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## Increasing Access to Nonprescription Drugs

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A Hybrid Public Meeting



## Increasing Access to Nonprescription Drugs Transcript

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Marianne Hamilton Lopez:

All right, good afternoon. Welcome to today's meeting, Increasing Access to Non-prescription Drugs. I'm Marianne Hamilton Lopez, Senior Research Director at the Duke-Margolis Institute for Health Policy, where I oversee our biomedical innovation research portfolio. And I'm excited to welcome both our virtual and in person attendees to today's meeting, which is being convened by Duke-Margolis and our colleagues at the U.S. Food and Drug Administration. Our meeting today will focus on increasing access to non-prescription drugs, in particular through a new drug application process, which includes direct to non-prescription applications, prescription to non-prescription switch applications, and applications with additional conditions for non-prescription use.

So a few logistics before we get started. On the screen is a short note about our commitment to academic independence. You can find more about our policies at the links in the slide. Duke-Margolis is convening this under a cooperative agreement with the U.S. Food and Drug Administration. The conversation, while we're supported by a cooperative agreement, is not a federal advisory committee, so we will not be doing any voting or making recommendations or any binding actions. Today's meeting though will be very successful if we can foster some productive discussion. So we're looking for discussion on opportunities to improve individual and public health outcomes with the safe and appropriate use of non-prescription treatments.

Attendees, both in person and online are encouraged to submit questions through the Slido Q&A function. Those questions will be passed along to our moderators. They'll be shared with our panelists if time permits. We want to ensure that the discussion is dynamic and is responsive to your interests. So please do not hesitate to submit questions. The QR code will allow you to submit questions. I'll be putting this on the following slide. A few additional logistics to note. For any of our virtual attendees who may encounter problems during our live stream, please either use the Q&A function on the Slido app or you can email any of the staff that will be on the slide so that we can resolve your issue.

Lastly, all the meeting materials will be shared today and they will be accessible on the Duke-Margolis website. Right now, you can view the agenda, the discussion guide, a speaker bio sheet with information on all the speakers, as well as disclosures of any relevant conflicts of interest for each of them. Shortly after the meeting, we will post a recording, the slides used today, and a transcript of the event.

Here's the Slido code you can use throughout today's session to submit your questions. Please feel free to right now go ahead and use your mobile device to access the code. We'll have the QR code displayed during each session and available to re-scan throughout the day. Now, according to my talking points, I'm supposed to awkwardly linger here for a few moments while you all go ahead and use your mobile devices. I was even suggested that I perform a dad joke, but I'm going to instead just give you a few more moments and then we will move forward.

Okay. All right. Our agenda, we're going to begin our event today with remarks from the FDA, providing an overview of non-prescription drug regulation. It's going to include the drug development pathways that can lead to non-prescription status, the regulatory requirements for reaching that status, and also some of FDA's more recent actions in this space. Then we're going to move into a presentation on the impacts of increased non-prescription drug availability on health outcomes, consumer access, and healthcare costs. A panel discussion will build on those topics, considering the characteristics that may make a product a good candidate for non-prescription status and some of the factors that may shape the impacts of a switch from prescription to non-prescription status. Then we'll take a brief break and return for our next session, Evidence Generation to Demonstrate Safe and Efficacy in the Non-Prescription Setting. Here, we'll have a presentation and discussion on the methods that are commonly used by sponsors to demonstrate that consumers can make the right decisions about whether and how to use a non-prescription drug without the council of healthcare providers, as well as opportunities to improve or enhance those methods.

Our final panel for the day will consider innovation and to enable increased access to non-prescription drugs. Here, we'll consider innovative tools and appropriately with a particular focus on tools that could be used to facilitate access to drugs with an additional condition for non-prescription use. These topics are particularly timely, as we at Duke-Margolis, as well as many leaders in the federal health policy space, are trying to think of policy solutions that improve individual and public health, especially when paired with well-designed care delivery and reimbursement models. We believe that non-prescription treatments and digital tools and lifestyle interventions and other approaches have the potential to improve individual and public health, especially when they are considered and discussed with groups like today and discussed in a broader context.

On that note, I will make the note that some of our discussions today will consider things around cost and insurance coverage and related points. Just want to make the point again that that is not within the FDA's regulatory purview and do not factor into the FDA's decision making. However, cost and coverage are critical factors for patients and consumers and as they make decisions about their health and their healthcare, so our discussions today will reflect that. So now, with that, it is my pleasure to introduce our first speaker, Karen Murry, the acting director of FDA's Office of Non-Prescription Drugs. Karen, please come on up and get us going. Thank you.

Karen Murry:

Thank you. And welcome everyone. I'm Karen Murry, acting director of the Office of Non-Prescription Drugs at FDA. I'll be giving a high level overview of non-prescription drug regulation. Here are the topics I'll be covering and I'll proceed right into them. Recently, there's been increased interest in non-prescription drugs from a variety of stakeholders. For example, an April 2025 executive order called for identification of candidate drugs and improvements in the process by which non-prescription drugs can come to market. And in December 2025, the FDA commissioner's office issued a request for information asking for people to share perspectives on increasing non-prescription drug access and on scientific, regulatory and practical considerations that shape that access. Input from that RFI informed the meeting we're holding today. As a longtime proponent of expanding non-prescription choices for consumers, I think this increased interest is good.

So what's the current U.S. non-prescription drug access landscape? We already have a very large number of marketed non-prescription drug products, over a hundred thousand. And while there's sometimes a perception that other countries have more non-prescription drug choices than the U.S., the U.S. actually has more. For example, U.S. has over twice as many non-prescription active ingredients authorized than any European country. Nevertheless, we would like to see more. FDA wants to improve U.S. consumers' ability for self-care through expanded availability of safe, effective, and affordable non-prescription medicines. ONPD has been working intensively on non-prescription expansion efforts and has established multiple active work streams to facilitate non-prescription development and review. FDA wants input and ideas from a wide array of stakeholders, and we're looking forward to what we hear today. To maximize time for stakeholder input, FDA is in listening mode for today's meeting.

How are non-prescription drug products used today? Currently, the majority are intended to provide temporary relief of minor symptoms or to treat self-limited conditions or diseases. This role of non-prescription drugs is important and will remain so. However, in the future, could non-prescription drugs be used safely and effectively to treat or manage symptoms of other kinds of conditions or diseases, perhaps beyond minor and self-limited conditions? FDA encourages development and innovation, both in the traditional use paradigm and in a possible future use paradigm.

When is a drug considered non-prescription? Before 1951, prescription and non-prescription drugs didn't really exist as separate classes. Doctors prescribed most drugs. In 1951, the Durham Humphrey Amendment established two drug classes. RX legend or prescription drugs were those that required practitioner supervision because of "toxicity or potentiality for harmful effect or method of use." Everything else is non-prescription, commonly referred to as over-the-counter or OTC. Essentially, non-prescription is the default status in the U.S. A drug is non-prescription unless it has to be prescription. Note that in the United States, we only have two classes of drugs, prescription and non-prescription. The U.S. does not have a third class of behind the counter or pharmacist dispensed, and that's often an area of confusion.

What are the characteristics of a non-prescription drug product? The drug has to have a good safety margin, meaning that there is a wide distance between the dose at which the desired therapeutic effect occurs and the dose at which toxicity or adverse effects occur, so that the benefits of non-prescription availability outweigh the risks. The consumer has to be able to self-diagnose, self-treat, and self-manage the condition being treated. The drug needs a low potential for misuse and abuse. By law, the drug cannot require a healthcare practitioner for safe and appropriate use, and labeling is key. It has to enable consumers to self-diagnose, correctly self-select purchase, use properly, and to know when to stop using or talk to a healthcare practitioner. Often, consumer studies are needed to show that the labeling works for these needs.

Here's a figure of drug development pathways. If you look at the branch on the right for non-prescription drugs, that class is broadly divided into two types, application products, which require an application for approval prior to marketing and the over-the-counter monograph drug review process. Within the application group are three possibilities. A sponsor can develop a drug product to bring to market directly as non-prescription. A sponsor can also pursue a prescription to non-prescription switch of a drug product using labeling alone to support safe and effective use. If labeling alone is inadequate, a sponsor might be able to use a new approach, which can add something beyond labeling called an additional condition for non-prescription use, abbreviated ACNU. Today's meeting does not focus on the OTC monograph pathway, but I'll touch on it briefly later.

While ONPD wants there to be more non-prescription drug choices, we cannot simply declare a drug to be non-prescription. Data are required, whether under the NDA or monograph system. An applicant seeking to market a non-prescription drug under an NDA must submit data to satisfy the applicable

statutory and regulatory requirements for approval of an NDA. Among other things, by law under the Federal Food Drug and Cosmetic Act, an NDA must include adequate tests to show that the drug is safe for use under the conditions in the proposed labeling. And again, by law, there must be substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use in the labeling. Often, consumer studies are needed to evaluate proposed non-prescription drug product labeling and to demonstrate that the drug is safe and effective for use in self-medication as directed in proposed labeling as required under the code of federal regulations.

You're no doubt familiar with the drug facts label or DFL, which is required for all non-prescription drugs. It's intended to enable consumers to self-select appropriately and use the non-prescription drug product safely and effectively without assistance from a healthcare practitioner. One thing you'll notice about the DFL is that it is small and one cannot fit a lot of information in it.

Some people don't realize that a direct to non-prescription category exists, but many non-prescription drugs come through this route. These are application products for which the conditions of use were not marketed as a prescription product under an approved NDA prior to being approved for non-prescription marketing. Development programs vary. Some do new clinical studies and most do some consumer behavior studies. After they've conducted studies demonstrating likely safe and effective use in the non-prescription setting, that is without healthcare professional assistance, the applicant submits an application.

Prescription to non-prescription switch is often what people envision when they think about how a non-prescription drug comes to market. It is an important pathway, although the majority of non-prescription drugs come to market via other pathways, such as the monograph and direct to non-prescription. With a switch, the proposed drug product has been previously marketed as an approved prescription product. Programs rely in part on safety and efficacy information that already exists for the prescription product. Sponsors need to identify the key elements of the prescription label and translate them into consumer-friendly terms.

This is often hard. Literacy in the U.S. is low with an average adult reading level somewhere between fifth and eighth grade, and health literacy is even lower. Consumer studies are often needed to evaluate the suitability of the product for non-prescription use. Sometimes new clinical studies are needed. Almost all sponsors meet with ONPD to get development advice. After they conduct studies to demonstrate that consumers are likely to be able to use the product safely and effectively, the applicant submits an application.

An important concept for prescription to non-prescription switch is that the exact same drug product cannot be marketed as both prescription and non-prescription at the same time. Simultaneous marketing is only possible if some meaningful difference exists between the prescription and non-prescription products, for example, in the indication or some other condition of use, and that meaningful difference makes the prescription drug product safe only under the supervision of a licensed healthcare practitioner.

Some switches are full and some are partial. With a full switch, a sponsor switches the drug product covered under the NDA to non-prescription marketing status in its entirety. After a full switch, the drug is only available as a non-prescription drug. With a partial switch, a sponsor switches some of the conditions of use, for example, indications to non-prescription marketing status while retaining others within a prescription status. After a partial switch, the drug is available as a prescription drug for certain conditions of use and a non-prescription drug for other conditions of use. Now, on the other earlier slide about the drug facts label, you saw the DFL's small size. The point of this slide, which is an image of the full prescribing information for a prescription drug, is to show how challenging it can be to condense everything the consumer needs to know and fit it into that little drug facts label.

Now, let's say a sponsor has developed what they think is a good drug facts label. What next? Generally, one or more consumer studies are needed. Label comprehension studies are commonly needed. No matter how carefully one writes a DFL, consumers often don't understand key aspects of it. The label is tested in an iterative fashion, getting better and better comprehension until there's good evidence that study participants are understanding the label, and thus that consumers are also likely to understand it. Sometimes self-selection studies are needed. For this, a study participant considers their own personal medical situation. For example, interacting drugs or health conditions they have that might make it not safe for them personally to use the drug.

In some cases, concerns about the likelihood of safe or appropriate use in the non-prescription setting lead to the need for what's called an actual use study, where study participants actually purchase the product and use it in a clinical trial setting with data collected on correct use and safety. And finally, there are sometimes human factor studies, usually when a device is involved. ONPD is selective about what studies are requested. We try to only request what is needed to demonstrate likely safe and effective use in the non-prescription setting.

Prescription to non-prescription switch NDAs have resulted in the approval of many non-prescription drugs that have provided clinical benefits to consumers and reduced healthcare costs. However, as time has gone on, the low hanging fruit has switched, and few prescription drugs these days have all the characteristics listed in the bullets on this slide. Ideally, the condition would be self-diagnosable and requiring a lab or monitoring. The drug would have simple dosing and administration, few serious adverse effects, minimal drug-drug interactions, and no risk of misuse or abuse. However, candidate drugs now often have difficult safety concerns that make it more challenging for an applicant to demonstrate that the drug will be able to be used safely and effectively without assistance from a healthcare professional.

So what can be done now that the low-hanging fruit is gone? ONPD currently works with sponsors to find solutions to challenges, and for some difficult programs, ONPD and sponsors have found a way to get to approval using labeling alone. The traditional path that until recently was the only path. What happens though, when despite the sponsor's best efforts with labeling alone, participants in non-prescription studies are not demonstrating correct self-selection or correct actual use. Can something in addition to labeling be used to try to overcome this challenge?

Well, now that's possible. In May of last year, a final rule went into effect that enables a new approach called an ACNU, short for additional condition for non-prescription use. When labeling alone is not enough, something extra might be used to overcome a hurdle. To be specific, as noted in the bottom right bullet, the ACNU rule establishes the requirements for a non-prescription product with an additional condition for non-prescription use that an applicant must implement to ensure appropriate self-selection or appropriate actual use or both by consumers without the supervision of a healthcare provider. So if study participants aren't getting key messages with labeling alone, a sponsor could perhaps propose an ACNU.

Both traditional non-prescription drugs and non-prescription drug products with an ACNU must be safe for use without the supervision of a healthcare practitioner. Unlike traditional non-prescription drug, in the case of drugs with an ACNU, labeling alone cannot ensure that consumers appropriately self-select and use the non-prescription drug product. Instead, labeling in combination with an ACNU will ensure that consumers can self-select appropriately and use the drug appropriately without healthcare practitioner oversight.

While an ACNU may utilize technology to operationalize the ACNU, the specific type of technology used such as a web app is not the ACNU. Here are a couple of ACNU examples. One example would be when in order to purchase the non-prescription drug product with an ACNU, the consumer must respond with

specific answers to a set of questions on a self-selection test available by either a mobile application or an automated telephone response system. Another example would be when, before purchasing the non-prescription drug product with an ACNU, the consumer is required to view labeling, for example, text or images in a video that describes how to use the non-prescription drug product appropriately, and the consumer is required to respond to questions to confirm understanding.

An ACNU is not labeling. It is something beyond labeling. It may utilize labeling. An ACNU is also not a device or a particular kind of technology, although it may be operationalized using a device. As an example, for a particular product, the ACNU might be a requirement that a consumer respond with specific answers to a set of questions on a self-selection test in order to purchase the product. In this example, the ACNU uses labeling, that is the list of questions to be answered by the consumer in the self-selection test. And also in this example, a device, in this case, a mobile app is used to operationalize the ACNU, but the app itself is not the ACNU. The applicant could operationalize the ACNU in another way.

While I won't go into detail regarding provisions of the rule, I will highlight one thing. Note the middle row. Recall earlier when I talked about how a drug can't be marketed as prescription and non-prescription at the same time, unless a meaningful difference exists. Well, with ACNU, simultaneous marketing is permitted with the ACNU itself being the meaningful difference. This is so that an ACNU does not prevent someone from getting the drug if they can't fulfill the ACNU requirement. They can still get it from their doctor without having to do the ACNU step. And for your reference, here are more provisions of the rule.

While not the focus of today's meeting, the OTC drug review or monograph is another way to bring many non-prescription drug products to market because the addition of a new active ingredient to a monograph opens the door for hundreds or even thousands of products as long as they follow the conditions of that monograph. In 2020, Monograph Reforms in the CARES Act allowed streamlining of monograph processes, and we're already seeing positive effects of those reforms. A company efficiently put together the necessary data and submitted an over-the-counter monograph order request or OMOR for addition of bemotrizinol as a sunscreen active ingredient. FDA then used the new streamlined processes and issued that proposed order. So this process can work quickly and efficiently for companies who are interested in innovation and provide the necessary data. And we hope that other manufacturers of sunscreen active ingredients will follow suit, and we also hope for OMORs in other therapeutic areas.

Today, we're looking for input from a variety of stakeholders with ideas for improvements to non-prescription drug access. As I mentioned earlier, FDA has also been working intensively in this area. I just spoke about the ACNU final rule and monograph reform, both monumental efforts that have great potential for increasing the number and types of non-prescription drugs. We're working on new and updated guidances that will be helpful to drug developers. ONPD has long emphasized minimizing animal testing and the recent draft guidance on the use of new approach methodologies and drug development applies to non-prescription drugs. We're working with FDA's quantitative medicine center of excellence on the use of modeling and other means to reduce the need for certain studies, and we've been conducting active outreach to major international regulatory bodies to exchange information on non-prescription regulatory approaches.

