book of labels with maybe 25 or up to

40 patients information, it's going to be very difficult to place that on a small container. So the idea is to limit the information that we need on that smaller container and then cross reference that into the secondary packaging. But obviously that's not working for the sites and that's really something I need to take away with[inaudible 01:30:04] labels for this in my experience. And that becoming the norm [inaudible 01:30:17] But these can actually add complexity and difficulty to the patients and the investigators, in my experience, I tried to limit the number of book of labels that I use. An example, I have an oral powder that needed to go to several countries. It would have increased the pack time tremendously, which was increased shipping costs. It would have made it difficult to open for the patient.

Tony Heeley:

I'm seeing lots of strange devices at the moment. Where once the patient has injected themselves, the needle is retracted back into the body. [inaudible 01:31:04] label would actually hinder the mechanism. So we were looking at different technologies for labels there but again it limits the amount of information we can place on the label. And then in a previous life we did studies in arthritis with auto-injectors. We have to put the proper label on the auto-injector. And at that point, the patient couldn't utilize the device. So we designed the label with a perforation so the patient could peel the label off immediately and the label was never read. We would put the label onto the container just because of the regulatory focus. Would have been the greatest [inaudible] against using booklet labels came from the Danish [inaudible] Inspectorate, about eight years ago, they were going into sites and seeing that.

Tony Heeley:

I think it was so much to an 89% of booklet labels were unopened on returned medications. Well, if that's the case, the patient is not receiving the information that they need. They're not see the directions, they're not seeing storage conditions. So those things can lead to errors in medication.

Tony Heeley:

So where does the industry try to move? We tried to move to... again, legends and graphics.

Tony Heeley:

There are standard graphics, I can go into a shop and I can buy a shirt. And I immediately know the conditions that I have wash it, store it, iron it. But we don't have standardized symbology for pharmaceuticals for where we store it, at what temperature, keep out of reach of children. But I think there's a lot opportunity there to harmonize. And then I think one of the biggest concerns that are going to hit, certainly from a European perspective, moving forward, is the new Annex 6 when it arrives and we're increasing the diversion of labeling and labeling requirements. We will need to add an expiration date to the smallest container. And I think that expiration date on the smallest containers will result in needing to manipulate containers downstream to put that expiration date. And we can say with small labels, there is no room to do that. We will need to work on containers.

Tony Heeley:

If we open the containers what are the effects on blinds and the material, what are the effect on the temperature conditions, what are the effects on light sensitivity. So these divergences will really hinder how we compacted this material moving forward. And I think that was about it, but definitely harmonization has got to be the way to go forward so that we can standardize our expectations and standardize our packaging, thank you.

Susan Winckler:

So, Tony, I do know that I say that's all between the content that both you and Neil presented. Could you join us back on camera and audio and let's dig into a couple of these and have a bit more of a conversation for a bit. You ended Tony on harmonization, but with a really interesting, at least

interesting expansion there of both regulatory requirement harmonization, and then you appeared to speak to what I would call a bit of a sub regulatory or an extra regulatory. So now outside of regulatory, harmonization on symbology and some of those other components. So Neil and Tony, let's talk a little bit more about this because I, my sense is most folks, when you hear harmonization think regulatory harmonization, and you've teed up a really interesting concept here that is outside of regulatory harmonization. So let's talk a bit about that. So, Tony, you raised it, Neil, what do you think about it?

Neil McCullough:

Yeah, I think it's a very strong point to raise and it hits on something that's a little sensitive, which is actually bringing intense regulation in this area may not be the way to go forward. I always assumed that one of the key things that was really beneficial around FDA is that there was relatively light approach from a regulatory perspective, which lends to us to give innovation and flexibility. Unfortunately, the downside of that can result in the lowest standard approach as well. But I think to, to, to try and regulate down to a finite detail would, in some cases, grind the process of the label and then the supply chain and changes within it to a halt. So I like the idea of a community behind this, that Tony's really starting to speak to where we could agree on best standards here of harmonization and graphics is an extremely interesting way to do it.

Neil McCullough:

There are examples, of graphical information being able to convey just as much as a written text, SOP or even a label. So I think we've under explored it. And not only that again, you can build in information to graphics as well, but could be drawn out electronically. So I think this is an important point. Again I'm very conscious that I don't want to be pushing for enormous regulation. I think that puts too much of the burden on the regulators. And paints ourselves into a corner where we can't innovate.

Tony Heeley:

I agree. [inaudible 01:37:41] At the moment we, we ended with all the regulatory requirements on all the labels and that just drives poor label design. And then all the errors that the first panel said. We need to think about this . [inaudible 01:38:08] set, which really are critical

Neil McCullough:

It strikes me that there's an opportunity here to engage more with patients. You know, I see a little bit, the analogy here between talking about clinical trial recruitment and engagement or retention 15 years ago, when we had all of the experts in the room from investigator sites, key opinion leaders, pharmaceutical companies, med tech, but we didn't really engage the patient. Then over the last decade, particularly, we've learned an awful lot from the patients about how they would like to be engaged on clinical trials. I think it's a good question to open up to them with regards to labeling, particularly in future horizons where a patient may be more involved with the level than they have been in the past. So again I'm very keen to hear their opinions, even though I think collectively the previous panel has demonstrated adequately just how much information we have around the issue. I think getting to the solution is where patients can be very helpful.

Susan Winckler:

And certainly, so let's use that to talk a little bit about... It is very important in particular as we think about some of that alignment on symbology or a harmonized symbol structure. But also as we look at what each of you mentioned, which is the expansion of the clinical research enterprise in efforts to improve the equity of clinical trials. And so that we have more diverse populations participating in clinical trials, at least in the United States, that's like the solutions involve, expanding where we do clinical trials.

Susan Winckler:

And so our panel one in five years might have many other types of folks participating as well as the expansion of virtual trials and things going directly to patients. So as you think about you're in the middle, between the clinical trial sites and the product sponsor and the expansion of that clinical research enterprise, what helps you kind of the most, or what might, what might concern you the most about new folks in the clinical research enterprise and in thinking about this challenge, and then how does it underscore that this is the right time to start to improve some of these changes?