ONPD has a busy schedule of engagement with sponsors with frequent formal meetings regarding development programs for both NDAs and monographs. We've held public meetings regarding specific areas of interest such as enhancing access to epinephrine in a recent meeting. We have active internal processes for identification of candidate therapeutic areas and drugs, and we're developing a pilot program for engagement with interested sponsors on development programs for a limited number of

candidate drugs that FDA identifies as having particular potential for public health benefit if found to be safe and effective as non-prescription, and we hope to launch that pilot later this year. Today, FDA wants to hear about diseases or conditions with non-prescription potential, challenges industry may face in developing non-prescription drugs, opportunities to improve access and stakeholder collaboration and other innovative ideas.

And finally, I'd like to close with an overall approach, and that is to think non-prescription first. Remember the slide that I showed earlier about how under Durham Humphrey, non-prescription is essentially the default. That is, a drug is non-prescription unless it has to be prescription. That's an important concept that I would like people to keep in mind. When sponsors pursue development of a new drug, I ask that they consider whether the drug could be a good candidate for non-prescription use rather than prescription. And for holders of prescription applications for drugs that have been marketed for several years, I ask that they consider whether the drug product could be suitable for non-prescription use. Thinking intentionally and proactively about suitability of drugs for non-prescription use rather than as an afterthought could lead to more non-prescription options that could benefit consumers by improving their ability for self-care with safe, effective, and affordable medicines.

We at FDA are really looking forward to the input from this meeting today. I'd like to thank all the attendees, comments, submitters, speakers, and panelists. I'd also like to thank the Duke-Margolis Institute for Health Policy for their expert work on this convening. I'd also like to thank Dr. Makary, our commissioner, and members of his staff who have been working collaboratively with me and have been very supportive of ONPD's efforts. And I'm very grateful to my dedicated FDA colleagues who keep working through innumerable challenges to ensure that Americans have safe and effective non-prescription drugs. Thank you.

Anna Hung:

Great. Well, thank you so much, Karen. That was a wonderful presentation. Gave us a very helpful overview. I'm Anna Hung. I'm an assistant professor within the Duke University School of Medicine. I'm also a member of core faculty with Duke-Margolis, and I'll be moderating our next session, Opportunities to Improve Public Health with Non-prescription Treatments. For this session, we'll begin with a brief presentation, and then we'll follow that with the moderated discussion. So I'll introduce our panelists when they come up for the discussion portion, but for now, let's start with our presenter, Dr. Eric Brass, who is the Professor Emeritus of Medicine at UCLA's David Geffen School of Medicine. Eric, if you can come on up, please.

Eric Brass:

Thank you. And it's a pleasure to have the opportunity to meet with you this afternoon. I'm already losing my voice. To discuss some ideas on how expanded OTC access, particularly through the switch process, can improve personal and public health with a focus on how to inform the benefit-risk assessment when considering such improved access.

Because expanding access requires maintaining a favorable benefit-risk assessment for the drug. That's fundamental to the overall assessment. To begin, we need to recognize that non-prescription drugs have a unique benefit-risk proposition when compared to prescription drugs. When we focus on a switch from prescription to non-prescription status, we need to remember that the drug has already been established as safe and effective when used as directed. Therefore, the switch requires an assessment that's focused on the incremental benefits compared to the current situation and the incremental risks compared to the prescription status.

Because in fact, if consumers could simply replicate the use that they have in the prescription setting, then the benefit-risk proposition would be fully preserved and the drug should automatically be OTC, as Dr. Murry suggested as the default for drug classes. Thus, the incremental benefit and risks result in large part from how consumers behave, how do they interact with the product without a healthcare [inaudible 00:29:31] intermediary?

This benefit-risk assessment for non-prescription drugs may benefit from use of specialized tools. One example is the use of a customized value tree. This tool is designed to help identify attributes which contribute to either benefits or risks for the proposed OTC candidate. This particular tool uses common domain to help identify specific attributes which contribute to either benefit or risk. It's intended to be quite flexible.

For example, in the benefits section, there are domains designed to identify attributes which contribute to economic benefit or enhance consumer involvement in their healthcare, even though that in some environments, those may not be particularly relevant, but for many stakeholders they are. The risk domains are also designed to be comprehensive. For example, they include worsening outcomes due to self-management of the underlying condition. But key, once we've identified these attributes for any product, we need to be able to assess them, and how do we then assess each attribute to know whether and how they contribute to the overall benefit-risk? Again, we must focus exclusively on incremental benefits and incremental risks. The drug is already safe and effective when approved for prescription status.

To understand these incremental benefits and risks, they are partially informed by the frequency of the behavior that leads to the risk or the frequency of behavior that leads to the benefit. However, while that's one input, it's not the most important input. Actually, we need to know the clinical impact of the behavior to consider and understand its consequences in order to understand how it contributes to the overall benefit-risk. One example is to score this in a matrix, which scores both the frequency of the behavior and the clinical impact of behavior and how they contribute to an overall influence on benefit-risk. But key for any of these is that these assessments must be evidence-based.

The frequency of behaviors can easily be estimated through consumer research studies. You've heard alluded to self-selection and actual use studies, and I believe these will be discussed in more detail in the second ...

PART 1 OF 8 ENDS [00:32:04]

Eric Brass:

... use studies, and I believe these will be discussed in more detail in the second session.

The incremental clinical risks are often easy to understand. Does the consumer exceed the label dose? Does the consumer expose themselves to a drug-drug interaction? Do they use the medication when they have a medical contraindication to its use? Those are often easy to understand, the consequence is quantifiable, and the behavior is easy to assess.

Often more challenging is trying to quantify or understand the incremental clinical benefits, but these are critical to support the increased access proposal because remember, these drugs are already available. There must be an incremental benefit to justify any incremental risk. We rarely have the equivalent of a randomized controlled trial to assess these incremental benefits, but these benefits need to be more than simple consumer convenience when we start talking about offsetting clinical risks.

So what are some strategies for demonstrating the benefit of a prescription-to-nonprescription switch? As I've alluded to, prospective trials to address uncertainty and benefit assessment are rarely used to

support switch applications for a variety of practical reasons, but in fact, they could be used in certain circumstances.

There's great opportunities to leverage real-world evidence in support of these benefit assessments. Particularly important would be to establish the unmet clinical need, even though the drug is available in the prescription setting. What's the current prevalence of self-care for the consumer with the indication? Again, the drug is available, but consumers are still engaging in self-care. What's the clinical effectiveness of the current self-care options, which provides a floor for the benefits that might be achieved incrementally should they now elect to use the switched product? We can document the barriers to access in the target population. All of which help define the opportunities for benefit if the drug is switched.

We can also extend this to model the individual and public health benefits. After all, the efficacy of the drug is well-established through clinical research done as part of the prescription approval process. This can be combined with behavioral data. For example, who actually self-selected to use the drug in the consumer research and/or an understanding of the self-care population to estimate the incremental clinical benefits. I know this is exciting. Calm down. Okay.

We can also leverage post-switch data for other products, including switches that have occurred in other jurisdictions, but being cautious to understand that thus jurisdictions may have a number of differences, which must be understood to use the data in the US and other environmental differences, but that data can be highly variable. We'll talk a little bit more about that later.

So I'd like to demonstrate these concepts with just two examples briefly. The first involves the potential switch to nonprescription status of statins. These drugs are used to treat hypercholesterolemia and have been established to prevent cardiac events and death. Furthermore, research demonstrates that there's a large population of consumers who are eligible for treatment per guidelines who are not on therapy. Based on this, 20 years ago, efforts were made to increase access through the switch to nonprescription status of statins.

Importantly, at that time, there was an extremely complex algorithm that was needed to decide whether an individual consumer should or should not select to use a statin. That algorithm has been greatly simplified in 2026, but I'm just going to refer to the 20 years ago example to illustrate some points. So that algorithm turned out to be very difficult to use in a self-selection study when only the drug facts labeling could be used to drive the labeling. But the question needed to also be asked, were the deviations from that algorithm really important from a clinical outcomes perspective?

So these are data from a particular actual use study called CUSTOM, where consumers were asked to self-select to use or not use the statin. And in this case, each consumer was risk-stratified based on their cardiovascular risk after their self-selection to determine what their 10-year cardiovascular risk was.

The design was that patients between 5% and 20% 10-year risk were the appropriate target. And you can see there are great number of subjects outside of that risk range. There are subjects with very low risk who are felt not to be adequately benefited from the statin, and patients and consumers with much higher risk who were felt to be inappropriate because they needed more intensive therapy. And this poor self-selection outcome was one of the issues cited in the disapproval of that application. But let's look at it in a little bit more detail.

Let's look at that same profile and model what the outcomes really would have been. The model was based on inputs using the risk profile that I just showed you of those consumers who actually self-selected to use the product and that risk profile that I showed you. The event rates were then normalized to a million users and the relative risk reduction model based on the extensive data that was in the literature at that time.

And what can see in the right-hand column are the number of events that would have been prevented using the OTC model. Even in the low-risk group, a substantial number of cardiovascular events would have been prevented. And indeed, in the high-risk group, a large number of cardiovascular events would have been prevented.

Now, the high-risk group would have benefited more for more intensive therapy, but the vast majority of these subjects were on no therapy, so that this statin represented meaningful incremental benefit to them. And in fact, the program could have been designed to encourage them to seek the more intensive therapy once they've been identified through this kind of process.

So even though the label was imperfect, failed to be precise in its self-selection, the availability still would have resulted in a net benefit to the population that actually selected to use the drug. The overall result would have been 33,000 less cardiovascular events.

Another example involves the symptom of heartburn. Heartburn is the symptom of a medical condition, gastroesophageal reflux disease or GERD. This symptom has high prevalence, a high impact on quality of life, and is frequently self-managed. Proton pump inhibitors or PPIs are highly effective therapies, which were initially available only by prescription. We could then ask, "After the switch occurred of these drugs, what was the switch to nonprescription status impact on the healthcare system?"

This slide shows primary care visits specifically for GERD. And you can see that after PPIs were introduced into the prescription space, there was a marked increase in physician visits. Why? Because for the first time, the primary care physician had access to a therapy that was substantially more effective than the widespread self-care options at that time.

After the switch of omeprazole to OTC status, we can see a rapid plateauing in that trend that was associated with the wide over-the-counter access of this drug by consumers. In fact, if we plot the trend lines out, it was estimated that over five million primary care visits were saved through that switch process. That represents five million slots that were now opened up in the healthcare system for patients who needed more intensive care than the symptom of heartburn. It represents savings to consumers and insurance companies who didn't have to pay for those primary care visits and save the consumers the inconvenience of having to take time off work to go to the physician to get that prescription.

The same kind of approach can be used to look at safety data. For example, in the case of the PPI switch, there was no increase in ER visits for GI bleeds. There was no increase in the incidence of diagnosis of gastric cancers. Both clinical concerns that were widely articulated prior to the switch as potential adverse outcomes should the switch progress.

There are a number of other examples, because of time, I won't go into any detail, where benefit has been demonstrated to help support the switch process. In the case of oxybutynin for overactive bladder in women, real-world evidence documented the unmet need and the high prevalence of self-care with inferior treatments, which, again, allowed the incremental benefit of the effective treatment to be demonstrated.

In nicotine replacement products, it was one of the rare examples where a prospective equivalent trial was actually done. But post-approval will have seen the impact on smoking cessation attempts and the public health benefit thereof. Adapalene is an interesting example where post-approval will have seen increased use of this effective therapy with documented lower consumer costs.

Naloxone, again, the large public health benefit to help deal with the public health epidemic of opiate overdoses by providing ready access to an effective antidote. And I mentioned triptans, not because they are available non-prescription in the US, but because they are available in other countries with improved access paradigms. And that data can be leveraged if collected appropriately, recognizing the

differences in the access paradigms in the different jurisdictions to help inform what the benefits and risks of triptans might be in the United States where they switched.

So, in conclusion, prescription-to-nonprescription switches have the potential to improve personal and public health through this increased access paradigm. However, any switch proposal should include evidence supporting a net positive benefit-risk post-switch. Various strategies are available to demonstrate the potential clinical benefits of a switch beyond simple convenience. Generation of rigorous evidence supporting the clinical benefit should be prospectively incorporated into any switch development program, and regulators, in turn, should explicitly and comprehensively include potential clinical benefits in making approvability decisions.

I don't underestimate the challenges these last two bullets represent, and in fact, there's an example where using external advisors, like an advisory committee or other types of formats, can help the regulator and the sponsor better understand how those benefits and risks play out in the real world.

I thank you very much for your attention, and I look forward to the discussion and any questions.

Anna Hung:

Great. Thank you so much, Eric. That's a wonderful presentation, and I'm going to go ahead and introduce our other panelists now as well. And as I announce your name, if you could come on up to the stage. So Henry Lim, who is the former president of the American Academy of Dermatology and President of the International League of Dermatological Societies, Mariana Socal, an associate professor in the Department of Health Policy and Management of the Johns Hopkins Bloomberg School of Public Health, and David Spangler, Senior Vice President for Legal Government Affairs and Policy with the Consumer Healthcare Products Association. So I'll ask each of you to provide a few minutes of opening remarks. And so David, if you're okay with going first, we'll have you go ahead and begin.

David Spangler:

Sure. And where is the slide clicker?

Eric Brass:

Up there.

David Spangler:

Up there?

Anna Hung:

Yes. Are you able and [inaudible 00:44:39]?

David Spangler:

Mm-hmm.

Eric Brass:

No, he needs the clicker.

Anna Hung:

Oh, clicker?

David Spangler:

Yeah. Let me just-

Anna Hung:

Sorry. Yes. Perfect.

David Spangler:

Yeah. So, access, affordability, empowerment, three dimensions of OTC value. I'm David Spangler with the Consumer Healthcare Products Association. So we represent over 70 companies that make OTC medicines, dietary supplements, and OTC medical devices. So, at the core of how OTC medicines deliver on those three dimensions, access, affordability, empowerment, is through removal of friction.

This is a really, really complicated, almost incomprehensible slide. This is from an annual report on the flows of product, funds, contractual arrangements, and dispensing of a prescription medicine. I want you to close your eyes and when you open them, pretend that the right-hand side of that slide is gone. Pretend there are a few other little tweaks that simplify the left-hand side of that slide. Fewer layers, fewer steps, less friction.

That's the system level. At the individual level, there's the removal of time to get a medical appointment, the separate time to fill a prescription, and the copay for both. Beyond time and money, there's also an aspect of privacy in some OTC categories. That's among the reasons. Certainly, not the only reason, but that's among the reason. When nicotine replacement therapies were switched 25 years ago, utilization increased by over 200%. And we typically see utilization increase by around a third when something switches from prescription to nonprescription status. That's the power of OTC access.

One more empowerment example. From 2009 to 2015, that's a period that overlaps with the introduction of two switches for seasonal allergic rhinitis and shortly after, a third. In that time period, three things going on. One, number of allergy sufferers was increasing. Two, the percentage of allergy sufferers using an OTC medicine increased from 66% to 75%. And three, the percentage of allergy sufferers going to a healthcare professional decreased from 31% to 28%. That's a real impact.

As to direct out-of-pocket costs, that's one of the big elephants in the room. If you are fortunate enough to be taking a prescription medicine that's generic, if you have coverage for that medicine, which you might or might not, not every prescription medicine is covered, if you have a platinum or gold plan, if you got a prescription at a doctor's visit you were already going to have anyway, then yes, your out-of-pocket cost might be less for that prescription than it would be for the OTC, but that's not the America in which most people live.

Less than 15% of Americans have a gold or a platinum plan. One in eight Americans lacks prescription coverage altogether, and high-deductible plans are becoming more common where you could have easily not reached your deductible. And the OTC version could simply cost less. Adapalene for acne, for example, averaged about \$50 as a prescription drug, and now averages 16 as an OTC. That's a 70% reduction.

So, summing up. Every dollar spent on OTC saves the healthcare system over \$7 in healthcare spending, and value goes beyond convenience. It's costs, it's removing barriers, it's helping free up clinical resources where they're more valuable. I'm looking forward to our discussion.

Anna Hung:

Thanks so much. So let's go ahead and have a few remarks from Henry, if you're ready to give a few remarks.

Henry Lim:

Okay. Thank you very much. All right. So the topic that I have to cover is on the dermatology example. I will do that mainly because it is a very consumer-facing type of specialty. So if you look at the dermatology, many of the skin health treatment modalities, very much consumer-facing. If you think about acne, we mentioned twice already this morning about Adapalene or this afternoon. Pigmentation, hair, nail, inflammation, itch, wound care, and so on. The list is very, very long. Consumers can make the diagnosis themselves. They know what it is, and the question is then how to treat it.

There are examples in dermatology that has prescription to OTC switch and somewhat that we mentioned. Topical antifungals, actually, is a very big and common example in dermatology. You can see I put down here clotrimazole cream. It was first approved as prescription in 1975 and switched to OTC in 1989.