Susan Winckler:

Because we are going to expand the research enterprise.

Tony Heeley:

I agree that this is the right time. The availability of technology now can really help, the way the mobile phone has expanded over the last few years. Means there's probably critical mass there to be able to use that. But one thing that I forgot to mention was the industry tend to use technology to actually go against some of the requirements which it was specifying, so we would say ok let's use technology so we don't need to put expiration date on our containers, because our [inaudible 01:41:50]. But then we don't want to go down that route, we still want it on the label. We've got to be careful about how we apply technology, but I have seen some fantastic ideas previously with one bio company.

PART 3 OF 5 ENDS [01:42:04]

Tony Heeley:

If you took a video of the carton, you saw an augmented reality of the carton opening and the vial coming out, so that the investigator could see exactly what he had to do with that container. So, a

picture or a video is worth a thousand words. So, there are some really good opportunities to use technology as long as we apply it correctly.

Neil McCullough:

Yeah, I agree. When one considers the expansion, Susan, that you're referring to, the challenge becomes even more broader than it is right now, and to me, I don't think that bringing more label requirements, which we're just about to do, to the forefront, is going to help at all. In fact, the practicalities that Tony was talking to, particularly that hamper devices that can't be used. One of the problems we have perennially, is that vials are so small, we can't practically label them. So, I like the concept put forth by Tony, where you segregate two batches of information; one that's pertinent to the safety of subjects, and the other to describing what the actual drug product is, as well as getting towards using technology in perhaps smaller steps.

Neil McCullough:

First, we're getting it to a ... you can visualize through technology a label that looks closer to a commercial label. The [inaudible 01:43:51] is so better designed, it's so much easier to deal with and so easy to receive, that I think if we move slowly in that way, we could get there. I think as the barriers to entry from a cost perspective start to reduce, then the example that Tony was citing with virtual technologies. And I have to say, the cellphone, or the mobile app on some sort of platform is going to play a very large part in the future, because it is so easy to adopt.

Neil McCullough:

So, I would really be in favor of pushing those things, but I don't think we need to be overly exotic right out of the gate to see enormous progress.

Tony Heeley:

I don't think we're going to lose that paper label for any time soon. There's no way. But it's quite disappointing to me to see that we're still making the same mistakes and making two protocols, and two separate products looking very similar, and just a little bit of color to differentiate protocol A and protocol B, can make a major difference to the sites and how they handle the medication.

Susan Winckler:

And so, to that end ... So, I hear you both saying not a new problem, definitely time for an intervention, time for ... It need not be a wholesale fix. We should aspire to dramatic improvements, but there are also some small steps that can be taken; perhaps those regulatory and non-regulatory, to improve the situation. Is that a fair summary?

Tony Heeley:

Mm-hmm (affirmative).

Neil McCullough:

Yeah. It's an excellent summary. It's a case of not letting perfect be the enemy of good here. I was looking at IRT systems, which have the ability to build in a lot of extra checks and controls and make it easier, then just little changes can go a long way. So, I think what we can't do is just continue down the path of let's try and manage. Let's have sophisticated sites with checklists. I think as we bring more and

more diverse scenarios into the clinical trial, we're going to be ... I think the challenge is there for us right now and we need to rise to it.

Susan Winckler:

So, on that, I want to pull a thread that we heard from the sites, was a bit of, we learn a lot, but then we perhaps don't have the opportunity to share a lot. So, if we think about it, we have folks in sites learning the same lessons over and over, instead of saying, "Oh, we saw that."

Susan Winckler:

How do you hear about challenges from sites, and is there an opportunity here to do more of that sharing? Or is this the type of thing that we just have to learn over and over again by different participants?

Tony Heeley:

I can say, from experience, I don't think I have ever had any official feedback to say, "You've done something wrong," or, "This wasn't correct." I'm part of the industry organization in the U.K, and there's an equivalent organization on the NHS, so, from the hospital pharmacy side, and we work together. So, we have regular interaction, we ... Well, pre-COVID, we had meetings twice a year where we would come and discuss these sorts of things. All unofficial, really. Nothing official that I've seen myself.

Neil McCullough:

I think this is a place we can start right away. So, this idea of having a knowledge center, I think, would be a great solution. In fact, it's one of the key challenges I find presently in trying to employ quality assurance models in large companies. We go through perpetual isolated problems and find solutions to them. Sometimes we're really good and we write those solutions down. It's like lessons written. But

then that still doesn't go anywhere except for locally. So, to bring a knowledge sharing lessons learned true forum together with the key stakeholders that we know, I think will be a fantastic start. It doesn't require to be high-tech. And I've seen tremendous other areas, often around therapeutic area groups of patients, organizing themselves to some degree, which has really been exemplary for us in the industry.

Neil McCullough:

So, I think it's been proven and can be done. And to answer, do things come to me? They come to me because of my role as the head of QA, typically not as good news, but I do have to put models in to extract that from sites, or from the pharmacists, or from the supply chain organization, or regulatory affairs, otherwise there's just no easy mechanism for that to funnel. But once you have it, it's very important to categorize it in a way that one can make decisions from. And I think it's really important to try and address ... there's a lot of noise there, and really, to try and get the key decisions about what will improve the situation, is paramount.

Neil McCullough:

I would think that would be an excellent course of action to begin with.

Susan Winckler:

It's always good when we can say, "Okay. Here is something that could be done that we think would make a difference." And if you sit in between the sites who are implementing and the sponsors who are designing and trying to navigate size of the vial or the product and all of the information that you need to put on it, helpful as you sit in between and saying, "Yes. This type of sharing might ... might be of interest, and help us take step forward in addressing the challenges."

Susan Winckler:

With that, we have just a couple of minutes left for the two of you to have the stage and the microphone. So, I want you to think about what else is it that you want to share as we're thinking about how to address this challenge. Is there something that we haven't talked about as a problem? Something that you want to offer as a solution? Or something that you want to underscore as a solution? Or just something that you wished you'd said when we started this conversation just about 40 minutes ago?

Susan Winckler:

Tony, you didn't get to go first. I'm going to go to you first, and then I'll close off with [crosstalk 01:51:35you Neil.

Tony Heeley:

Again, I think it just comes down to the harmonization and standardization. The new [approaches that, certainly I'm dealing with, that they understand what the concepts are. A concept that may have agreed with Europe or the U.S, [inaudible 01:51:59] down to Latin America and it's interpreted slightly differently [inaudible 01:52:03] there. Regulations to[inaudible 01:52:06], "No, you can't do that." Which means we then need to go ... we need to cycle back to all the other countries and say, "Well, we need to rethink now what we're going to do."

Tony Heeley:

So, just that global consideration of everything.

Susan Winckler:

So, Tony, you're helping remind us that new requirements may be helpful, but new competing requirements head us in the wrong direction.

Tony Heeley:

Correct. Definitely.

Susan Winckler:

All right.

Susan Winckler:

Neil, to you.

Neil McCullough:

So, there are four things, and I've just written them down so that I remember four things, and I will repeat some of Tony's. Firstly, I think harmonization. Without all the burdening, the regulatory authorities with requests for detailed regulation. But I think harmonization and the standards would be tremendously helpful.

Neil McCullough:

The second thing. A forum for knowledge sharing around label best practices, would be my second ask.

Neil McCullough:

My third, related to that, is the engagement with patients to give them a voice in this conversation.

Neil McCullough:

And fourthly, I think, as we explore technology in the very near future, probably, to be open to that and not have a bias that is has to be perfect while we live with human error every day to a much greater degree.

Neil McCullough:

So, my intent there is to encourage innovation and progress, otherwise I fear we may be having this open panel again in 10 years time.

Susan Winckler:

Neil, I was talking with a whole set of communicators earlier today, and they said, "When you number it and then you outline it, we can all internalize it better." So, thank you for helping Tony and I organize better. Tony, I'm going to take that you had great thoughts, and Neil, categorized them for us, which was really helpful.

Susan Winckler:

Tony and Neil, thank you for joining our conversation today and helping us with that middle section between the clinical trial sites and the drug sponsors. Really appreciate your contributions, and thank you again for joining us.

Tony Heeley:

Thank you.

Neil McCullough:

It was a pleasure. Thank you.

Tony Heeley:

[inaudible 01:54:38].

Panel 3: Industry (Sponsor) Perspectives

James Duhig, PhD, AbbVie

Alexander Mills, Merck

Susan Winckler:

And with that, we're going to turn to our third and final panel of today. Again, we are reconvening tomorrow, but we have one more session this afternoon. And so, I'm going to ask our colleagues to, Dr. Mills and Dr. Duhig, if you would come on camera, as well as unmute. Let's make sure ... This is the virtual equivalent of you walking to the stage so that we have you joining us. There we go. Jay, we have you joining us, and then we'll have Alex pick up after that. There we go. Double check there and make sure that we're all set.

Susan Winckler:

So, this panel, we're going to talk about things from the product sponsor perspective. You generate the information, the products that are being used and the labels that the clinical trial sites are navigating, and that the CROs, who we just talked to are helping to work with. And as trial sponsors, it may feel sometimes, I guess, like it all comes down to you, and you want your products to be used correctly so that you can get to the assessment results of the clinical research to see whether or not those interventions work, and so, there are a number of different things that you're navigating.

Susan Winckler:

So, I'm going to open and say, tell us a bit about how you balance the container labeling and error prevention, and what it makes you think about when you hear the input from the clinical trial sites, as

well as the CROs, and bring your perspective to the table. So, I want to confirm here. I'm going to turn first to Alex. And you are joining us from - I was going to name where in the world you are joining us from, and then I realized that I don't have that. But you are the Director of Combination Products, Commercialization for the manufacturing division at Merck.

Susan Winckler:

And so, Alex, where in the world do we find you today?

Alexander Mills:

Susan, good afternoon. Can you hear me?

Susan Winckler:

Yes, I can.

Alexander Mills:

Great. Great. I'm joining from Philadelphia. Usually I'm based in Merck's west point manufacturing site, but of course, for the last year we've been working remotely. Good afternoon the to the meeting organizers and attendees. I'm Alexander Mills. I lead the combination product commercialization function in Merck's manufacturing division. My team's responsible for later stage commercialization of Merck's drug device combination products that incorporate commercially available medical devices. We also support medication error assessment and usability engineering activities across all the product modalities as needed.

Alexander Mills:

Through experience with human factors and risk management, I've developed a passion for patient empathy, health literacy, and building patient and user focus into our designs. While most of our work,

of course, is aimed at supporting the commercial image of the product, we recognize and understand the clinical processes can yield important insight into product usability and essential medication errors that apply all the way across the life cycle. This principle holds true for other elements of clinical product labeling too, which are very interesting to me; such as the other labeling elements, packaging designs, instructions for use, primary container selection, as well as product presentation and carton design.

Alexander Mills:

So, Susan, I have prepared some answers to the questions that were shared in advance. Is there a specific question that you want to start with, or should Jay and I do introductions and then move through those?

Susan Winckler:

Sorry, Alex. I'm coming back online. If you want to do just a bit of an introduction and if you want to make sure that we hear what's the one thing that you want us to hear from you on this topic, and then we'll go through some of those questions.

Alexander Mills:

Sure. Sure. So, if I had to choose one thing, one of the things that I'll say that I have particular experience in my field. Now, of course, since this is a big company and the scope of the discussion today crosses many functions, I have to thank my colleagues that I interviewed to prepare for this. But specifically, one of the things that I get engaged with is a medication error risk assessment framework that we have developed to analyze the impact of potential medication errors that we identify based on product characteristics, which can include primary container labeling, but also extends to other packaging and user interface elements.