Topical minoxidil that many patients use, many public use, minoxidil solution approved in 1988 as a prescription item. 1996, is an over-the-counter medication. And Differin have been mentioned twice already, 1996, switched in 2016. We all use this on a clinical practice on a regular basis in terms of recommending to the patient using this medication. We know the safety profile. We all are very, very comfortable with it, mainly because there are robust clinical studies when approval was granted as prescription medication, as Eric had mentioned.

Consumer use safety and risk management data available. We all know, and we have dealt with patients who are using this real-world use. Consideration is already there, and then plans for post-marketing commitments and monitoring, post-marketing monitoring already is there. So it's very, very safe medication, very commonly used medications, and consumers know what are the things that they can do or what are the side effects to look for.

There are other methods of getting nonprescription medications. For example, as I think Karen had mentioned. One is through new drug application process. I'm going to use specifically a dermatology example that somehow did not work. Ecamsule, Mexoryl SX, is a UVA filter, dermatology sunscreen, UV filter. It's considered to be a nonprescription drug, so it goes through a very, very rigorous approval process.

This particular medication, the manufacturer decided to go through the NDA process. So this was finally after very significant expense from the manufacturer and very significant effort, it was finally approved in 2006. Keep in mind that Ecamsule has been in use in Europe since 1990. So we are quite far... By then, even then, it was quite far behind already.

But looking at the second slide here, the second bullet, inability to modify the final products, because in sunscreen, manufacturer would, a lot of time, put in different type of other active ingredients that are approved. Even changing the concentration or changing the size of the tubing, it was not allowed, because under NDA process, it requires very significant effort, so the decision based on purely on business reason is no longer marketed in the US. So the bottom line is that this particular filter is no longer approved, no longer available in the United States.

The other one is through OTC monograph. Karen had already mentioned, we are very grateful to the FDA for proposing the BEMT, bemotrizinol, which has been approved globally since 2000. So we are 26 years behind. But nonetheless, we are catching up very nicely. It is now being proposed by the FDA to be approved to be monograph filter as generally recognized as safe and effective, the grace nomenclature that Karen mentioned about her slides. Meaning, that even if it is approved, it is considered to be a very approved usable sunscreen, UE filter that can be used in the United States.

Currently, the comment period is over, and then FDA is in the process, I'm sure Karen is very much involved, in getting all the comments put together so that they can respond appropriately to all the

comments that had been raised. And this was done in December 2025. So comments period is three months after that, so the three months comment period is over.

Just want to highlight the last chemical organic, which is the preferred term by the FDA on UV filters for this type of UV filters called organic UV filter, was approved in the United States since 1999. 1999, ensulizole, a UVB filter. The advantage of this particular filter is because it's larger molecule. So in terms of penetration to the skin, which is a major controversy within dermatology and within medicine in general, the penetration to the skin is significantly, significantly less, and it is very, very photostable, which is another very important consideration to keep. Again, had been used globally since 2000.

Example of other countries. I think we just have to be careful about switching prescription to nonprescription medication. The one I want to highlight is high-potency topical corticosteroids. In many countries... and people nowadays travel all over the world. In many countries, topical corticosteroids can be obtained without prescription, and there lies the potential for abuse.

It is used for skin bleaching, which is currently a global epidemic. It causes stretch marks on the skin, skin thinning, bruises, and skin cancer, and significant public health issue. Clearly, this is cultural. In many parts of the world, people want to be fair. And then in Africa, for example, a lot of times, children, as soon as they're born, they started using topical corticosteroids so that they can be growing up fairer skin.

A typical example is shown here. This is in 2010, Sammy Sosa. For those of you of certain age, you remember him, and he was a baseball player. You can see that after two years of using topical corticosteroids, he was significantly fairer. Clearly, this is not something that we want to recommend to any of our patients. So one has to be very, very careful.

So, in summary, the switch would improve access. There is no doubt about it. It's less expensive, easier for patient to get. I think Adapalene was a good example of that, but there are many others. Minoxidil being another one. Would decrease the economic burden to the society. However, proper selection of the class of medications, the right medication use is obviously very, very essential. And lastly, approval process needs to be efficient, yet have to be data-driven and scientifically based. And I'm very, very much looking forward to the FDA now that... Hopefully, this will continue to move forward very smoothly and in a user-friendly fashion. Thank you very much.

Anna Hung:

Thanks so much. And Mariana.

Mariana Socal:

Thank you, everyone. And thank you so much for the opportunity to be here and discuss with you today. I think I'm the last one in the panel because I'm going to talk about money, right? So I'm Mariana Socal. I'm an associate professor of health policy and management at Johns Hopkins University, Bloomberg School of Public Health. And I work in a team that is called the Johns Hopkins Drug Access and Affordability Initiative. And I think we already talk a lot about access right now, right? Like, "How much having to go visit a provider, get a prescription, and then get the prescription sent to a pharmacy, go to the pharmacy, the drug is in stock, and then how much the whole process can often hinder access?" But I'm going to focus now on the specific issue of affordability, and I'm sure this is at the very top of all our minds. This has not left the public conversation for a long time.

Every year, surveys of the American public show that about one in four, one in five Americans has reported difficulty affording the drugs that they needed because of the cost. Right? Even fully insured individuals often have difficulty affording some prescription drug. So our focus here is understanding

how does cost matter in this conversation. If we are to expand access, what are the trade-offs that we're going to be facing when it comes to cost?

It was already demonstrated today or brought up today that non-prescription drugs can be cheaper than prescription. The same product, the same molecule, oftentimes, the same formulation. It can be available into these different channels, but it is possible that a nonprescription version can be cheaper because, like David was just mentioning, it bypasses this entire infrastructure that has to do with billing, et cetera.

Well, we tried to examine that from an empirical perspective. We are academics. We're going to try to bring evidence into this conversation. And what we did in the 2024 study that came out in JAMA, we identified 19 drugs that they had a dual regulatory status. They were approved for prescription status and approved for nonprescription. Of course, they had minor difference in terms of indications, but it was the same formulation.

We tried to compare therefore apples to apples as much as possible, and we compare the prices paid in Medicare by the plan and the patient. What we found, of course, there's always fluctuations, right? We're looking at nationwide data, so it's not always that the same drug will have the same pattern, but these are averages. So out of 16 out of the 19 drugs had, on average, per unit, nonprescription prices that were lower than the Medicare spending on that drug for the same unit. So if we're talking a milligram, it's a milligram. If it's a pill, it's a pill, et cetera.

If we consider each individual drug, savings could have been between 10% and 97%. I bet if anybody put it in the bingo, me too, I would not have put 97%. It's a very high value. It's a very high discount, and we were not expecting that. Overall, the total spending would have been reduced by 57% if Medicare had consistently used the nonprescription cash prices instead of those prices that were actually recorded in the claims. And savings in this one year would have been 406 million. We're talking only 16 drugs, only a very small number of drugs.

I think one important and really, really important finding here is that when we look at what the patient had paid... I'm going to show this in this graph. It's very low font, but these are the specific drugs we examined. There is ibuprofen. There is omeprazole that was already discussed today. What we found is that for several drugs, more than 10% of claims, the patient had paid more for their copay as compared to the total cost of the drug in the full nonprescription market. Okay?

So here's a few problems that we have moving forward with this conversation. The first problem is that it's not a consistent story across all drugs. We'll see for some drugs, patients would not have saved, so it's different. It varies drug by drug. And a second issue is that in this situation, often, plans will not cover this drug.

If it is fully over the counter, there is... We often talk about how much of a patchwork our healthcare system is, right? Like, different rules, different coverage, different everything. But when it comes to coverage or reimbursement for nonprescription drugs, that's the point that we see the biggest patchwork some plans will cover. Some plans will give you an allowance for that. Some plans will not cover and some will, as long as you bring in a prescription, which defeats the purpose, right? So we have to consider, "Can patients... From a mathematical money standpoint, can they be making the best option for them?" And I'll explain what I mean.

So, for most chronic conditions, patients often need multiple drugs for their treatment. In assuming that one drug is not covered by their insurance, then patients will pay out of pocket for that. Well, that doesn't count to the deductible, right? And so the future drugs that they want covered under insurance, they will lose those dollars that went into the nonprescription that could have counted into the

deductible. So I think that the message here is that ideally, we would have one clear pathway through which these drugs could be at least covered or at least more clarified in terms of reimbursement.

I'm listing here the main trade-offs between nonprescription access and insurance coverage to try to clarify this point. So when patients have insurance coverage, insurers will share the cost with the patient, but it is the insurer that determines cost sharing requirements. It is a function of the plan to say you're going to end up paying more unfortunately than you could have, and many patients will not see there. Patients must meet the deductible first, and most insurers do not cover OTC drugs. Therefore, in these situations, patients must pay cash.

Using insurance may be beneficial for patients who use high cost-drugs or multi-drug regimens. Nonprescription status facilitate taxes because it removes this prescription requirement. However, patients, they do not need to see a provider. They can generate medical care savings like we just saw, but cash pay cannot always be cheaper and not contribute to the deductible.

So we think that OTC drug costs can be progressively more reimbursed. Today, they are reimbursed in Medicaid under prescription. In Medicare, some plans in Medicare Advantage give you a card that you can just pay for your OTC drugs and also health savings accounts in the commercial market. So these are some thoughts. I think there's a lot of work to do in this space as we consider expanding this market, especially for more expensive drugs, and I look forward to your questions. Thank you.

Anna Hung:

Thanks so much. Those are all very, very nice presentations. And I feel like we've covered quite a few topics already, right, talking about the access, talking about the potential risk, talking about the cost side of things. So, let's go back. I'm going to bring up a couple questions I have here, but I...

PART 2 OF 8 ENDS [01:04:04]

Anna Hung:

Let's go back. I'm going to bring up a couple questions I have here, but I also want to remind the audience that we've got this code up because we will also take some questions from the audience and you're welcome to scan that QR code and enter your questions as we go along.

Mariana Socal:

I don't think we have the right QR code.

Anna Hung:

Oh, I'm sorry. Right, that's right. So if we could show that QR code. Oh, perfect. Thank you so much. Okay. So let's go ahead and start with just a couple questions here. So thinking again from maybe the patient perspective and considering we've heard a lot of very helpful examples, thank you to the panel. But just thinking about historical switches, modeling of potential future switches, how do these prescription to over-the-counter switches generally affect outcomes, cost, access? What are the things that contribute to improved health outcomes or reduced costs for patients? And maybe David, I'll start with you, but then kind of open it up.

David Spangler:

I think I mentioned a couple of clear examples. Smoking cessation, a really obvious one, where it's not as though doctors don't want you to quit smoking. It's a question though of it's a super personal journey. It

takes lots and lots of quit attempt. The Mark Twain quote is, "It's easy to quit smoking. I've done it hundreds of times." And having that OTC access so that as people were going on their journey, they had control of the timing, they had control of the motivations. I think that was a huge win. I referenced the allergy example where yes, there were antihistamines out there already, but the introduction of that new class saw a meaningful reduction in visits for allergy. Dr. Brass talked about the PPI example. Really old example that Dr. Lim referenced was the switch of vaginal yeast infection products where you did see a reduction in women having to go back for another visit when they could get it immediately. So those are four pretty classic examples, and I think there could certainly be a lot more.

Anna Hung:

Thank you. Yeah, I think it's hard to weigh all of these different pieces. And so I guess maybe I'll go to Henry, to Dr. Lim, to thinking a little bit about, from your perspective as well, what are some of the other aspects of this and factors that will contribute to improve health outcomes or thinking about the drug classes that makes sense.

Henry Lim:

Right. I think I would fully agree with David that access is an important issue with the switch with the non-prescription medication. Patients can diagnose, they know what they have and they put on the medication and they save a visit to the physician. I think it is definitely a significant and significant advantage. Cost obviously is another part. That is also a significant advantage. The cautionary part is that, and most patients are quite educated enough that sometimes they misdiagnose the condition. Again, in skin, we just example that there are plenty, ringworm is one thing. However, nummular dermatitis. Mycosis fungoid is [inaudible 01:07:09] cell lymphoma. Clinically, sometimes they look the same. You cannot expect patient to know the difference sometimes. Fortunately, all these medications are benign enough. Even if patient misdiagnosed it, they use the medication, the condition didn't get better, no harm is done. Except for some delayed in diagnosis, they eventually come to the physician. So that's the part that I think we just have to be aware of.

Anna Hung:

Yes, please.

Eric Brass:

So just a couple of points. First of all, I think this last point is really important because the other thing, the drug FAQs label or any other labeling can do is guide informed deselection. So once you've started using the product and you don't respond properly, the label then tells you what to do and we can actually improve timely access for more serious conditions through that kind of labeling. The second point I'd make related to what David said, excuse me, is that we have to be careful not to create new barriers in the non-prescription space. So for example, again, there's just a wealth of information available. So when smoking cessation products were introduced in Australia, they were initially introduced behind the counter and it was a small tick in access, but then they went from behind the counter to in front of the counter and sales and smoking cessation attempts exploded. So we have to be very careful even when we talk about innovation, that that innovation doesn't unnecessarily impose new barriers on consumers.

Anna Hung:

Great. Yes.

Mariana Socal:

What I would add is that from a health services research perspective and like health system management perspective, what we don't observe, what we can't measure, we can't take into consideration. So just yesterday I was in the hill, was testifying on a hearing about pharmacy benefit managers, and there was a huge number of health data organizations just talking about AI and medical records and so on. Well, if you completely move a drug to non-prescription status and it doesn't get covered, it doesn't also get captured and your provider may not know about it. So I do think that because, and by full disclosure, I'm a provider myself, I'm a physician, so I'm kind of like speaking for my people here, but patients often will need the provider help to understand what's the best deal for them on the long term. Given my condition, given the drugs that I'm taking, what is going to be the best alternative for me?

Is it still, can you send me a prescription so I can get this with a coupon from the drug manufacturer, for example. Given my plan, can we do this therapeutic regimen so we can optimize costs? So thinking specifically from the cost perspective, I think it is still very important that the prescription environment exists so it can be, while with the tools we have, it can be recorded in some ways and also patients can access the provider and the provider's ability to then expand coverage for them.

Anna Hung:

Yes.

Henry Lim:

If I may, add to the point also, I think as Marianne had mentioned at the end of the talk that there's still a lot of work, a lot of thinking that has to be done in this space. And this reminds me about, for those of you who read the New York Times Magazine this weekend, they have a whole writeup about finasteride, oral finasteride, which is primarily used for prostate in the beginning, but now finasteride at one milligram is being used for hair growth. So they're talking about how all these young people, men, are asking for finasteride. Mothers who bring in their teenager son to come to see dermatologists to get a finasteride prescription, mainly because this is known and accurate clinically, that if you start finasteride earlier, you would prevent the progression of the hair loss. So they wanted to make sure that everybody would prevent hairs.

David Spangler:

Why didn't I know that 40 years ago?

Henry Lim:

Now you know. So I think that comes for us to think about and for FDA to think about, is this something that needs to be regulated? Is it something that eventually ... Because right now, there are a lot of companies that can get finasteride by filling up some certain forms without having to be seen by physician. So I think there's still a lot of areas that has to be thought about.

Anna Hung:

Absolutely. All of these system considerations and how do we ensure that the safety of all of this makes sense. I also want to circle back and we've given a lot of examples, but for FDA, for other sponsors who are thinking about the therapeutic drug classes and the areas that maybe they should look at, or maybe the characteristics of those drug classes or therapeutic areas, are there comments that you all could

make in terms of features that make a specific drug class maybe a good target? And I think we've talked a little bit about some of that already today, but maybe to kind of formally just start thinking out loud about that and maybe I'll open it up to anyone to start for that question.

Eric Brass:

I think the opening presentation gave a good high level view of those considerations and then everything else needs to be individually assessed in terms of what the benefit risk is and your ability to mitigate those risks through labeling or ACNU or some other strategy that ensures you end up with a favorable benefit risk. And I think there are lots of examples where I can cite where it's really easy to get it wrong, where the risks would greatly exceed the benefits. And that same example, I can articulate ways to make the benefits exceed the risks. So I think it really just requires careful example by example consideration. And as I say, the obligation initially is on the sponsor to do an evidence-based assessment to show how those benefits are going to outweigh the risk, because nothing is going to be zero risk. It's always going to be easy to articulate what the risks of a switch are.

And unless you can articulate what those incremental benefits are, those risks cannot offset the already availability by prescription. So there has to be some additional benefit, and that's almost always rooted in unmet need, that how self-care is being delivered now, how populations are not accessing the product because of barriers, cultural or otherwise that represent barriers to access. And those, as I say, need to be individually accessed. And I think there are lots of examples that can meet that and others that can't.

Anna Hung:

Yeah, that's so helpful. I think about public health needs as well, like Naloxone we talked a little bit about and even like the OPIL, so that barrier piece is really helpful to hear about.

David Spangler:

I think you're on it too. Again, definitely agree with everything Eric said, that it is about the drug, got to have the margin of safety, got to have the data. But when you think about things like migraine, like BPH, like a wider range of contraception, anaphylaxis, hormone replacement therapy, things that are really, really prevalent and you only need to go to that doctor once probably to know, "Okay, this is what I got. I've got the bees. I'm going to go hiking this weekend. I better pick up my anaphylactic emergency treatment." And again, assuming the molecule meets the muster with FDA, things like that are just ripe for prescription and non-prescription switches.

Mariana Socal:

I think it's really at the trade-off between how risky the treatment it is by itself. And we've talked a lot about many scenarios that generally speaking is the risk is not that high, but really also about conditions that are lifelong, that the patient can self-manage because they got the diagnosis at one point in time. I think severe migraine is a very clear one. But I would add one layer here that the lack of access or a delay in access by itself is a risk for that patient. We're talking about vaginal yeast infections. We can talk about severe migraine again, or even asthma attacks, that if you have to wait one day, two days to go to your doctor, maybe those are two days you're going to be in bed because you don't have access to your sumatriptan or some other anti-migraine medication. And I think that from a patient perspective, a quality of life perspective, that's a risk that if we can mitigate, it would be great.

Henry Lim:

The other aspect that I think we can think about and discuss about, and coming back to dermatology, is the treatment for hyperpigmentation, especially for doxin individually that acne is a blemishes that is bothersome to the patient because they don't go away for a long period of time. Nowadays, with the science being developing very, very nicely, they are over-the-counter medications. It's very, very effective and very good and scientifically based in decreasing the hyperpigmentation. Currently, we do have a prescription medication, hydroquinone to use. The question is that do we still need hydroquinone because it does have side effect, cannot be used for long period time. It is prescription at higher concentration, but not that lower concentration. So those are the, again, discussion that may be out of the scope here, but then we have to think about that. We have to be aware of the advances.

Anna Hung:

Yeah. So that individual case by case and looking at the evidence, I kind of want to go into that a little bit too. I know that's going to be our next session as well, so we'll kind of segue into that. But just thinking about some of the studies that have been done to look at how well consumers understand these products, these drug FAQ labels and be able to self-diagnose. Can we talk a little bit more about that? We saw some examples. I guess what have been key lessons that we've learned and going forward, what are some of the things that stakeholders can do to keep supporting that evidence? Or maybe there's areas of improvement as well.

Eric Brass:

So whenever you begin a statement, can you say a few words about ... The answer is yes. So I think this is an area where we've grown a lot because we've had now 30 years of experience with the kind of current structure and I actually chaired the NDAC meeting where we first developed expectations for how self-selection and actual use studies should be done. And we said a lot of things are really smart and now we look back and say we said a lot of things are really dumb and that I think we need to leverage those learnings into how we think about self-selection and actual use studies. The number one consideration for me, as I alluded to, is we always have to incorporate the clinical consequences of any behavior and understanding its contributions in those studies so that it's typical to try to benchmark endpoints and what the expectation is for a successful outcome in terms of the behavior.

X percent of people should get this right. I think we have to make sure that how we set that bar is evidence-based and that evidence has to be based on the clinical consequences should that behavior occur. And I think that's a learning we've learned the hard way. The second thing we've learned is that what is really simple for us when we write these studies is really hard for consumers when they try to execute these studies. And it may be very clear what we mean when we ask questions. It's not always clear what the question means to the consumer who tries to answer it. And I think we've learned that taking their responses at face value as to what they truly understand, may underestimate how much they truly understand about the label. And I think that we've learned a lot as to how we can modify our assessment of responses in both self-selection and actual use studies to better understand what the consumer really understood about the label and what they really intended in their behavior.

So those would be two learnings I think that I've come away with after doing this for 30 years.

Anna Hung:

Great. Any other thoughts from the panel around how we assess that and how do we continue to ensure that there's good evidence to support the kind of drug classes that we think about for these prescription to non-prescription switches?

David Spangler:

I also wonder, this isn't a recommendation, I'm just wondering. Sometimes when there's a condition that the drugs have a common element of challenge that the medical community or FDA thinks needs to be overcome, if there's some forum in an advisory committee, be it a round table, be it something else at the front end before the sponsor gets too far down the development path, as opposed to the advisory committee meeting at the end. That's not going to be always the solution, but that might solve and help folks figure out and get more minds or crowdsourcing almost to think about how to solve that challenge. I can't come up with a hypothetical right off the top of my head, but ... Well.

Eric Brass:

Again, the example is when we held the NDAC on how to do consumer testing. That was a generic question that benefited from a really broad discussion, from a variety of areas of expertise. I think some people who might've participated are in the room, that's how old we all are. And I think there are a number of questions like that where I think a general discussion can help the regulators going forward and help the industry better design and provide the regulators the information they need.

Mariana Socal:

I would add, even though we have so much work ahead of us, I think we already have very good, powerful tools to do that work. And I'm thinking specifically of the FDA being ever more open to real world evidence. We're having more artificial intelligence incorporated into electronic medical records and so on. However, I do think that we have to come up with better ways to incorporate the information from the non-prescription environment into the medical record environment so that we can monitor that utilization over time, monitor how many patients end up going to the emergency department or whatever the hypothesis is. And partnering with patients themselves, I think it's a good way to do that. And having patients, some sort of platform that patients can enter that information maybe to get reimbursed or maybe just to share that information, I think these are some of the pathways to combine these two environments.

David Spangler:

Can I ask a fellow panelist a question?

Anna Hung:

Oh, absolutely.

David Spangler:

On that point, do you think ... Well, this is a true question. I do not know the answer to this question. I'm doing what lawyers aren't supposed to do. I'm asking a question I don't know the answer. Do you think Medicare Advantage plans are taking advantage when they do have supplemental benefits with an OTC benefit? And that's about two thirds of them. They have means to capture that. They know who's using that debit card for what? Are they integrating that? Do you know?

Mariana Socal:

They might. But what I do know is that those benefits are very rarely used. About 30% of the dollars in those benefits are actually used by patients. So there's a huge opportunity there. And I think that could be a very good test pilot so that we could learn more about how to do it right.

Anna Hung:

And this actually feeds into one of the audience questions that I have. So again, feel free to send along any audience questions. There's a couple that's kind of more related to this insurance coverage piece. So the question is, what are some pathways, either hypothetical or in practice, for insurance to monitor and incorporate OTC drug purchases toward plan spend?

Mariana Socal:

Yeah, I think one of them is using savings accounts. Today, patients are already authorized. They can already use their savings accounts to get reimbursed for over-the-counter drugs, non-prescription drugs. So that's one way is just a lot of information that is just sitting there and perhaps just not being used. And it may be time to change that.

David Spangler:

Like spending accounts, health savings accounts, for sure, you can gather that information. You could also ... The Medicare Advantage supplemental benefit plans, recognizing, as you said, if you get two-thirds even offering the OTC benefit and only a third using it to its full extent, but you're still getting information there. And then third, it's about buyers as opposed to users. So for a family, they're not going to be a one-on-one correlation, but you're going to get some good estimations of retailer information. When it goes across that scanner, they're gathering it. And if you've got a loyalty card at that store, they know who the buyer is. Again, that's not a one-to-one correlation, but what's the average family size? Two and a half people. So I mean, if they're getting a pediatric cough cold product and I was the buyer, you know I'm not the user, but you know, okay, there's a child in that household. So you can make ... And when you're talking population level, when you're talking hundreds of millions of units, that's a lot of data to mind.

Mariana Socal:

Even Medicaid programs often cover these drugs. Not every single state does, but several states do. So it's one more area where the information is there. So we just need to use it.

Anna Hung:

Yeah.

Eric Brass:

This also poses a challenge for the medical community because medical records don't capture, even though they're offered to ask, even though the medical record prompts the question, they don't capture OTC drugs with any precision whatsoever. And so that I think the medical community needs to do a better job of asking patients explicitly about over-the-counter drugs, not just assuming, because most consumers don't really consider them the same as drugs. So when asked what drugs do you take, they don't volunteer that they use over-the-counter medications and physicians don't push. So as I say, every visit I get to update my medication list, I don't tell them about the OTC drugs.

Henry Lim:

Along that line, I think the other group that we really need to get engaged with is the patient support group. And because they're now very, very well organized, a lot of them are disease specific, but if we're considering one particular class medication, for example, for eczema, there's very well organized patient

support group. They can provide very significant and important input upfront. They are going to be the one who is using it if indeed it becomes, say, not prescription.

Anna Hung:

Absolutely. Yeah, this is wonderful. Let's see. I think we do have ... Okay, so I'm being asked to put in one more final question to ask a little bit about more of the kind of potential downsides of expanding into non-prescription access. So we've touched a little bit on it. Could we maybe talk a little bit more about this, the downsides? Will any of you start?

Eric Brass:

So as alluded to, we have to avoid cost shifting that just because there's an opportunity doesn't mean the cost savings to the consumer or patient will be realized if all we do is cost shift. So we have to be very cognizant of how that actually is going to play out. Two, again, medications have risks and we need to be explicit in understanding them and making sure we've mitigated them to a degree that maintains the benefit risk proposition, and those risks are real. I think I cringed at your example of finasteride because I think you just put a nail in the coffin of a switch of finasteride because of the off-label use that we all need to be worried about.

And the final thing is public education is so ... I don't mean public education in schools, but public education about medications and treatments is so horrendous that it's impossible to differentiate an advertisement or influencer advocating the most bizarre unapproved therapy from an approved therapy. And differentiating those in consumers' minds is really critical to the success of this effort if we're going to improve public health. If we can't differentiate safe and effective drugs from quack therapies, we're going to lose.

Mariana Socal:

Important to add to this, so from a direct to consumer advertisement perspective, we ran a behavioral experiment with consumers. And we did a fictitious insulin product, and the only thing we changed in the advertisement was you need a prescription for this biosimilar versus you don't need a prescription. And that language of you need a prescription, consumers reacted to it, questioning how good that product was, how equivalent it was to the ... It was like a fictitious biosimilar to the originator insulin, but when they knew, I need a new prescription, I can't just substitute, just that language signaled something to patients that they were more skeptical of how good that medication was. So I think there's still a lot to learn in that when it comes to, you're going to empower patients, but what else can we learn from that?

From an insurance perspective, I think it also, we need to change the mindset that insurers have. They often get paid based on the severity sometimes of people's actual events. So if you think about a patient with migraine who's doing almost all treatment with non-prescription drugs, how can that patient then "prove" that they have that level of severity, right? If it's not in the medical record, they didn't come to a provider, they don't have a prescription. So I do think that some elements of our culture, both in the provider side, but also in the patient side, we need to at the very least just understand better.

Anna Hung:

If no other comments, we are at the end of our session right on time. And so thank you so much to our panelists. If you can all join me in thanking them.

Valerie J. Parker:

Welcome back everyone. My name is Valerie Parker. I'm an assistant research director with the Biomedical Innovation Team here at Duke Margolis Institute for Health Policy, where I lead projects on our regulatory and RWE of portfolios, and I'll be the moderator of this next session. For the next hour and a half, we'll be focused on evidence generation to demonstrate safety and efficacy for non-prescription drugs. This process looks different for the non-prescription setting than it does for the prescription setting. It centers on non-prescription consumer studies that Karen described for us earlier today. Label comprehension studies, self-selection studies, actual use studies, and/or human factor studies may be necessary.

We'll begin with a presentation overviewing what some of those studies may look like and how they can answer key questions about a drug's appropriateness for non-prescription status. Then we'll have plenty of time to discuss some of the key challenges in the space and opportunities to improve and innovate. To provide that overview presentation, we have Russell Bradford, Senior Vice President at PEGUS Research. Russ, could you please come up?

Russell Bradford:

Good afternoon. As Val mentioned, I'm Russ Bradford, and I appreciate the opportunity to speak today, and I seem to be missing a clicker. Is anybody ... So Dr. Brass focused many of his comments on the benefit side of the equation when it comes to evaluating a product for OTC availability, and I'm going to spend my time talking about how we understand, quantify, and mitigate risks a little bit. So who am I and why do I have the microphone? I'm a physician who practices inpatient pediatric care. And so in that capacity, I get to see how patients that in their families interact with non-prescription products all the time. I'm also senior vice president at PEGUS Research, which is a contracts research organization that specializes in consumer behavior research of all sorts, particularly involving products that companies are interested in switching from prescription to over-the-counter status. And that leads to my disclosures.

I work for PEGUS and we are contracted by sponsor companies to provide consulting and conduct of consumer behavior studies. And in that capacity, I get to work with teams from those sponsoring companies, but I have no financial or other relationship with them outside of that. Now I'm going to give you a disclosure of a different sort. Today, I'm going to be talking about a fictional new product, and this is to demonstrate some key principles of consumer behavior research. So with that, I want to introduce you to Loweritol.

The manufacturer of Loweritol is very excited about its potential to fill a need for a safe and effective non-prescription antihypertensive. It has some interesting characteristics, so I'm going to show you a little bit about why they're excited. First, Loweritol is an antihypertensive with a novel mechanism of action. It has minimal interactions with other products. It's dosed once daily. It's dosed as an inhaled powder formulation, supplied as powder-filled capsules, and the capsules are loaded into a dry powder inhaler and activated and inhaled. Dosing is weight-based with the number of capsules per dose depending on body weight. And it's recommended that Loweritol be dosed first thing in the morning, because that's when it's most effective. Studies show that morning dosing is about 5% more effective than evening dosing.

In clinical trials and subsequent clinical use, the company has demonstrated that Loweritol is safe and effective, especially when used as directed and in fact has a very favorable efficacy and safety profile compared to some of the other antihypertensives. And that's one of the reasons why the company is excited about its OTC potential. However, there are a couple of warnings that we should note. First, while it's not contraindicated to use with other antihypertensives, caution is advised. Because of its mechanism of dosing, it's ineffective in those with cystic fibrosis because of their thickened pulmonary mucus. And riociguat, a pulmonary vasodilator, potentiates the action of Loweritol, which can lead to

some dangerous systemic hypotension. So you can see that there's some interesting features potentially intriguing about this new product, and you can imagine why the company might be enthusiastic. However, some of those features also raise some significant questions and concerns.

The company has just had their first interaction with the division of non-prescription drugs, and during that interaction, they got some advice from Dr. Murray and team about the features of Loweritol and what concerns they might raise for potential OTC approval. Antihypertensives have long been sort of talked about as a potential for OTC availability, given what you might imagine the public health benefit could be, but this would represent a brand new indication to the OTC marketplace. It's largely an asymptomatic condition, so it raises the question to-

### PART 3 OF 8 ENDS [01:36:04]

Russell Bradford:

It's largely an asymptomatic condition, so it raises the question, do consumers understand it? Would they understand the chronic nature of treatment? To judge whether an individual should use Loweritol, they would need to know their blood pressure numbers before beginning use. And so the question would be, can they accurately measure their blood pressure? Can they interpret the results in light of the label directions? And during use, the consumer needs to monitor their blood pressure to know whether it's working for them. Do they understand this instruction? Will they follow it? And can they actually use those results to guide their future use of the product and potentially seek care if it's indicated?

This product's an inhaled powder. That might be an unfamiliar concept to some consumers. Will they understand that it's a powder to be inhaled and not a capsule to be swallowed? Will they be able to follow the directions to deliver an appropriate and accurate dose using the dry powder inhaler? Will they understand how many capsules they need to use based on how much they weigh? And do they understand when they should deliver a dose, and will they comply with those directions? Do they know if they're taking an antihypertensive already? And if so, will they seek advice from a healthcare professional? Will consumers with cystic fibrosis understand that this product is not appropriate for them? And perhaps most importantly, do those taking riociguat recognize the instruction not to use Loweritol, and will they follow it?

So this represents a considerable list of potential issues. And yes, we already know that the product is safe and effective when it's used in a prescription and directed environment, but in a non-prescription setting, those directions come from the product labeling, not from a healthcare professional. So then how then do we generate the data that helps us address those many questions? These are important issues. They're not answered in a randomized clinical trial, but they cannot be ignored. And these are precisely the kinds of questions that consumer behavior studies are designed to address. So we've heard a little bit about these studies, but let me briefly describe five of the most common behavioral studies used in product development programs.

The first is a non-clinical study known as a label comprehension study. And the goal of label comp studies are to assess how well each of the key messages from the product labeling, particularly the drug facts label, are understood by typical consumers. A research program for a non-prescription product with new labeling might require iterative testing of a label with revisions to the label based on learnings from each study. Next are label discernment studies. These are less commonly used and are typically focused on helping evaluate whether product labeling effectively communicates the differences between a new product and other products that might be a source of confusion. And these two first

studies are generally conducted in a general population sample. But the next, self-selection studies, are focused on those who have a potential interest in using the product.

The goal of a self-selection study is to assess whether those who should not use a product appropriately recognize that and correctly identify that the product is not okay for use, all while guided only by the drug facts label. Next are human factor studies. These assess how well consumers can use devices or systems that either themselves are the product or that are a key component of the product. And then finally, actual use studies. These are observational clinical trials that essentially simulate the non-prescription environment and measure the use behaviors of interest among the participants.