Alexander Mills:

The approach that I'm talking about, leverages the established risk management techniques, as well as the FDA guidance Safety Considerations for Product Design to Minimize Medication Errors, from 2016, which we believe is a very important set of principles and set of approaches that we realize has gained, or pointed more towards commercial product design, but very important, I think, in a lot of the cases that I'm seeing in the session today. We've so far used this approach across several stages of project development and it established a consistent approach to assessing product and user attributes against the FDA guidance, as well as international standards and guidances pertaining to medication errors.

Alexander Mills:

I think, very importantly, this approach provides a risk management approach, provides a framework for critical thinking, for identification of medication errors, as well as identifying appropriate risk minimization measures and verifying their effectiveness on an ongoing basis.

Alexander Mills:

So, this is one of my primary contributions to this area here. Of course, the labeling generation supply chain of custody, as well as, there's quality functions in there as well, but really, what I'd like to highlight to FDA and to our partners in the clinical investigation process is that frameworks for identifying medication errors, doing the critical thinking to assess and mitigate them, are extremely important and robust, and should be sought after and applied on a case-by-case basis.

Susan Winckler:

Alex, that's really helpful, in helping us underscore. So, you're reminding us that this is part of the broader enterprise and work that you're undertaking. And so, it seems, then, that conversations like this can be helpful in feeding into that, as well as leading to future interventions.

Susan Winckler:

With that, I am going to turn it to Jay, for him to make a few opening remarks, and then the three of us will come back for a conversation. So, Dr. Duhig, thank you for joining us and coming up to the virtual stage. Let's double check your AV, right, as we get started.

Jay Duhig:

Okay. We okay?

Susan Winckler:

Yes, we are. Thank you for joining us from AbbVie, where you are Director of Patient Integration for the International Pharmacovigilance Network.

Susan Winckler:

So, do some of that same thing. What are your initial thoughts that we should open this conversation as we think about the regulated industry or sponsor perspective?

Jay Duhig:

Well, first, thank you for getting me out of the house. I've been working from home in the office for the better part of a year. So, this is a good reason to come in so we could use a virtual backdrop and nobody wanted to see my unfinished basement I've been working out of. But greatly appreciate the discussion

today, the involvement, and that this is being approached very collaboratively. I think that that's one of the biggest take-aways.

Jay Duhig:

So, my name is Jay Duhig, within AbbVie's Pharmacovigilance and Patient Safety group. I have a small group of behavioral scientists that are really focused on applying best practices of health literacy, of human factors, very much consistent with, as Alex described, looking at understanding more of the why and the how when people are potentially injured or at risk with the use of our products, and hopefully proactively preventing those situations from occurring using the different behavioral sciences.

Jay Duhig:

So, we've done that over the past several years, and it really has been focused not only in working across the traditional lanes of pharmacovigilance; case reporting, data collection, working within our clinical trial patient safety teams that are responsible for coding different events, but also more broadly across AbbVie, including the medical affairs and other organizations responsible ,commercial, that are responsible for patient and physician education activities. And then, very much so with external partners, including all of yourselves.

Jay Duhig:

So, Susan, thank you to the Reagan-Udall Foundation, and to the FDA for hosting this meeting. From Mike Cohen’s leadership with ISMP. The work and the leadership of FDA has been really important, and I think that's the main point that I'm left with to kick off at their hearing discussions that I'd like to represent, is that industry is definitely wanting and willing to work to improve this. Now, there I am speaking as one person speaking for several hundred thousand people globally in the pharmaceutical

industry. So, not to exceed my scope too much, but I feel really comfortable doing it, simply because this makes a lot of sense what's being proposed in the reduction of medication errors.

Jay Duhig:

Three reasons within that, that I'd like to delineate from what we've talked about. First, within labeling design practices, extremely gratifying for me to hear the recognition and the identification, again, of the work that so many of you have led and built across the pharmaceutical industry, and the work done within patient safety in terms of human factors, labeling best practices, what's been done and how that's come about over, what, the past 12, 13 years in particular. Not to say it wasn't done previously, but to me, the model that FDA and other global health authorities have really embraced of the idea of focusing in on, again, as Alex said, usability research, application of best practices, as Mike and others on the first panel described, elimination and reduction of medication errors through crunching the data, through understanding, "Hey, this is what's more likely to lead to harm, to a hazardous scenario, and versus what's less likely." And then, really judiciously and systematically applying those principles.

Jay Duhig:

That very much works. And I'll take just a moment as we get into this and think about the conversation that I'm hearing, is taking that type of mindset, that type of behavior, and now, let's go from the post market and work there, move it into the clinical trial discussion. There's a lot of things that, again, makes sense for me with that. And I'll briefly contrast that versus a different model of saying, what if the regulatory standards or the ideas had been around coming out of from what we were going from having a couple of hundred products with REMS, to instead saying, let's take a different approach of what can be done through design.

Jay Duhig:

If the approach had been looking for multiple studies to support every new molecular entity, every new drug product or submission that includes patient reported outcomes, and multiyear usability studies, where we're really only focused on getting that level of inferential statistical differences between safe and unsafe. Well, that's really different, right? That would be a standard of evidence that would really threaten the idea of meeting unmet needs, and we'd be in competition. That wasn't what was done and I think that, again, that post marketing design and development model is something that's working, and continuing for all the partners to grow.

Jay Duhig:

So, that would be one of the first things of why I think this is a good idea, in that industry will be very receptive to it.

Jay Duhig:

The second part of that is that reducing med errors is a good idea. I mean, that works. There's nothing about having medication errors within clinical trials that's official, or that would make the companies in general, industry, unwilling to move this forward and to advance this issue. Again, we're in a ... I see this as a bit of a fact-finding, where we're opening up this discussion of what comes next, and of problem solving. I do feel that that's important to remark. Med errors are a threat to patient safety, of course. Medication errors, as was briefly discussed in the last panel, also introduce noise into the data. That means, trials in general would take longer and cost more money.

Jay Duhig:

And then, reducing med errors to that end is cost effective. So, we recently have been expanding, and my team in particular, what we're doing around clinical trial diversity, and how to expand access and

knowledge within traditionally marginalized communities about participating in clinical research; what that looks like, having that level of outreach at the community level. So, if we're doing a study and have gained that degree of participation from traditionally marginalized communities, and then lose people because of medication errors, people that no longer will want to be part of the study, well that's a tremendous loss. And I think some of the things that were discussed earlier today with respect to having culturally competent materials for patients to be able to use, to understand the expectations around it, including those things that could avoid medication errors.

Jay Duhig:

Again, these are all reasons why it makes a lot of sense, and industry will want to participate.

Jay Duhig:

The last reason, before we move into the broader discussion, I think, is around the points of harmonization that were discussed. When you think about harmonization and that end result, as Dr. McCullough described, that harmonizing towards what it looks like, harmonizing towards that set of standardization. Again, in my mind, I'm thinking in terms of what's been done in the post marketing space and what works very well. That's where I think harmonization from an industry standpoint makes a lot of sense and has a lot of value.

Jay Duhig:

Again, when we're talking about reducing, if it's global harmonization and the reduction of individual country, or area, or regional standards, into more centralized, that's process efficiency and that makes a lot of sense, again, from many levels. I contrast that with harmonization of systems. So, for saying, "Hey. Let's go make everyone's global labeling system, how we do good labeling practices and GLPs, make

those all the same, or how we do quality control all the same. Well, those things are, of course, overly complex and are not things that we move towards.

Jay Duhig:

Again, I know that that was not the ... Or, I believe that that was not the suggestion, but just to, as we continue our discussion, to frame it. When we start talking about this is what good looks like, these are the areas that we want to get to as healthcare partners, as systems, as collaborators at a whole. Those things make a lot of sense to me for harmonization. It's saying, make everybody look the same, while, again, that would inhibit the potential for creativity and innovation, and somebody coming up with something that's a better way.

Jay Duhig:

Again, very happy to participate and glad that we are having these discussion, and I think that there is a substantial opportunity for us to benefit people within the clinical trials, and also open up clinical trials to more people than we have previously.

Susan Winckler:

Great. Thanks so much, Jay. And, Alex, I'm going to invite you back to the virtual stage as well. And, Jay, I'll note, it is lovely to join our virtual stages and get out of the house where we had that opportunity.

Susan Winckler:

I want to pull something you just said, Jay, about harmonization, and let's dig into that a bit. I want us to think through, where is that harmonization helpful, where we get standardization and you decrease the risk of error without, I think as you were saying, inhibiting innovation? Let's talk more about that. And,

Alex, I don't know if you want to pick up that piece and say, what are some ways to think about harmonization that we get to better consistency without getting to lockstep, that it might actually create more problems in the future?

Alexander Mills:

Yeah. Well, first of all, I think I want to agree with Jay here, in that harmonization of things at the quality system level is going to be overly complex given the complexities of global supply chains, the number of sites, the size of companies, and so, I definitely agree there.

Alexander Mills:

Harmonization in terms of principles; identification of medication errors, better awareness of coding errors and getting them into the databases appropriately so they become searchable across all phases of development, I think is important and a goal. And then, again, harmonization of practices, right? I think risk management practices are a great example that I'll probably come back to a few times. But that kind of critical thinking and setting the expectations from a regulatory perspective for industry to then demonstrate how they meet those ends, I think is very helpful, and it's one element from the post market space that I can say could be successfully deployed in here, where it's, "Show us your process or how you approach this." Right? And then, some designated frameworks that, then, we can map to as needed based on the complexity of the circumstances.

Jay Duhig:

Mm-hmm (affirmative). I agree, Alex. And we started through the first panel talking about some of those examples, and I appreciate and respect the panel-

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Jay Duhig:

Talking about some of those examples. And I appreciate and respect the panel saying, "Hey, we're not throwing shade at any company or anyone that has these under the bus or are throwing people under the bus, and these things happen." Because these things do happen. When we're talking about, you mentioned the number of studies happening at MD Anderson right now and it's it's... Wow. So, I think part of that, when I think of harmonization of where that work is focusing on that end result and saying, okay, this is what good looks like and having that degree and then industry, cross functionally within the companies and across companies, working towards that end. What I'd like to know more about or what I'll be continuing to talk and discuss more about within our teams and would like to learn more about from others is, where that breakdown is.

Jay Duhig:

I mean, very much consistent with how we would do safety investigations or anything else within a post-marketing process. We worked with ISMP in the past couple of years, on things that will happen within the label and okay, it's not just, we'll fix it and we're done. You want to find out, how did that happen? Because just as within the post-marketing space, we'll have good labeling practices, standard operating procedures and quality checks to make sure that someone's not getting a box of drug product with no drug in it. So, you're going to have those within the clinical trial space, or within clinical trial study support. I went back and spoke with some of our team experts that are in those groups within clinical study labeling managers, representatives, clinical trial supply managers, and was looking through their systems, their checks, their processes, and then the criteria that those clinical study supplies need to meet in order to be released to a site and how the series of triple checks, of standardized labeling systems that happen.

Jay Duhig:

And it all looks good. So, I'm not saying that to throw sunshine at Abbvie or anything. So because again, mistakes do happen. They happen anywhere despite having these systems. But I think that that's an interesting question for industry moving forward to understand, even when these systems are in place, where are the breakdowns? And I think that similarly to how we have with ISMP and or with FDA is, issues come up. So, in post-marketing that, that will be helpful because that idea of having a naked bottle show up or something with no labeling, that's harder for me to say, okay, this is where the breakdown exists.

Jay Duhig:

On the other side, to Dr. Feng's point, I wrote down saying, well, the kit number is not in a consistent place. Just in my experience, okay, I could see how that might be something that would shift around and that the potential for harmonization on something like that could work very much like harmonization has been in post-marketing, with the use of the font size of the drug strength with respect to the drug name and having that relationship. So, that to me is within the vein of harmonization where I think it can be very effective for the sites, for industry, for the health authorities and of course, for patients.