So with that bit of background, let's circle back to the issues raised by the characteristics of Loweritol with an eye towards how those issues might be addressed by consumer studies. So how do we evaluate whether consumers understand what this product's for? Well, label comprehension study is probably the first study you'd look to for this and is the primary tool for this question. And in that study, we would assess how well they understand this message and all the other individual labeling messages. To know whether someone should use the product, we've mentioned that they have to know what their blood pressure is, and the labeling might instruct consumers with normal blood pressure not to use the product, and potentially consumers with blood pressure higher than a certain threshold to seek the care of a healthcare professional rather than to use the product.

So a consumer essentially has to understand what blood pressure is. They have to know how to measure it. They have to be able to interpret their own blood pressure numbers and make an appropriate decision about whether they're a candidate for use. And demonstrating these is going to require essentially all of the consumer study types at our disposal at varying stages of the developmental program, but probably most prominently self-selection and actual use. After starting use, a user has to be able to monitor the effect and make correct decisions about continuing use and seeking healthcare professional when indicated. And while comprehension will help us understand how well the label communicates these messages, it's the actual use study that will show what consumers actually do.

How about the novel dosing method? There are no dry powder inhalers available over the counter. And you could imagine a confusion for a consumer who sees a capsule that might look like another oral capsule and assume it's to be swallowed. So how do we sort that out? Well, label comprehension, again, is important, but it's actual use that gives us that data. This product requires that the user interact with a device, and they would follow a set of instructions that essentially directing them how to use it. This is the classic problem studied in human factors testing, which outlines the ways in which consumers interface with a device like this one and identifies the ways that they might fail in their use of that device and help us understand the consequences of those failures.

This product requires variable dosing based on body weight. And it may be common in pediatric OTC products, but I'm not aware of an adult OTC product that uses this strategy. And so how might we study this? Label comprehension studies, self-selection studies, actual use studies will all be needed to demonstrate and reassure to the company and the FDA that consumers actually understand the message, apply it to themselves, and then actually do it. And then similarly, while assessing the comprehension of the dose timing message, that comprehension element is important. Observing how the product is actually used in the OTC environment is the domain of an actual use study, and is the proof of the pudding.

So now onto the warnings. Certainly, comprehension is of interest, but whether actual potential users will recognize that this warning applies to them, whether they will follow the directions to discuss with a doctor or pharmacy is the domain of self-selection and actual use studies. Will consumers with cystic fibrosis understand that they should not use this product? This is a classic self-selection question, and in this case, it would probably require what we call a targeted self-selection study, which specifically

evaluates a cohort of participants with cystic fibrosis because a general self-selection study is not likely to have a sufficient sample, if any. And then finally, perhaps most significant is the warning of the contraindication with riociguat. And again, a targeted self-selection would help demonstrate and generate the data to understand whether this warning is understood and heeded.

Let me just speak for a moment on the standards of performance when it comes to consumer behavior studies. In order to support the benefit of making a product available over the counter, for the most important labeling messages and endpoints, we typically establish the necessary thresholds for success a priori in collaboration with FDA. And each endpoint's threshold ought to depend heavily on the clinical relevance of that message, as Dr. Brass pointed out earlier.

So here are a few examples for this product. And looking at this list, while very few people may be taking riociguat, the consequence of ignoring this warning might be extreme, so we might need to demonstrate near perfect adherence to this message to be successful. In contrast, the consequences if someone with cystic fibrosis erroneously takes the product or if somebody takes it later in the day than the morning are quite low. So the messages might still be included on the labeling, but any associated performance threshold would either be low or perhaps unnecessary for these particular warnings.

And then finally, I'd like to say a word about additional conditions for non-prescription use. You could imagine a product like this, there might be several ways in which additional tools to support non-prescription availability might be useful. Those could be anything from supportive educational materials to an assisted self-selection tool. This tool could be focused and aimed at blood pressure measurement and interpretation or perhaps concomitant medication warnings.

However, the label is likely to be quite complex with a high cognitive load that is associated with a complex label like that. So you could also envision that a broader tool might be necessary to walk a consumer through all the important labeling elements. You could imagine materials aimed at giving instructions to consumers about how to use the product or tools to help a user monitor their blood pressure over time and make appropriate decisions.

So it appears that the company has a fair amount of work to do, but keep in mind Dr. Brass's discussion of benefit. At the end of the day, the public health benefit of an antihypertensive available over the counter should certainly be a driving consideration in light of the potential risks. And while fictional, I hope that this has been a useful illustration of the kinds of issues that new products might have and the possible strategies for addressing those concerns. Once again, thank you for the opportunity to participate. And certainly, especially if I've raised more questions than answered, feel free to reach out anytime.

Valerie J. Parker:

Bit of a height difference here. Okay, thank you so much, Russ, for the rundown of consumer behavior studies and some of those key pieces of evidence sponsors aim to generate as they conduct those studies for the non-prescription candidates. Now let's bring up the rest of our panelists to the stage, please, to build on these initial points. And as I call your name, please feel free to join us on stage.

So first we'll have Barbara Cohen, president of Cohen Non-Prescription Consulting, and formerly a social science reviewer in FDA's division of non-prescription drugs. Next, we'll have Ruth Day, director of the Medical Cognition Lab at Duke University and a professor in psychology, neuroscience and linguistics at the Duke Center for Aging. We'll also be joined by Alankar Gupta, Vice President and Head of North American Medical Affairs and Safety Sciences at Kenvue. We also have Irene Laurora, Senior Director for Medical and Regulatory Affairs at Perrigo. And finally, we'll have Michael Wolf, the James R. Webster Junior Professor of Medicine within the Feinberg School of Medicine at Northwestern University. And then for opening remarks, we wanted to begin with Ruth to talk a bit more about key factors for

consumer comprehension and some related points. And I see we all got settled. So Ruth, I'll give you the clicker.

Ruth S. Day:

So hello, everybody. The topic is cognitive accessibility of non-prescription drugs. My name is Ruth Day, and I direct the Medical Cognition Lab at Duke University, where we study comprehension, memory and use of drug information. I was a charter member of the Drug Safety and Risk Management Advisory Committee for FDA, and have served as a voting member of all of those other committees as well, including the Non-prescription Drugs Advisory Committee, fondly known as NDAP. And in all these experiences, I kept noticing problems with cognitive accessibility. Cognitive accessibility is the ease with which people can find, understand, remember, and use drug information and in a safe and effective manner. Poor cognitive accessibility occurs whenever people have trouble with any one or more of those processes. The drugs facts label, the drug facts label is key for self-selection and safe and effective use, but what about its cognitive accessibility?

Well, there are pros and cons. On the pro side, it certainly condenses a lot of key information. It's well-structured. It appears on all the OTC products. It's familiar and consumers expect it will be there. On the con side, it has limited real estate, which poses comprehensive challenges, but we're going to focus on the under-use or violation of cognitive principles. Let's look at some examples.

First of all, for directions. At the NDAC meeting back in the day, we were discussing different directions for different age groups and how to write it. And there you see one of the things that was proposed. There's lots of 12s and fours and sixes and one numbers in it. And the discussion went like this. The committee said, "It's way too confusing. We can't do it. We can't fit it on the label." And then somebody said, "Oh yes, we can. Use a matrix, age by direction." And that person was me. And since then it has been adopted, and the last time I checked in a pharmacy, it looked like that. But even it can be enhanced. So here in the enhancement, we have three of the key factors in taking a non-prescription drug. How many tablets, how often, and what is the maximum? And this display can then facilitate search and find tasks that a person might have, understanding certainly, but remembering later.

Now an example for warnings. Here we have a original version for aspirin. It looks great. We have three chunks of types of warnings, but uh-oh, at the bottom, we have stomach bleeding, which has been pushed into the alcohol warning chunk. And so we made, in our lab, an enhanced version where we simply pulled the stomach bleeding warning out and gave it its own title. And then we performed an experiment where people read either the original or the enhanced version in the drug facts label, and we tested comprehension and other cognitive processes.

So now we're going to plot percent correct for stomach bleeding, excuse me, stomach bleeding for the original with a hidden warning versus the enhanced with the accessible warning. And there are the results. There's 100% improvement simply by doing that. So warnings can be physically present, but functionally absent. Physically present, but functionally absent. Any information can be. Because it's there, it doesn't mean it's going to be functionally processed by people.

There are many other opportunities, not only on the drug facts label, but on the package itself, especially for self-selection. We can ask the question, "Is drug X right for you?" And then we could have factors in boxes and flesh things out about age, condition, contraindications, drug interactions, or we could show it in terms of appropriate people. Here would be like the ideal person versus people who should not. And of course, all of these can have various enhancements to flesh them out.

There are many more examples where we have sample changes... Excuse me, small changes lead to big improvements and comprehension, and big changes can lead to even bigger improvements. So the drug facts labels useful framework, but it does have cognitive violations. There are unused and underused

cognitive principles, yet we can increase cognitive accessibility and thereby increase attention, comprehension, memory, problem solving, decision making, and thereby facilitate safe and effective use.

So today we've only looked at a few cognitive principles. We look at clustering, put together what goes together; chunking, separate it from surrounding information; and alternative displays. For alternative displays, how to decide when to use each, we have to consider what is the content, uses, warnings, directions, and so on, but also what cognitive processes are we trying to facilitate, attention, comprehension, memory, and so forth, and then start considering what form of representation. That's it for right now about cognitive accessibility. Oh, by the way, I should have said back on this slide that the paper on the right tells more about alternative representation, and there's a link to it. So that's it for now. Thank you.

Valerie J. Parker:

Thanks so much, Ruth. So we're actually going to pass the clicker down. I realize I introduced you all in alphabetical order, and now we're going to go in presenting orders. So I think next we'll hear from Michael, who's going to provide a bit more of a sponsor perspective.

Michael Wolf:

This is the right Michael. Yes. So in the three to five minutes that I have to just basically talk, I already knew who was going to be presenting and I was just going to try to reiterate a few points that I thought about in the context to the non-Rx switch. And one, I was going to talk... From my perspective, I've been spending, much like Dr. Day and Dr. Brass and others, a lot of time thinking about how patients use medications, whether they be prescription or non-prescription, and where you want to make sure to have those assurances because people do unintentionally misuse products even when they're wanting the best for self-care. And so a lot of the work we've done has been focused on consumer studies, and I appreciate that great example -- love the fake drug, that's amazing -- in really kind of deconstructing all the different elements of what you need to cover and how people might misuse medicines.

I also want to talk about, we are trying to do a lot of work in our own healthcare system at Northwestern Medicine to identify safety signals. And there's the pros and cons of using real-world data and evidence and what you can think about and the validity of that evidence and how it can also though really, truly supplement the work. And I really appreciated Dr. Brass's comment about how it's really good to identify need. And I think that's a really important piece. And then third, I was going to just make a brief couple comments about monitoring opportunities that we're working on among many others and where we can think about it because I think it is a great opportunity to give people. Again, where we started off this morning, I think that its incremental benefit is a really important point that a lot of these products, especially when you saw some of the earlier presentations, drugs that have been available to patients through a learned intermediary for 15, 20 years.

And so we know a lot about how it's being used, even though many times we don't in clinical care have signals that are necessarily very apparent as to whether or not someone is maybe misusing a product and not getting optimal benefit, or they're experiencing maybe more minor effects that don't really get captured. So just thinking first about the issues around consumer studies, a few points I just wanted to make in thinking about what we've been doing in working with industry and also just within our own healthcare system and making patients safe around promoting health literacy and medication use.

I would say that our first point is I feel like a lot of the dialogue we've been hearing for a long time, and also having worked with the FDA for a long time, is that having more explicit guidance to industry on the study designs and goals and thinking about what is the optimal target for behavior versus just also just

helping people make informed health decisions around these products is going to be really critical. What is the goal? And I think also brought up at the beginning of this session, that may be tailored to each product. But even still, I think helping it being very clear, especially when people oftentimes come to us from industry wondering how large of a sample should I be doing in a consumer study, what should the outcomes be, how we design these things. I think all of that would be really important for us to continue to work on and seeing if we could find more articulate, more operationalized ways of doing that.

A lot of the work we do is focused around health literacy and have been for the past 25 years in thinking specifically about prioritizing populations in the study samples for consumer studies, whether it be label comprehension or actual use studies or self-selection studies. It's making sure the people who are maybe at highest risk for having not the benefit of a learned intermediary, whether that be a physician or a care team or a pharmacist, would be what we view are people with low health literacy, older adults, those with contraindications for those medications.

And so, one, we also talk about thinking about, if you've never taken the product before, I think that's a great way to understand how someone will experience it in their own setting. For low health literate patients, what we've shown in countless studies is that really there's a third of patients who are going to be well mitigated in their problems and comprehension will be solved with a lot of evidence-based practices on how you do the labeling, and that's well available. We've published that through Agency for Healthcare Research and Quality and CDC. There's about one in six patients that you will find will always struggle and will have a difficult time even with some of the high threshold targets that were brought up earlier this presentation in terms of knowing whether it be a self-selection task or a contraindication that really you shouldn't be using this product.

I think that's important to pay attention to and that should inform how you actually do your studies. Dr. Brass brought up a really important point that I think is really [inaudible 02:00:23]. How you ask the question is incredibly important. So you're really, really thinking when you're doing these studies, making sure you're asking questions that make it easy for patients to really demonstrate what they're looking to do. We try to focus on comprehension, but also again, the demonstrated use where can patients apply that knowledge in an appropriate manner to really show that they could actually work and problem solve with that product.

And finally, thinking about all of this work, we always have this iterative process of formative research, making sure that a lot of that can't be captured without really getting more of the qualitative nature of how people think about their medicines. Because also that was brought up in an early commentary in the first session, people really do think about prescription drugs differently than non-prescription drugs. And oftentimes there's a lower bar. So people think that they can exceed maximum daily dose, and it wouldn't be as harmful if it were for a prescription drug. They think that it's not that important to space the medication out accordingly within the timely intervals. We've seen that a lot in our studies.

A couple words on real-world data and evidence. A lot of what we've been trying to do, and I think another great point that was brought up earlier is a lot of what we've been trying to figure out is what can we use pre-approval or post-approval in this space? I'm in a healthcare system that has about three million to four million lives covered over an expanse of about 300 ambulatory care sites and 12 hospitals. The EHRs, to Dr. Brass's earlier point, we don't capture non-prescription drugs. In fact, it's not just unintentional, it's intentional. A patient will rattle off to you, we've seen this with medication reconciliation activities, that they are intentionally leaving off non-prescription drugs. They just don't get captured.

So finding ways to do that better is one possibility, although I think that's a bigger bridge to have, especially when industry has a little bit of a separation from these healthcare systems and capturing this data. It also is going to miss people who are not as health seeking, and they're using self-care. So I think

you have to be thinking about the intrinsic bias in a lot of these sources that you're getting and what that data can use. It's also meant to be supplemental, I would think, to a lot of the comprehension studies.

Finally, even again, we talk a lot about registries or loyalty programs. We've been talking to industry for a long time about how do you bring the back of store data to the front of store data to kind of understand that better. I'd love to learn more about that in conversations here. But a lot of that, again, you're capturing a very specific group of patients that might not be reflective of those who are going to make a lot of errors.

Finally, on the monitoring piece, for us, again, we are trying to work about how do we help clinicians and care teams do a better job of understanding, especially for the more increasing number of products that might have a contraindication with a non-prescription drug, you just don't know what patients are doing. Patients who take an acetaminophen product for sleep because it's a combination product or thinking about other things that we just don't know that people are taking on a routine basis is something I think that has been motivating our healthcare system. Again, follow-up periodic consumer studies might be helpful, especially if it means that you're expediting and helping some of these safe products that have 15, 20 years of data on them in the prescribing space to help them at least cross the marker and yet still have some safety signals post-approval might be interesting. And also, again, just doing more to proactively ensure safety. There's a lot of innovations right now, again, with social media and other online and RWD sources to think about. So I'll pass it on.

Valerie J. Parker:

Actually, we're going to go back down the line. Thank you so much for that overview in this space. Now we will hear from a sponsor perspective, beginning with Irene, who are going to share your opening thoughts with us.

Irene Laurora:

Thank you. I'm Irene Laurora. I head up the Rx-OTC switch scientific group for Perrigo, and I want to share with you an example from the recent approval of Opill, which was the first oral contraceptive approved by FDA for over-the-counter use. So I thought I would start with the FDA's framework for evaluating benefits and risks. And I always have to think about starting where that person has to start and they have to fill out this form. So my thoughts are trying to say, "How do I make the reviewer's job easier?" And they need to understand what condition is being treated and also understand, as has been said several times, what other things are available to consumers to use, and are those effective or not effective? Are those safe? Are those not safe? And how does this fit into a new regimen? Then of course, explicitly understanding the benefit, that's very important. And how we might do that is something that we want to make sure we're supporting the reviewer when we're presenting the information.

And finally, the risks, what are they, and what we can expect in this new setting? And those risks, as Dr. Brass said, mostly come from the consumer's behaviors and interaction with the drug. And importantly, the risk management tool. The risk management tool in the OTC setting is the OTC label. And with the advent of ACNU, potentially it's the additional condition. So these are, again, some of the questions that the FDA reviewer might ask themselves, and it's our job as a sponsor to answer and give the FDA reviewer to inform them because they're not experts on all of these things either. And we want to make sure that they have data to support their assessment.