Susan Winckler:

Really helpful in underscoring kind of where the... So, it's really to the piece of kind of how it looks and less about how it is that you get there. And in some of the work that you do to identify the challenges and improve your functioning, that's where you can still innovate and continue to stay ahead of the requirements. So, one of the things... We heard a lot about medication errors and potential for medication errors in that first panel. How do you typically hear about medication errors and the potential for medication errors from sites or how do you learn about it? I'm confident it's not, well, this

meeting was very instructive, my instinct is that you have processes outside of meetings like this. How do you hear about challenges? Alex, you're muted again.

Alexander Mills:

Okay. I can take that first.

Susan Winckler:

There you go.

Alexander Mills:

So of course, in the clinical protocols, we have the medical monitoring plans and then deviations then go and get moved through the quality system for our clinical supplies organization. So, things come to us through there. And I think that, that will incorporate a large amount of the type of medication errors that we're seeing as part of this discussion, with respect to the primary container label. When you see other things, and of course, there's some challenges too in detecting medication errors, if it's going to be based on PK data evaluation or reports coming back in the field, other times things will come to us through the team structure, right? So, there's quality driven investigations and responses and then there's things that perhaps with some foresight, we say, hey, this could potentially impact the design of the commercial product.

Alexander Mills:

That's going to make it through clinical teams, up to the supervising teams and then to the new product development teams. So depending on the nature, there's going to be mixed approaches for getting these signals. But one thing that I would stress is that, we have touch points built into our process where we look for feedback from clinical investigators on generic labels prior to the start of the study. And so,

for clinical sites and investigators I would say, look for and exploit those communication pathways and understand how they're moving through the sponsor organization and how to leverage that, to make sure the information gets heard at the right level.

Alexander Mills:

So, I think it goes both ways, right? There's a sender and a receiver, where you need to understand what those pathways are to get the information through to the sponsor or to wave your hand and say, 'Hey, I think there's an issue here.' Because some of the especially challenging situations that were highlighted here where you might have a later stage acquisition where you're moving from one sponsor to another or a combination of multiple sponsors, there's no one organizational answer to that.

Alexander Mills:

So, I think there is kind of like an equal onus type of relationship where, understand the pathways that are available to you to report these, understand that the sponsors and to echo what Jay said at the start here, right? Research-driven companies, our clinical data is very, very important to us and the safety of our patients and our study participants is very, very important to us. So, we want to know, but there is no one size fits all approach. So, I think understand and leverage those pathways as best as you can. Knowing that some larger companies are going to be organized based on therapeutic area, you need to sort of connect with those pan modal groups that are looking over this kind of thing, like our patients' safety or our human factors or clinical supplies groups.

Susan Winckler:

So it may differ, but there are definitely those who want to gather that information and you want to hear from it. Jay?

Jay Duhig:

Again, agree as a matter of both principle and process, and action. One thing I will pull on, I believe it was Dr. Feng earlier mentioned something that I wrote down, I was very curious about this. The sponsor not responsive to the reporting, saying something's coming in from the pharmacist of what's happening. That to me, is a curious situation. And again, not defending this. We're trying to find the bottom... The root cause of this. Now, when I'm thinking about that with medication errors as they may relate to packaging, to labeling, to those sources, is the potential that the mindset is, hey, that's just the investigational stuff, we're going to change it anyway. Let's not worry about it. And that to me would be by any sponsor industry, if that was happening, that would be very myopic.

Jay Duhig:

That would be very shortsighted to think, well, the error that's being reported, it's not about the drug product, it's not an AE that we're going to report within the study or within the combination product. So, it's just something that happened according to... Not if it's to be reported. So, but it's just something that happened according to... Because this package, but we're changing the package anyway. And that would be a lost opportunity. And fortunately, I think, I believe very strongly that in organizations that do have that focus on patient safety and recognize the value of those experiences, that that type of mindset is being phased out. Certainly again, as I stated that the first reason being the safety of the patient, the participant in the trial. But also from a standpoint of efficiency, so I think having things like that, that are not listening to the pharmacist, the clinical study pharmacist. That's so incredibly inefficient, so that when it's happening...

Jay Duhig:

So to me, would be very curious and something worth more investigation. That said, from a systems perspective, one of the other things that could be happening is that site pharmacists, specialist

pharmacists that often are within doing the oncology trials, they're really good. I mean, they are really, really good at their jobs. They rely on the systems that they have for managing these studies. As we said, that the number of studies for just oncology agents being 173 times three at... It was mentioned earlier by Dr. Wheeler. That's incredible. So, and I think that, that is one element that is industry at times always expecting the specialty pharmacies and others to be that good and to have that level of standard. So, I think as we think about the path forward in understanding, that there is an opportunity to learn from sites, hey, this is what we need.

Jay Duhig:

This is what we need to continue at this level, have these degrees of efficiency. These are your expectations with executing to the industry. If you want the protocol executed in this way, this is what we need from you. I think that those are upfront discussions that can continue, again, across all stakeholders in this, and should be a continual source of give and take. So, saying that, look, we need you to focus in on what this label looks like and move towards practices that are more consistent with what we understand are best practices. Here's why this is going to help with our overall efficiency and helping you administer and complete the study. I think that those are the type of value based conversations that everybody can get behind.

Susan Winckler:

Which then ties to some of the conversations about, you can learn from what's happening in labeling in phase one to phase two, to phase three, to the helpful structure you gave us to think about, what are things that we do in post-market? That we could apply that same type of learning pre-market and help us improve what it is that we're doing. And here, perhaps it's establishing it as part of that relationship with the clinical trial site, that it's not only your kind of, here are expectations but includes, let us know and how to most efficiently do that. Because we all have been in situations where we might have really

good feedback, but if you take the wrong route to share it, it's far less beneficial than if it went through the channels that you've established and made clear.

Jay Duhig:

Certainly. Exactly right, I agree with that very much. And as Alex mentioned, it was mentioned previously, it can be like the telephone game. When you start talking about multiple sponsors for a given study, or let's say companies merge and then, or that there's a change in who's participating, or that there's a change in, the site stays the same but the PI changes. So, all those things are kind of like the telephone game, where you have those communication things, those things set up, but in each iteration is, we won't know so that there are slight changes and there can be a little bit lost. Now, we don't naturally just want to rely on the vigilance of the individuals, but instead have good change management processes to address things like that, to address safety updates, or when products or changes in any type of labeling, and that's something that can happen.

Jay Duhig:

But still, it's a complicated system. You're talking about administering many of these trials globally. There can be a very intense focus on the speed and the execution and the efficiency, and those are all added factors that can lead to difficulties. So, I think that as you said, Susan... But having what we do very well in the post-market is when something like that happens, investigate and get to the root cause and understand, okay, it's not just, we didn't fix it just because we made the update, we fix it where the communication breakdown or whatever the issue was within the system. And then we can replicate that fix across other trials and share that.

Susan Winckler:

And if you could even kind of share it more broadly, I want to... So, our last panel said, this idea of having a place where we could share experiences and learn, perhaps from a trip and fall that occurred for one company and share and say, how might we protect that? What's your sense of regulated industry's appetite for just that type of an opportunity, to share challenges identified, and then also best practices, maybe on how to move beyond those challenges?

Alexander Mills:

One thing that jumps to my mind is, and it's an area that's important to me that we do a lot of work on is pediatric product development. There is a great... Pediatric product development poses some unique challenges, both in clinical and the commercial space, as well as, it's never going to be a huge profit driver for companies, but we understand it's importance. That's one area where I've seen really, really positive collaboration between industry sponsors, academic research organizations, as well as regulators. And one group, the European Pediatrics Formulations Initiative has regular meetings on this, and I think it's a model for this kind of sharing in a non-competitive space. So, those kinds of venues are super, super helpful for getting best practices out there and helping people bring important medications to underserved groups. But I think also, if you can frame that type of a community of practice up in terms of implementing significant change in other spaces, those kinds of things are very good models to look to.

Susan Winckler:

Really helpful. That's a good one for folks to think through as an approach. Jay, generally, do you have the same... Alex, I'll label that as some enthusiasm there, for that idea?

Jay Duhig:

I do. I think in some areas in particular, let's say overall awareness about the value of participation in clinical trials. Well, that's a pre-competitive space. That's a discussion that can happen across the board. They're more in areas more largely of public health, I think, such as having these types of best practices again, that are shared within that standardization, harmonization, regulatory framework, I think can work pretty well. EMA has a couple of examples over the past couple of years and naturally, FDA does as well. So, where it goes have been that having it happen at the health authority, that the regulatory FDA and EMA has been very helpful. Where I think, in hearing the earlier discussions about knowledge sharing, where I think it gets more difficult is to talk about ongoing active studies and have evaluation of safety data in those points, at the sites, or trying to share learnings for data that's not yet published.

Jay Duhig:

I think that, that would be much more challenging to have those types of discussions. Now, to talk about that, to look retrospectively after that and into those studies and into that data, that to me would be a different story. So, and I know again, that, that would be a bit removed from time, I'm aware of that, but I do want to be... In my opinion, I think there would be concerns about basically cracking open your safety books for our ongoing studies. I think that would be very challenging, or even those reduction strategies could be thought of as competitive advantages. So, I do make a distinction of what's happening within there, so of how studies being executed within that way versus, but there's enough that can be done in these non-competitive or pre-competitive spaces, I believe, to make significant differences to the issues that we're talking, with respect to the clinical supply labels.

Alexander Mills:

And just to add on,

Susan Winckler:

Let me add one... Yeah, go ahead, Alex.

Alexander Mills:

Yeah. From an innovation perspective as well, right. Things like E-labeling, which can answer a lot of the questions and challenges that we've seen. I'm not too close to the technology myself, but we see... We see that is a known competitive technology, that's an enabler for safety. And by toggling from English to Spanish or by updating x-ray dating remotely, there's a lot of opportunities there, or even just changing label configurations to match what's there at a site, to reduce... Because some medication errors are going to be based on local site practices or existing mental models that those individual can... that the investigators have. Right? So, finding opportunities to build community and sharing around innovation, I think is something that industry is very much interested in.

Susan Winckler:

And so, you started to address... I want to hit on two topics quickly. One, this idea of technology. And Alex, you just gave a thumbs up to the E-label, I'm going to take it there. Generally, is this a space... I mean, there are those who believe that technology can solve everything, which we know is not what either of you are saying. I'll go ahead and take that off the table, that's not what I'm going to ask you. But is it accurate that there are some spaces here where embracing... There are solutions that might be deployed through technology that help us address the situation? If so, is E-labeling kind of one, anything else that rises to the top? Or is this another space where it's definitely worth talking about potential technology intervention?

Alexander Mills:

Yeah, I mean, I think we have to open up the conversation. Although, technology is a double-edged sword, right? Because new and novel dosage forms as well may have smaller and smaller containers or may have usability requirements or user interface requirements that become at odds with the labeling requirements. So, perhaps in some case, expanding the definition of primary packaging to include some larger format component that goes along with your drug product, if the drug product itself maybe needs to be packaged in a sterile barrier with opening instructions or something along those lines. Right. So, we have this sort of ebb and flow of what technology is giving us here.

Jay Duhig:

I agree. I think we're firmly at the end of phase one of hey, let's build an app and then that will make everything better. If you just build an app, yeah, everybody will use it. So, that's now understood that, that's not what happens. Where I see the opportunity... Very much as Alex and you are saying, Susan, are things like, for barcode scanning and barcode dispensing. I mean, those are very practical tools that we know work and going back to barcode medication administration and the work that Mike Cohen and IMSN and ISMP and the FDA and all those others have co-created around that. When you think about having... When judiciously applied, I mean, that's far beyond the vigilance of even the best practitioners. So, embracing things like that and then applying them in ways that fit with the workflows.