Again, in analysis of condition, we look at it as what is the consumer pain points? Where are they struggling? How can we improve that struggle? We talked about adherence and access to care and all

kinds of things like that. And I think again, that is what sets up the unmet need. There's got to be an unmet need, and this product should be looking to fulfill that unmet need. We have to understand the benefits, and we have to articulate them very well so that they're not just theoretical. As much as we need to articulate the risks, we need to articulate the benefits so that they are as tangible as those potential risks, understanding the risks very well and how might those risks change when the consumer is interacting with the product and the product label in the OTC setting. And then those risk management tools, are they successful? And that's where the consumer studies you heard about today, those are the ones that demonstrate that the risk mitigation tools are successful.

Since it seems like modeling the benefit might be difficult, I'll share an example from the Opill program. And what we did is we developed a model to predict the benefits of Opill in the OTC setting using data from the actual use study. And what we did was we created an easy to understand and database model that demonstrated the potential for significant impact on unintended pregnancy if women would be able to choose an OTC oral contraceptive. So we very simply-

PART 4 OF 8 ENDS [02:08:04]

Irene Laurora:

... OTC oral contraceptive. We very simply took all the people who were entering into our actual use study and asked them what method of birth control we're using before today, and they told us, so we had the distribution of contraceptive use before having access to Opill. We modeled if those people continued using that product for one year in 100,000 women, how many unintended pregnancies can we expect? Then we said if those same 100,000 women chose to take Opill, how many unintended pregnancies would we expect, and we saw an 81% improvement or decrease in the number of unintended pregnancies. So this became a very tangible way that we could articulate the benefits.

The program didn't stop there, because an unintended pregnancy may seem like a very simple dichotomous thing, but it's not, and there are risks with unintended pregnancies that don't happen in regular pregnancies, and those, too, are benefits then if you can prevent that unintended pregnancy, and those were all included in our application. I thought I would just tell you how the FDA saw all that data when they completed their review.

This is from the FDA reviewer response. It says, "Overall, I expect the availability of nonprescription norgestrel tablets will result in a substantial increase in the use of effective contraception among people who wish to avoid unintended pregnancies." It finishes with nonprescription norgestrel tablets... availability has the potential to reduce the number of unintended pregnancies in the United States, and thereby to reduce the negative medical and socioeconomic impacts of unintended pregnancies." That's very powerful when you can articulate the benefit in those ways for the reviewer, and so then the reviewer can align that, yes, those benefits are available. Thank you.

Moderator:

Thanks so much, Irene. Next, we'll go to Alankar.

Alankar Gupta:

I'll just walk there. Okay. I don't have any fancy slides like Russ, so I think I will be just speaking based on the notes.

First of all, thank you to FDA and Duke team for this invite. Good afternoon, everybody. My name is Dr. Alankar Gupta. I am a physician scientist and a member of this panel today. For the past 20 years, I have worked in an Rx-to-OTC switch programs with various sponsors like Schering-Plough, Merck, Novartis,

Sanofi and Kenvue. I currently serve as the head of North American Medical Affairs at Kenvue. I've participated in over 40 FDA meetings related with Rx-to-OTC switches. I've headed two FDA advisory committee for Oxytrol and for Singulair allergy and have led multiple medical and clinical development programs for more than 15 Rx-to-OTC switch programs across these companies.

I strongly support the ACNU pathway, but I believe we can and we should modernize its evidence requirement to reflect the progress that FDA has already made in other centers and suggest that we are open to novel innovation in there. The current ACNU rule still relies almost entirely, as you saw in Russ's presentation, on traditional small-scale consumer trials, namely label comprehension, self-selection, and actual use trial. While these studies are necessary like in the past, they are expensive, time-consuming, and often involve only a few hundred participants in there. They simply don't capture the diversity or the scale of real-world consumer behavior.

This is why I'm recommending and suggesting three practical updates [inaudible 02:12:36]. You have heard this from Eric and Michael as well. FDA should allow real-world evidence to support ACNU approval. Just as the device center have done since December of 2025, same principle of relevance and reliability that CDRH now accept for registries. Electronic health records and digital platforms should apply here. Digital ACNU tools already generate thousands of real use interactions. This is rich real-time data that can tell us far more about the safety and the correct use much more than a 300-person study ever could.

Second, we should also embrace adaptive clinical trials. These are new trials clearly supported under the new ICH E20 guidance. Inside these digital platforms, because the ACNU is digital<sup>1</sup>, it can continuously direct the data and adapt the study in real time, refining questions, adjusting enrollments, or stopping early once clear safety thresholds have been met. In place of current ACNU requirement of demonstrating failure to conventional DFL first, an alternate could be an adaptive study designed with parallel arms and a-priori-defined interim analysis for stopping criteria. This can save both time and effort for sponsor. This adaptive trial design also makes switch much more efficient, less costly, and much more reflective of how people actually use medicines.

Lastly, we can go even further with the AI power tools, which are now mature. We have the ability to analyze these larger-scale real-world data sets, I think Eric has talked about this, Michael has suggested few of this, in real time, identifying safety signals faster and personalize the self-selection process, with far greater precision than static questionnaire ever could. This combination of RWE, adaptive design and AI creates a modern scalable safety net that actually strengthen consumer protection.

These three pillars, real-world evigation, adaptive design and AI together, represent the next generation of non-prescription drug development. They should dramatically lower the barrier for bringing safe medication from prescription to nonprescription status, especially for a chronic condition that millions of Americans suffer from each day. FDA has already shown leadership on this with the device division. The drug centers now has a golden opportunity to do the same thing with ACNU. Thank you. I look forward for our discussion in the panel.

Valerie J. Parker:

Thank you, Alankar, for those remarks. Finally, we'll hear from Barbara before we go into our moderated discussion. Barbara?

Barbara Cohen:

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<sup>1</sup> Moderator's Note: An ACNU is an "extra step" that must be completed by a consumer to ensure appropriate self-selection and/or use. A product with an ACNU is not required to be linked to a digital health tool.

Thanks. Good afternoon, everyone. I'm Barbara Cohen and it's a pleasure to be here today with all of you in person and online, and thanks to the Duke folks and to FDA for inviting me here today. I'm honored to be here with such an illustrious group.

I've been asked to speak today on best practices for sponsors to characterize the benefit risk profile of a product to regulators. First, a few caveats upfront. First of all, I haven't been at FDA for the past year and a half, so if you have any questions about what I've said, check with FDA. Second, on the issue of benefit-risk profiles, the social scientists are not the medical reviewers. We're not MDs. So social scientists, there's been some discussion here about clinical risks and the importance of the clinical implications of significance of those risks, now that's obviously a pretty big part of the risk-benefit profile, and I'm not going to attempt here to provide, as a social scientist a comprehensive overview as to best characterize that profile.

What I'll do now is to offer some targeted suggestions from my time at the FDA. First, when you're presenting a benefit-risk profile, it's really important that it be derived from studies that are as much as possible generalizable to the entire consumer audience for that product, potential entire audience. What this means in practical terms is if you're trying to show from self-selection study data that labeling mitigates almost all of the risk, but that study was largely made up of, say, Dr. Mahoney spoke before about low literacy, limited literacy individuals, if it was made up of almost no limited-literacy individuals or if it was made up of almost all people with postgraduate educations, I'm exaggerating a bit here, but we've seen both of the, we, when I was at FDA, had seen both of those phenomenon in more than one study.

And the question then becomes, how is FDA supposed to extrapolate to the general population with those findings in a way that is rigorous? It really presents a conundrum for the reviewers. You could potentially look into waiting, but there are issues with that as well. The bottom line is it's best to try to avoid this situation, if at all possible to begin with, by really pushing to recruit diverse populations. But if you do find yourself in this situation, think carefully about it because the benefit-risk profile that you put up and there was uncertainty, the word uncertainty there, you are introducing real uncertainty for FDA if the study is not really generalizable.

So if you have the situation, practically consider how you can somehow thoughtfully and rigorously address FDA's concerns prior to them raising it to you. I'll also talk more about generalizability in the discussion about real-world evidence, and Eric kind of teed that up a bit about appropriateness of certain kinds of RWE.

Second, when you're presenting your benefit-risk profile, it could be a good idea, for example, to hyperlink the individual risks and benefits to clearly-articulated study findings. I say this because, as a reviewer, there were many times when we saw it in a data submission, and I'm not talking about just NDAs, I'm talking about data submissions that we get in the course of a long development program, and the report presentation was not clear and the data tables were not clear, and that was to a subject matter expert. I want to just explain that when you send something to FDA, it's not just going to the subject matter experts, it's going to a whole bunch of medical reviewers, both in the nonprescription division and the Rx division. Everybody has their eyes on this. They may not be the key reviewers, but they are interested. They can look at whatever they want and opine.

Team leaders or doctors and a lot of people don't have the social science background and you really need to be very, very clear in your presentation as to what's going on, because meetings take place and people come away with opinions if it's not presented clearly. If there are any misunderstandings, they'll eventually get sorted out, but it can really impact, I'll just say, the efficiency of the review process. So I think it's really important to be very, very clear.

The third is that I would just recommend, and this gets to people's points about putting benefits into, thinking about the benefits upfront, but this is just about the studies that you're doing already. Always be thinking about how your study results and not just the endpoints, but things you might hear in the verbatims, even things that you might hear and, I don't know, iterative research that leads up to it. Obviously, the evidence from the pivotal studies is best, but always be thinking about where you can mine the benefits to show FDA what the benefits are in addition to the endpoints. How can you use other things to strengthen your case? Don't just check a box, that's my bottom line, to give FDA the minimum. I really recommend that you mine this data for valuable insights. Thank you.

Valerie J. Parker:

Thank you, Barbara. So with that, if we could have our Slido slide back up, we're going to move into our moderated discussion. As a reminder to everyone, whether you're online or in the room, you can participate and submit questions by going to [slido.com](https://www.slido.com) or using that QR code.

When a drug product's benefit-risk profile is assessed for the nonprescription setting, outcomes of interest may include how well consumers understand product labeling, whether consumers can accurately determine whether a drug product is right for them, and whether consumers can use the drug correctly, all without the supervision of a healthcare provider. For our first question for the panel, which maybe we can begin with Russ, what may be appropriate thresholds for consumer comprehension and/or demonstration of correct self-selecting usage in nonprescription drug programs? How can appropriate thresholds be evaluated or determined?

Russell Bradford:

I think that's a critical question, and I wish there were a simple algorithmic answer to it. Unfortunately, it really takes a lot of consideration on the part of the team to essentially outline what we think are the actual risks associated with behaviors. I didn't mention this, and I think it probably is self-evident, but consumer behaviors are really a surrogate for risk, and they're at some points, at some times not a very great surrogate for risk. Certainly, failures in behavior are not a one-to-one match with a clinical risk or a bad clinical outcome at least.

I think Eric touched on this this morning or this afternoon as well, but really defining if someone does not heed this particular message, what is the ultimate potential outcome? I gave a couple of examples on a slide about generally where you might position certain risks in terms of higher and lower thresholds, and I think that's essentially the task.

Valerie J. Parker:

Thanks so much. Yeah.

Ruth S. Day:

What threshold you have depends on what task you're asking the people to do. In our lab, we often test the same information in three different ways. First of all, say for example we just want to know what they know about warnings. We might say, "About how many warnings are on this package or label?" We don't care what the answer is if they get it correct, but do they know there are a lot or few or many somewhere in the middle? That's just surface information. That's called just a number estimation.

Then we go a little deeper and we say, "What are they?" We have had people actually looking at something in their hand and reading it off and they don't read all of them. They don't catch all of them. Then we can go a little deeper, which is called recognition memory or recognition processes where we say, "Is this on the label? Is that on the label? Yes or no?" What threshold you set depends upon what

task you use. At the sort of a simple level, they might know well, but as you go deeper and deeper not, or even vice versa. So I think setting out in advance what a level should be needs to be reconsidered.

Valerie J. Parker:

Thanks so much. Irene, I see you want to weigh in, and then Alankar.

Irene Laurora:

Yeah. I look at setting up a threshold as that's where your benefit is not outweighed by your risk, right? You're trying to say, "If somebody does this behavior this many times, then it's not right." Again, I can use an example for Opill. We were concerned that people wouldn't be adherent to their medication in the OTC environments, so we went to look at how adherent are they to their medication in the Rx environment. We found data that said they were about 85% of the time adherent, so we said, "Okay, 85% is a good baseline to expect consumers to behave."

Now we had to ask, well, how often can somebody be less than 85% adherent and still obtain the benefit of the product in the OTC setting? So we did a lot of research and collaboration with FDA and we said, "If 85% of the people were 85% compliant, then there would still be a net benefit in the OTC setting," even if, again, an individual might not get the benefit because they might not be as compliant as they need to be, but in general, the population benefit would be better.

So the concept is there is no one threshold. The threshold has to be developed from an understanding of the drug and the behaviors a consumer might do, and then which behaviors are acceptable at what failure rate are they become unacceptable.

Alankar Gupta:

You want to go first, Barb? Please.

Barbara Cohen:

Thank you. Just to add to that a bit, I think that it's, and somebody mentioned this in the first panel, I think that we have to think about what under the supervision of a healthcare provider means in 2026, because I think that it's important to use what's really happening in the real world as maybe kind of a way to look at the threshold, if you will.

Irene just mentioned adherence, and there's a lot of ways that you can get real-world adherence data. That's probably one of the easiest things to do when we're looking at all the things that these consumer studies measure, and I think that's a really good way to measure, are we trying to be better than what's today? Maybe we are, but we should just then acknowledge that as an explicit factor.

Another way in which I think somehow we can think about the threshold is, again, this business of being under the supervision of a healthcare provider. A lot of healthcare providers really don't have the time, as I think we all know, to sit and go over the drug facts label and they're not necessarily calling us to check on where and when we're taking our medicine and all of that. Even in the Rx world, there is a lot of responsibility on the consumer to know when they should go to the ER or something if they're having a situation with the drug. People just don't get that information. I don't know if they ever did completely, but I think more and more they're not getting it now.

The other point I wanted to make about the thresholds, and I think that particularly applies to, I've just been talking about actual use, I think where it applies to self-selection is when we're thinking, well, the doctor's looking at the contraindications, all of that, I just want to point out the EHRs, I'm constantly having to correct what's on mine. There can be wrong information. It can be based on a self-report,

which may not be correct. The EHR themselves can be often a factor of what the person puts in, and it's not necessarily verified.

So I wanted to make this point because I think sometimes we think, oh, everything's perfect, and I think this was echoed, and I do agree with what some people said in the response to the RFI here. I think that we think everything is perfect in the Rx world, but it really isn't, and then I think we have to really consider whether one of the benefits, and maybe it is, to be better than Rx, but maybe it isn't, and it's just to be equal or maybe slightly less, but with a tread of a much greater benefit that Rx can't provide.

Valerie J. Parker:

Thank you so much for those remarks, Barbara. Alankar, I want to make sure you have time to weigh in-

Alankar Gupta:

Sure.

Valerie J. Parker:

... but I did have a question in my back pocket here from our audience, which was asking us to compare that prescription setting versus the over-the-counter setting and the differences there. So I should say, Barbara, thank you for answering the question that I didn't even get a chance to ask. With that-

Alankar Gupta:

Maybe I will try to build in this one as well in the answer, right? I think what I wanted to bring to table here is it's not just about the threshold, because the threshold, I think as Russ were showing, it can be 100% for some very acute and possibly fatal interaction that can be observed, but I think then it becomes a little bit more complex, right? Especially, I will give an example of a drug-drug interaction that when we are trying to switch a molecule that was considered as 99% lower bound or 100% as what is needed, but then what we realized, that even in prescription world, that access to those two medicines is not zero, it's more than zero. So we actually utilize some of the known methods, like real-world evigation, to get like that data. In fact, we also got EHRs from those patient which has access to both of those medications in there.

Later on, we figured out and we found that when they are in the OTC world, when they are saying that, "Yes, I'm going to use this, and this medication may be okay, knowing that I am on the other drug which can lead to that dramatic decline," their explanation was good because they did identify that I know that both of these drugs should not be taken together like in there. On the face, they had a wrong self-selection, but when you mitigate like that, when you see the understanding that these patients have, maybe a little bit lesser than 100% is okay because they themselves say that, "In no condition we are going to use the other drug when the first drug is already on board in there." So just wanted to bring that, it seems like 100% is there for some condition, but in real life, maybe a little lesser may be acceptable or should be acceptable based on a sound rationale which can be clinically outlined.

Michael Wolf:

I think going back to the prescription side, whether it's prescription or nonprescription, I feel like even in the prescription side, 99% of quality control and problem-solving around taking medications happens outside of the doctor's office. You may have a learned intermediary, but most patients, for a lot of these medications go on and they make decisions about how they choose to make their medications, how they take them, they make decisions about, what if I miss a dose? So I think there's a lot of issues we've

seen and there's enough evidence to support that patients in both spaces are making issues, they're having challenges.

I think, going back to the thresholds, we've heard if it's in a controlled comprehension study and are you targeting 100%, I would argue in a real life is impossible. Even if the task in the context of things, if you have a truly diverse sample, even some of the most simplest tasks of being able to just find and retrieve a piece of information like a contraindication, like your example, I think that's unreasonable. I think 90% is tough, and you've seen 80 and 85% thresholds put out there.

So I agree that there's so many aspects to what you're asking people to do that determine what a right threshold would be, but I think that's also been a challenge, at least from my experience with industry partners, is that they're always looking for that and they're trying to get feedback on what they should be expecting. In some cases, maybe it's not... it's a bit of balancing art and science, but people are going to do things unintentionally or even intentionally in how they think and how they want to get benefit out of a product.

Valerie J. Parker:

Thank you, Michael, and thank you all. I knew this was going to be a great discussion. I want to shift gears a bit in terms of the next question, which is, what approaches to evidence generation could decrease the time required to demonstrate that a drug can be used safely and effectively in a nonprescription setting without the supervision of a healthcare provider? Any takers there? Perhaps we could start maybe with Michael or Alankar?

Michael Wolf:

[inaudible 02:35:11].

Alankar Gupta:

Can you repeat that? Sorry.

Valerie J. Parker:

Oh, that's fine. Yes. What approaches to evidence generation could decrease the time required to demonstrate that a drug can be used safely and effectively in a nonprescription setting without the supervision of a healthcare provider?

Alankar Gupta:

Yeah. I think in my talk, as I have talked through, there are new methods of doing research which is becoming available. If you just use ChatGPT to look into how much of new data is generated per day, it's 150 million terabytes of patient data which is generated per day, right? It's really a missed opportunity that we are not using or we are limiting the use of real-world evidence or adaptive clinical trial or using AI to look into these data, because majority of the switch are coming from prescription molecule, which has long history, 10 to 20 years history of use. Utilizing these novel ways to get that history, get that safety and to utilize that to see what areas are real areas, I think that may be a real time-saver and a cost-saver to meet that high unmet need in certain areas. Michael?

Michael Wolf:

Yeah, and... Go on.

Moderator:

Oh, Michael, please, and then I was indicating Irene, you can go next.

Michael Wolf:

I think that, again, going back to... It is somewhat stark when you have that much time of observation on products that that should be factored, and then there are data sources, I think all of them, none of them may be perfect and you do need to be careful about being attentive to the data source and who you might be missing, but for the most part, I feel like... And I don't know to the full extent that if we're just ramping up right now in terms of how much RWD or EA we were talking about that is actually incorporated into these switch applications, but I think that clearly, I think whether or not you can expedite, or even, can you actually imagine if a product has demonstrated a safety signal and whether it's these Sentinel programs or whatever that can inform it, can you actually feel comfortable that you can expedite the switch yet still have something post-switch that might still give you confidence that you're not just ending the surveillance at that point?

Irene Laurora:

I would say collaboration and focus are the two things that we could do better to expedite switches, the collaboration between the sponsors and the FDA to really articulate the important clinical risk and the important benefits that need to be demonstrated as opposed to demonstrating everything, and that focus on, well, what is it in terms of the behaviors and/or risks that we are really mostly concerned about and that would make a difference to the benefit-risk equation? If we could do that, we would expedite switches.

Valerie J. Parker:

Ruth? And then Barbara.

Ruth S. Day:

One way to speed things up is to do it electronically, have data collection online, but you need to be able to compare online versus in-person and are you getting the same thing. In both settings, there are concerns that I've observed in in-person market research settings and online, and it has to do with things like, are there prompts after questions? How long do you wait for somebody to respond? Say for example you ask a question and a person says something, and then the in-person tester says, "Okay," and goes on to the next thing. We know from cognitive research that when people are pulling things out of their mind, they sometimes have a spurt and then a pause, and then another spurt, and then they change their mind and they have more. How is that handled? So there are pros and cons of in-person and online, but online certainly speeds things up.

Valerie J. Parker:

Barbara.

Barbara Cohen:

I think there's a couple of ways that the whole process could be streamlined a bit. Although I said to Eric during the break, I really would like to hear more about his learnings in the last 30 years, and maybe we can have another workshop where we're really talking about that, but I think that, to what Irene said

about a sort of agreement coming to a consensus on the benefits and risks, I do think that it would be as helpful as possible to do it at...

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Barbara Cohen:

I think that it would be as helpful as possible to do it as upfront as possible, which I think was also mentioned by several people. I think it would just help everyone focus. Now, it would obviously involve a lot more time upfront. And I will tell you, there's a lot, I'm throwing something out, but from a practical point of view, I don't know if it could really be done.

First of all, companies might be not really wanting to have this discussion in a public forum, so you might have to have subject matter, other kinds of non-public discussions about this. And then is that helpful? I don't know.

But I do think that it would be a good idea for FDA to get outside perspective as to some of the benefit-risks. And although that would be a lot more, and sponsors could bring in real world evidence, and maybe FDA could even look at that beforehand.

And even though it's a lot more time upfront, it could potentially save a lot more, even more time in the back end. So I just offer this as a suggestion for people to possibly consider. It's really thinking about all these things up front and then the sponsor can go their path and they know they kind of have a roadmap for the research. The other... oh, you go, oh.

Russell Bradford:

When you're done.

Barbara Cohen:

Oh. The other thing, I'll try to be quick because I know we've got a lot of other things to talk about, but the other idea I have, I'll just mention it briefly, is that it's possible that in this upfront iterative research, and maybe companies do that today, I don't really know, but to kind of marry the labels comprehension with the self-selection, not in the same people, because when you're doing that, it biases the respondents.

But iterative research, just so people know, is you show a stimuli to one or two people and they make comments, and then based on those comments or maybe you go three or four or five, you then make changes to a label, and then you take it to a next group. And then it's a way to really develop a label based on the feedback of a lot of people on an iterative level.

We did that with the Naloxone label comprehension study. And it's a best practice, but what you could maybe do in this is take a label comprehension finding and then bring it into another group of people who are a self-selection population and say, "What do you think of that?" And then back and forth.

And it's almost like doing a lot of the upfront work. This work isn't necessarily going to FDA because FDA doesn't look at the iterative research, but it could be a way on the sponsor's end, kind of doing things relatively quickly. And you're killing two birds with one stone because you're seeing how a label would be comprehended in label comprehension and then how successful it would be right away with certain self-selection people. And then take that back and forth.

Again, it might involve, and I'm just throwing this out, there could be a million things wrong with this, haven't really talked about it with anybody, but just as an idea, again, it could be a lot upfront, more

time upfront, but it could help save time on the back end. So I just offer that as something to think about.

Russell Bradford:

If I could just tag onto that. In my experience, programs that have moved quickly are programs where expectations were very clear from the beginning. And the question itself sounds like, what could you do for the studies to make them go faster? I don't think that's the real question. There is always incremental things you could change to run a study a little quicker or whatever.

I think those are interesting and part and parcel of what we have to deal with on a day-to-day basis. But I think the real question is, how does this whole program function faster? And without question, having a much clearer set of expectations between the agency and the sponsor about what is important and what might be required is, I think... So if we're trying to take from this meeting some ideas about how this whole conversation could progress, the idea that Eric brought up this morning about maybe not exactly an advisory committee, but the advisory committee in development in the developmental stage would be really, I think, beneficial.

Alankar Gupta:

Just a very quick 30-second addition on speed. I think both Michael and Russ, you talked about. So literally the fast, the speed these engines are maturing is amazing because in 2008, 2010, Eric had this oxybutynin on his slide. We did a rudimentary real world trial using the paper medical record. It took us three years that time because we had to take it and then we had nurses who were looking into this to find bladder cancer and so forth. We had done that with Henry Ford Urology Center, that time.

10 years forward in 2020, when we were looking into a different thing with EHRs, it took us three months to look into much larger data. And now what I'm seeing is within three seconds, I can get those answers. So those engines are reaching that maturity and the cost and everything is coming down. So perhaps if you want to adopt like these one, this is the right time to get to those engines like in there.

Valerie J. Parker:

And Alankar, that tees us up quite nicely for my next question, which is how could real-world data from the US or from other jurisdictions be used to characterize the benefit-risk profile of a drug in the non-prescription setting to support regulatory submissions from prescription to OTC switches? So maybe Michael, we haven't heard from you in a bit, you could start us off with that.

Michael Wolf:

That's a good question because in the non-prescription space, that's where it gets challenging. When there's just this disconnect between the healthcare system and you're always... My big concern would be just trying to understand a little bit more about where you get data that's actually going to be truly representative and not missing people, and that you're actually capturing the true experiences of it.

So that could be something where you start to gather. And I think it's been brought up before about how do you understand remotely how people are experiencing a product after the switch. And I think that's possible, but just when thinking through just the resources right now that have been tapped in real world, I think of, again, I get concerned about registries and loyalty programs because I think they're a selective cohort.

I think of health systems, electronic health records are completely missing the case. I think if you have other, you said jurisdictions, I think if you can learn from other healthcare systems, other countries that

have some... I think there's cultural differences in general in how people think and use medications. We've seen it. And I think in the US, we're much different from what we've done in some prior studies with working with the FIP that maybe the US is a little bit more cavalier in how they use prescription meds versus other countries.

So I don't know how much of a crosswalk that would be. So I think that it's worth thinking about, but I do think that we need to be cautious about the reality of the data that we would get.

Valerie J. Parker:

Let's see, Irene and then Barbara.

Irene Laurora:

There are very myriad ways of using real world data. Not all of it is evidence, it's just data. And the idea is that it's all around us. We've used NHANES data. We've used data from surveys that have been conducted by government. Government has the most data available and it's informative in that case. It helps us understand where things are.

Remember, when we're switching something from Rx to OTC, we don't have how consumers are going to use it in the OTC setting because it's not in the OTC setting. So what we have to do is understand what is happening for that patient, for that consumer, what are the data sources we use for understanding anything that happens to consumers? All of those are relevant. So then it's about picking the most relevant to help us understand how things will change in the OTC setting.

Michael Wolf:

Just to answer that. So yeah, in the pre-switch space, you do have a lot of data that does pull in that still, in terms of behavior, we all like to call it, I think, therapeutic misadventures or other things that they label when we think it might be a patient issue around their behavior. But yeah, you should tap into that fully in terms of how people are using it and also in regards with other products.

Irene Laurora:

Mm-hmm.

Valerie J. Parker:

Barbara?

Barbara Cohen:

So I think there's two uses of real world data. One is sort of to see what happens after a product goes OTC for all the benefits and all of that. I'll just say that and looking at what happened in other places. I'll just say that there, we have to be careful about looking at overseas because what's OTC here is not the same as what can be OTC overseas.

OTC overseas could be a behind the counter option. So people get a lot more counseling that way and it's not really that analogous. You're not comparing really apples to apples there. It could be useful for some particular things, but you have to look at what you're using it to make the case for.

But the other way you can use real world data is, to what I was saying before about the benchmarking, what's going on right now with this prescription product in the prescription world. Because that's what I'm saying, things might not be perfect right there, right? Look at adherence there. And that's where you can find data.

And look and see who's really being prescribed the product. There are audits, there are different kinds of real world evidence companies that marry the pharmacy benefit data with the EHR data. There's a lot going on there at this space. I think it would be good to possibly investigate these sources further.

And I just think that it can help make your case. I'm talking to industry now in terms of we're talking about, "Doctors would never prescribe these products together or doctors wouldn't prescribe it to a specific person." Obviously, people can prescribe off label and the doctor has the knowledge that a person shouldn't be taking on. But it's still good to see what the landscape is when we're thinking of thresholds and how to make your case.

So that's all. I think there are two uses for real world evidence and I think they're there, but we have to be careful how we use them.

Valerie J. Parker:

Alankar?

Alankar Gupta:

So one, just like food for thought, if I can? So first, a comment on OTC data. So OTC data is very patchy in the US. I think when it comes to Nordic country or maybe Denmark, these are the only countries I can imagine that they have a process to get OTC data.

The second point I want to bring is just a suggestion, it's not approved, it's not under law currently, but CDRH do allow to run prospective pragmatic trial when the product is actually going through the phase three trial. So maybe thinking on those things that allowing pragmatic prospective trial, when you're thinking about switch prior to even approval, I think that will get us some behavioral data that all of us are desperately looking for, without breaking that barrier in there. So just an innovative thought for everyone.

Valerie J. Parker:

Just one more follow-up question for you, Alankar, and then Michael, go to you. You mentioned the Danish models, for instance. Could you just expand a bit more as to why they have systems in place or what those systems-

Alankar Gupta:

Yeah. So Danish countries and Nordic countries have social health. So they do capture those points there because of just the social health architecture in there. Here also, if you look into the HSA, Health Saving Account, and those one, those are still some of the robust data that you can get for OTC. That since I'm paying something that I can see.

Again, it'll be tough to suggest the use, right? What you can suggest is someone has bought that. Now, this product is for their family or for themselves, I think that is still need to be processed through that one.

Valerie J. Parker:

Very interesting. Michael?

Michael Wolf:

Just a small comment. I think a lot of what we've been doing on the EHR side is, it's not a complete solution, but for some things, like if Lorazolol, like you know of, if you have a medication contraindication or a chronic condition, there are things, you can mobilize EHRs quite well to help.

The problem right now is it's oftentimes a one-off. So you're going healthcare system to healthcare system or going to the EHR vendors to create tools that will at least help you maybe preemptively engage patients to inquire about their OTC use in case that there is something that you'd be concerned about. And I think they've been using it for recalls and other things like that. So those are helpful tools in the real world data space, I think, to help out with some assurances that you can do some surveillance.

Valerie J. Parker:

Thanks so much. And I do want to make sure we have time for our final question, which should tee up our next session quite nicely. So for this question, we have, what evidence might be needed to demonstrate that an additional condition for non-prescription use sufficiently ensures appropriate self-selection and actual use in the real world? So Irene, perhaps we can start with you and then just quickly run down the line.

Irene Laurora:

I think that has to be demonstrated in a use study. I don't think there's any other data to show that the right patient got the right drug.

Russell Bradford:

And from my perspective, the answer's pretty simple. It's the same set of studies that we have in a traditional sense, with the potential addition of human factor studies that help us understand that the ACNU system or whatever is also understood and used as intended.

Barbara Cohen:

I agree with what's been said.

Moderator:

Efficient.

Ruth S. Day:

I think we need to think about time zones for consumers. There's at the point of purchase, there's the first time taking, and then there's later. And later often means that there has been a loss of knowledge, and I think we have to start doing something about memory. So what on the drug fax label and the package stands out, grabs attention that they process, they learn, and they retain anything of.

Later, they're not likely to look at it again. Might be the middle of the night, they come and need something and they go and they grab the bottle and take it. So I think that we need to add consumer memory as well as comprehension and other cognitive processes I won't talk about today.

Alankar Gupta:

One different perspective I'll bring, because the topic is how we can modernize our thinking, is, yes, I fully agree with Russ and Irene that we do need actual use data. But if we can adopt some of the novel trial designs like adaptive design and have two arms, right? So one is conventional arm and the second one where we are using, ensure, additional condition of use, not in a sequential way, but in a parallel

way. I think obviously it has never been done. So you have to think through a priority, how you're going to robustly describe those things in there?

But if that can be done, if that can be thought through, then it can lead to three to four years of savings. And I think in the OTC and being a sponsor, what I can say is that will be a huge benefit, not only for sponsor, but also for the patients who are waiting desperately for decreasing the excess barriers in there.

Michael Wolf:

I think that if you have a demonstrated good safety in the prescription space, the actual use studies, as been said earlier, are in place, a culture that recognizes that there is truly a benefit to expedite the switch is important.

And then fourth, I think you really need to make sure that as long as in these studies, you're prioritizing some of the at-risk populations we talked about. And, Barbara appreciate your comment about, in making sure you're not stockpiling it to people who are going to do well, that you are appreciating people with low health literacy in the naive populations that don't have prior experience to support their use.

Valerie J. Parker:

Well, thanks so much everyone for this really robust discussion. So with that, we're going to wrap up and I'm going to pass it over to my colleague, Thomas Roades, who'll be leading our next session.

Thomas Roades:

Thank you.

All right. Good afternoon, everyone. I'm Thomas Roades. I'm a policy research associate on the biomedical innovation team here at Duke-Margolis, and I will be moderating the final discussion today.

Here, we're focused on innovation to enable increased access to non-prescription drugs. And all of our panelists can go ahead and join me on the stage now, please. We'll be jumping right into panel discussion, some opening remarks, and then our panel discussion here.

So throughout the day, we've heard about some potential new candidates for a non-prescription status, some examples of how increased non-prescription access could affect individual and public health. And then in that last session, some great detail on what the evidence generation process looks like and how it could be enhanced or made more efficient.

Here, we're going to be shifting a little bit from that process of evidence generation to think a little bit more about what implementation might look like. So we'll be thinking about innovative tools or technologies or approaches that could be involved in supporting consumers in understanding key information about whether and how to use a product in the non-prescription setting.

Think about sort of a future state where potentially we have more options available to consumers than they do today for new indications, new types of conditions, new product classes that maybe previously were not available. What sort of tools, approaches can we use to support them in making decisions about managing their health?