Jay Duhig:

I think with technology that is in the application on the sponsor side, that's a big consideration that, what's the workflow at the site level? Because that can often need to be very customized or the expectations of what can be done and what works for their systems. I think that's one of the ramifications in the U.S. of having a very fragmented healthcare system. Certainly not the only one. So, but as we've seen that regional growth, that area growth and for healthcare systems to really get good at being and administering trials. And so, in leading studies, participating in them or inviting industry in

to participate in them. So, that's one thing that's happened. So, everyone has a lot of their own systems, a lot of their... For what that looks like at the pharmacy levels. So, there has been some degree of standardization that will come from the companies with their... From the sponsors within that.

Jay Duhig:

But that's also an area where I think can enter into that non-competitive or pre-competitive space around that, where we can look to say, okay, these are the things that work. And again, that may be more of the health systems, that may be more at the regulatory level of standardization, but it's not without risks either. If you're a big academic medical center that wants to facilitate and be a partner in a lot of studies and you've built this system up, telling someone... I mean, it's like electronic health records saying, no, no, no, now you have to do it this way. Again, I'm speaking outside of my area. So, but I mentioned it that, that's quite challenging, but those are some of the things in interviewing and listening to other people within my organization that we've heard about, so that they have to allow for that degree of flexibility at the site, that, that's the expectation there, how we address that and move that forward, I think is an ongoing question.

Susan Winckler:

Well, I think, Jay, no one will fault you for saying system change is hard, whether that's at the product sponsor level or at the health system, the clinical trial level, or in homes. Just within daily lives, system change is hard and challenging to do. I do want to ask one question that I hope is not too much of a challenge, but when you talked about sharing and then obviously, you don't want to... Sharing is difficult in pre-competitive space, but sharing can be really helpful post-competitive when you have those compounds that didn't make it. So, where you completed the clinical trial, but it's not moving to a product launch. I mean, I imagine there could be lessons that we learn with those products. How does

industry think about that or how might we make it attractive to say, yes, we can still learn from that as that product and exploration is being closed out, or does that land in a challenging space?

Jay Duhig:

It's a very interesting question. So, to think about that, when I think about, can we remove that idea of, well, there's IT associated with this? And, but I don't know. It feels like nothing's ever really dead. So, it's the way it goes. So, I mean, and that makes sense. It's not a matter of, it's a good drug or a bad drug, but have you figured out the right population? Have you figured out the right condition and the parameters where this may add value? So, I connect to and identify what you're saying. Where can we have these type of explorations that could be essentially used the real, versus something where we're speaking in abstractions to help us to learn and facilitate? That would be one I'll need to think more about, I don't have a ready answer for that one. Alex, do you have?

Alexander Mills:

No. I'm going to be right there next to you on this Jay. But right, Susan, it's a fundamental principle of innovation, right? Is to fail fast and learn from those failures and take it forward, right? Finding the right venue, the right way to share case studies and getting it out there is something that we try to do internally, of course. But yeah, I think that... Along with Jay, I have to think a little bit more or talk to some folks here to talk about venues for getting that out there more widely, right.

Susan Winckler:

Fabulous. Well, Alex and Jay, I knew I was throwing a curve ball at you at the end, but it's always good to close out with a head-scratcher and say, huh, maybe so, in that fail fast and then learn from what it is that we've done. So with that, we've wrapped up your session. Thank you so much for joining us and for

your candor in sharing. And I'll add that sharing to all of our speakers today, but you can close out your webcams and I will help us close out this session. Thank you again for joining us.

Susan Winckler:

So to the group here, I will say we have gotten quite an immersion in the topic today. And I have to say, thank you so much for joining us. We think about where we've been, we opened with an overview of the challenges from pharmacists on the ground, working with multiple investigational drugs and helping us understand the reality of working with drug names, the concept of a license plate versus an actual drug name, different legends and keys and information that would be helpful as well as the opportunity to continue to improve the labeling through each phase of the clinical research process. So, we need to thank that first panel for grounding us in the challenge.

Susan Winckler:

Our second panel, those who were in the middle, we heard that this isn't new, but a challenge that they have seen, facing and have been working on and saw and underscored the value of standards or some standardization, as well as the increased use of technology and teed up a few ideas, as well as encouragement to take baby steps to get to a better place in our efforts to decrease medication errors and improve the labels that are on investigational drug containers, even giving us kind of four steps to look at harmonization, not only regulatory harmonization, but actually beyond that and some places where could have harmonization on symbology or just best practices.

Susan Winckler:

The merit of a forum for knowledge sharing so that we can learn more about the challenges and share the solutions. The importance of engaging with patients and getting their perspective, and then the opportunity that technology might present and we'll have to learn from some of it. So, it may not be

perfect, but that technology may present a solution. And then we closed out day one with this discussion from regulated industry, from product sponsors who really approach it from a broad risk management approach with ongoing assessment and critical thinking. And underscoring that in fact, industry wants to improve this situation and saying, there are places where standardization would be helpful and harmonization of principles and perhaps the presentation. So, harmonize on what good looks like while allowing the innovation around the systems to get there and an appetite for continuing to share and saying where technology might make a difference.

Susan Winckler:

So, we have taken this tour of those who are using the investigational drug label products, those who are facilitating the interaction between regulated industry and those clinical trial sites, and then regulated industry themselves. So, thank you for joining us for that discussion. We will reconvene tomorrow to think through a couple of other perspectives related to the role of IRBs, hearing from international regulators and how they've looked at it, it's not unique to the United States challenge, and then also hearing from FDA.

Susan Winckler:

So with that, I'm going to close us out just a few minutes early, and we will look forward to seeing you tomorrow at day two of the public meeting related to investigational drug container labels and our efforts to address exploring the potential medication error risks, and talking through what some of those solutions might be. Thank you so much for joining us today.

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