So I'll be asking our panelists here to be really creative and forward-looking about what that future state could entail. We'll be talking, of course, a good deal about the additional condition for non-prescription use rule that Karen described for us earlier, and which we've heard a little bit about in the previous

sessions. And thinking about what, I believe Russ referred to it as the system or whatever it could be that could be part of implementing those additional conditions.

So we'll talk about that here, but also innovations and approaches that could be helpful even outside of the ACNU pathway or our product with an ACNU interested generally in how we can improve access and outcomes for patients here. Whether that might involve a product with an ACNU or other products in the non-prescription setting.

So without further ado, we can get into it. Let me introduce our panelists here, and then we'll start with some opening remarks. We have joining us, Michelle Cope, Director of Federal and State Pharmacy and Regulatory Affairs at the National Association of Chain Drug Stores. We have right next to me here, I'm not necessarily going in the order that everyone's seated on the stage, so bear with me. Mary Alice Lawless, just to my left here, Chief Executive Officer of Biograph.

Down at the other end, we have Dustin Little, Global Clinical Head in Late Cardiovascular, Renal and Metabolism in Biopharmaceuticals Research and Development for AstraZeneca. Next to him over there, we have Sue Peschin, President and CEO of the Alliance for Aging Research. And then two down from me, we have Shonna Yin, Associate Professor of Pediatrics and Population Health at the NYU Grossman School of Medicine.

So thank you all for joining us for opening remarks. Let's start with Dustin, and if we could just pass this down to him real quick, or if you want to come up to the podium, that works as well.

Dustin Little:

Yeah, I think I'll come up. Thanks. It's nice to be with everybody.

So my name's Dustin. I work in late stage development at AstraZeneca. I actually spend most of my time on prescription drugs, but I'm really happy to be here to talk about non-prescription drugs.

And we had a theoretical example, I believe it was Loratol, and so I'm here to talk through a concrete example of using an innovative pathway to work on a non-prescription drug.

And I do have... Oh, here we go. Okay. So the statistics on cardiovascular disease and statin usage are really, really stark, and a lot of you are familiar with them. So heart disease is the number one cause of death globally and in the United States, and the numbers are only increasing. LDL cholesterol is in the top three as far as modifiable risk factors for cardiovascular disease burden, but as we've heard, statins are underutilized with less than 50% of people with a guideline indication being treated.

So to put it bluntly, whatever we've been doing, it's really not working, and we need to do something different. We've tried to do something different. We've tried to convert statins to non-prescription status, five times actually, and all five of those have come up short, mainly because like we heard from Dr. Brass, it's been difficult for consumers to make the appropriate self-selection decision. And maybe that's not such a surprise. Oftentimes this involves calculating a risk score, things that might be difficult for people to do without a little bit of help.

So the drug I'm going to specifically talk about is rosuvastatin, which like many other statins was approved a long time ago, in this case more than 20 years. And has more than 180 million years of real world experience, and importantly has a really quite wide dose range from five milligrams to 40 milligrams. The non-prescription candidate dose is five milligrams, and there's more than 30 million patient years for that dose.

Now, I think it's also important to think about what will motivated people do who want to, in this case, lower their LDL cholesterol in the absence of proven treatments. And in some cases, that might be starting a supplement. And there's actually a randomized controlled trial called the SPORT trial looking

at rosuvastatin five milligrams versus placebo and one, two, three, four, five, six commonly used supplements for LDL cholesterol lowering. And not a shocker here that in this case, the supplements didn't lower LDL cholesterol, but rosuvastatin did.

So what we've been working on is helping consumers to use, in this case, it's a web application to determine whether they are appropriate for initial use of a non-prescription statin and continued use of a statin.

And the way it works is consumers log into a web application, they answer a few questions about their medical history, their blood pressure, they provide some lipid values, and then the web application calculates a ASCVD risk score and determines whether or not they are eligible for moderate intensity statin treatment according to the guidelines and according to the drug fax label. And if consumers qualify, they would have the opportunity to order rosuvastatin five milligrams for home delivery.

So we've talked a bit about the development pathway for non-prescription drugs, and our program is a good example of that. I think we've had 18 consumer studies total, but what I really want to focus on is the results of the actual use study. This was a fairly large study, 1,196 participants who completed the web application, received an outcome where they were cleared to use a rosuvastatin five milligrams, and they ordered rosuvastatin, and they were treated for up to six months.

And as you can imagine, we were looking at how well did consumers do in making the initial appropriate self-selection decision? How often did they appropriately continue to use rosuvastatin five milligrams? And what was the safety, and did they have clinically relevant LDL reductions?

So good news, 90.7% of consumers correctly self-selected for initial use, 98% of consumers correctly used rosuvastatin five milligrams during the treatment period. And importantly, the reduction in LDL cholesterol of 35.5%, quite consistent with what we've seen in the prescription use. And finally, the safety profile was consistent with prescription Crestor five milligrams.

So just to sum it up, I hope this real world example is helpful to ground our discussion on how we can use technology to increase access to non-prescription drugs. So there certainly is a large unmet need for increasing access to statin therapy. And I would pound my fist on the table and say we need to think about different ways to help meet that unmet need.

We talked about how there's a fail first criteria for ACNU, and certainly statins have failed to be converted to non-prescription. We talked about the results of our TACTIC actual use study demonstrating that with the use of the web app, consumers could make the appropriate initial self-selection decision and use Crestor appropriately, and have clinically relevant LDL cholesterol reductions with a safety profile that's consistent with the well-established safety profile of statins. And perhaps similar approaches can be used in the future to address other unmet needs. Thank you.

Thomas Roades:

Thanks very much for starting us off with that example, Dustin. And now next I'll go to Mary Alice with another example of an approach that could be used to implement additional conditions for products with that status. Please go ahead.

Mary Alice Lawless:

Thank you, Thomas. Good afternoon to everybody. It's such an honor to be part of this important public meeting. I really appreciate FDA and the Duke-Margolis team, including us in this. I am representing the Biograph by Amwell Center of Excellence for ACNU. This is a sort of progressive idea, obviously, but it is 14 years in the making at this point, so it's not an overnight success. I just want to say that.

This is an integrated service, and it's the collaboration of an expanding group of healthcare leaders, each bringing forth proven use cases, quality processes, and best in class capabilities to power ACNU care interventions, and really to support the future of self-care.

The BxA Center of Excellence has one goal to expedite access to treatment of common and chronic conditions with a new generation of FDA approved non-prescription drug products.

Okay. I got to do the clicker. Am I working? You already saw that.

So what is an additional condition? Let's just talk about this for a second. It's an extra step the consumer must take. I think Dustin's example just a moment ago tells us that consumers are willing to take extra steps, they're willing to take next steps, they're willing to use their technology to improve their lives, and I think that ACNU fits right into that paradigm.

So it's an extra step the consumer must take, and this step is intended to calculate an individual risk and then guide the consumer on the appropriate pathway forward, providing that information to the person seeking treatment.

The objective of an ACNU is exclusion of certain individuals for whom non-prescription use presents a serious risk. It's not inclusion of everybody, it's exclusion of the few. Of course, there are many, many things we can do once we're digitally communicating with consumers to educate them, to support them, to give them other tools, but essentially the ACNU in its purest form is really serving that one purpose.

Dr. Murry told us this again this morning, the ACNU is not the technology, but the use of technology and data can modernize this access pathway. With modern capabilities, applicants design each additional condition following a logic-based and transparent and auditable approach that can be brought forward to the agency in formulas such as these illustrations.

And, basically, laying out and documenting every possible consumer experience in this total additional condition, all the details of data queries that may take place. Whether it's analyzing data the consumer is providing or data that's on the back end of the healthcare system. And of course, all of the additional labeling that is specific to the ACNU. Whether that's delivered by, we heard it earlier today, by video or some other kind of interactive media to help folks to process some of the complexity of what we're talking about going forward.

As you can see here, all non-prescription applications start with the drug fax label, that's also been well established today. And the ACNU is additive and intended to address those specific labeling challenges for safe selection or use, or both, again, by certain individuals. It should be a fine screening to exclude only those individuals for whom that risk, as I mentioned, is inherent.

This framework facilitates alignment with the FDA and renders the required key elements of the ACNU that can be part of the FDA... Or part of the NDA. Sorry, all these acronyms. It's a lot of work upfront, but we now have a paper trail for how we're getting to that final NDA submission, conversations with AdComs, et cetera.

One note, and I think it's important as we go forward here, is the whole concept of simultaneous marketing. That is a convention or a part of the law regarding ACNU products. The ACNU itself is a meaningful difference. And so, one thing just to keep in mind is as we're talking about ACNU today in this session, we're not talking about taking anything away. This is not a full replacement model. This is an opportunity to simultaneous marketing, keep people who are on statin therapy under care, under their provider's care, and basically open a door to the folks that are not treating, that have risk factors that perhaps should come into care.

The clicker is new. Okay. The ACNU demonstrates... No, that didn't go. Sorry, guys. Okay.

Mary Alice Lawless:

Sorry guys. Okay. The ACNU democratizes access and culminates in a modernized consumer experience of self-care. For consumers, the ACNU experience can be familiar, intuitive, friction-free, empowering, and essentially available through any front door a sponsor wants to open to them. Using our technology and having it in our hands and answering questions is not foreign to any of us. However, the actions of software, systems and data on the backend are all directed by the consumer inputs. So this is a totally consumer-driven model, and any predetermined health queries are agreed by the consumer. In fact, they push the buttons, they're checking their own data. The consumer actions may be responses to questions, as we mentioned, or uploads of personal biometrics and their agreement to drive a couple of queries against their own healthcare records. Of note in this illustration is the consumer's ability to activate queries against their own medication history.

So we talked about drug interactions and contraindications and so on. This is a similar use case to the well-established healthcare protocol for drug utilization review. It's what informs pharmacists at adjudication of drugs, and it also informs providers when they're writing these prescriptions. And essentially on the backend, as I say, drug-drug interactions are being flagged, comorbidities, and other contraindications, in our case for non-prescription use. In the current healthcare setting and the use of this data, the judgment is left to the healthcare provider. In our model, of course, according to the algorithm, it would be a go no-go, essentially, for the consumer. If there's a flag for risk that FDA cannot tolerate, the consumer will be given an alternate path. The data's processed through an automated care engine. So that's taking all of this input, it's running that algorithm, it's analyzing according to the rules that are put in place and renders an individual and personal risk score for the consumer seeking access to the non-prescription drug.

Calculation of the risk score delivers one of two next steps, as I was just mentioning. Either a path to purchase or do not use instructions with links and resources to help that individual connect with a healthcare provider and get their questions, whether it's about their actual health or about the product, answered.

For those consumers offered a path to purchase, the process is operationalized in the retail setting, really of the consumer's choice. There's nothing obstructing any qualified retailer from participating in a model like this. Really, the connections are API connections that all parties are very, very familiar with, and we set them up for other purposes all the time. And so the purpose of that API is to facilitate the transfer of the matching credential to the retailer and what the consumer has in their hands so that there can be a purchase. The goal of non-prescription access is access at scale. And so as we've been working for all this time trying to think about how to move forward here and what tools to use... We know that we want to be in drug, mass, food, club, even value retailers if possible, and if, again, approved for the product by the agency.

This experience is much like any other order online or pickup in store or any kind of familiar experience for many consumers as they deal with retail online or even in person. One really important note in this process, you can sort of see this little dotted line, the data loop continues beyond the purchase. So I know this came up a few times today as well. In this model, because we've got the backend systems working, we can actually track that purchase for that individual back to a medication record. The partner here is SureScripts, which does all of this work and handles the data on 99.98% of our population. Every prescription prescribed and every prescription picked up and not picked up, it's all in their data. And so they have those records and they're going to add this because we do believe that it's really important that providers have this information at future encounters with that consumer and patient.

Underlying the whole infrastructure, of course, and sort of governing the process is, of course, quality assurance, because FDA has requirements for reporting. So all of this has to be tracked, and so you really need a systemic QA system as an essential element of the ACNU. What's really important is that all of what I'm showing and sharing today is existing today, serving other healthcare use cases. And what we're doing is we're leveraging it now for the non-prescription setting and for self-care. So it is all operating, all existing, all proven, all credentials, all interoperable, and very, very possible. Thank you.

Thomas Roades:

Thank you very much, Mary Alice. And next for opening remarks, let's turn to Michelle, please. What's top of mind for you here?

Michelle Cope:

I'll stand up too, if you don't mind. I'm Michelle Cope, and I'm director of Federal and State Pharmacy and Regulatory Affairs at the National Association of Chain Drugstores. And our members represent chain pharmacies, traditionals, chain drug stores, supermarkets with pharmacies and mass retailers with pharmacies and their footprint. Chains operate over 40,000 pharmacies across the United States. So I'm speaking today to bring the perspective of how there are practical considerations for OTC products with ACNU and how to kind of operationalize those in the retail setting. I want to highlight two issues that will significantly affect access to non-prescription drugs with ACNU. First, the need to standardize mechanisms and processes for consumers to demonstrate that they have satisfied a product's ACNU requirement at the point of sale, and second, coverage considerations. Starting with standardization. Once available, drugs with ACNU have the potential to fundamentally change how Americans access care, particularly if we see medications that are currently prescription only transition into this new category of products.

The purpose of ACNU is to ensure appropriate self-selection and appropriate use by consumers without the supervision of a healthcare provider. FDA's final rule provides significant flexibility to manufacturers and how those conditions are operationalized for individual products. In practice, that flexibility means that ACNU could be implemented in many different ways. As described in the rule, a product's ACNU might involve a questionnaire completed at a retail kiosk, through a mobile app, via telephone, or via a website. A consumer might then receive a coupon, a voucher, a barcode, or something else to demonstrate that they have met the requirement that the product is appropriate for them, or the process could be implemented in an entirely different way.

From a retailer perspective, this variability represents some operational challenges. Implementing multiple product specific systems and software and then training staff on different workflows at the point of sale can be complex and costly. So all that to say, the more the ACNU related processes can be simplified and standardized across products, the more feasible it will be for pharmacies and retailers to implement them and offer a broad range of these products for sale.

The second point I want to make relates to coverage of non-prescription drugs, and that's kind of applicable across the entire class of OTC drugs. And really, historically, access to a product is only one half of the equation, and then the other half of that is coverage. Whether or not a prescription is covered by insurance plays a big role in whether certain people can access those products. So while prescription drugs are typically covered by payers, OTC products typically are not, and this can create some access challenges for certain patient populations, especially, for example, Medicaid beneficiaries who might have limited resources and who are accustomed to paying zero to just a few dollars for their copay.

For those folks, an increase in the copay, or even having to pay a copay at all, may put a medication out of reach. So all that to say, while coverage considerations are, as we've talked about today repeatedly outside of the purview of the FDA, they still are something that we need to kind of come together and work on and figure out to make sure that people can access these products. So thank you.

Thomas Rodes:

Thank you very much, Michelle. And then next let's go to Sue, please. Sue, would you like to come on up to the podium?

Sue Peschin:

Hi, everyone. I'm Sue Peschin, and I serve as president and CEO of the Alliance for Aging Research. I'm also a family caregiver to my mom who lives with Alzheimer's and multiple other chronic conditions, including severe arthritis, and I've managed all of her prescription and over-the-counter medications for the last six years. She recently actually transitioned to nursing home care, so I no longer manage those other than speaking to the medical director in the nursing home facility. And that's actually still a management issue, to be honest. So when compared to other countries, the US market for over-the-counter switching is exceedingly narrow. Fewer than 39 drugs have been approved for prescription to OTC switches since 2001, which is an average of about two per year over a quarter of a century. And in the US, switching has a perverse incentive structure for both manufacturers and patients. So when a drug is only sold as a prescription, manufacturers aren't beholden to the competitive market and can negotiate higher prices with insurance companies than what individuals are willing and able to pay.

And similarly, generic prescriptions are often cheaper for patients than buying the same OTC product because insurance covers one, not the other, and that was touched on a little earlier. So in March of 2025, the Alliance, my organization, and the Alliance for Women's Health and Prevention co-convened a round table of 16 diverse patient and consumer advocacy organizations to assess the current state of prescription to OTC switch process and identify opportunities for improvement. And our discussion underscored the urgent need to reform the process into one that will address regulatory uncertainty, improve education for patients and providers, and seek to identify ways to update antiquated delivery of care and treatment for patients, and then strengthen collaboration among stakeholders. We're really excited about the potential gains for older adults and family caregivers from a broader prescription to OTC switch policy.

Older adults and their families disproportionately manage chronic and recurring conditions, rely on fixed incomes and face multiple barriers to routine healthcare access. My mom with her severe arthritis, every time we had to go back just for a check-in, oftentimes it felt like it was to get the copay to do medication checks was not easy for me with the wheelchair, and certainly not easy for my mom because it hurt getting in and out of the car. And a lot of times, it just felt like it was not a necessary exercise. So just putting it out there. And also, I think sometimes there's this perception that doctors spend all kinds of time talking to their patients and family caregivers about how to manage medications properly, and they really don't. Appointments are super short. I talk a lot more to allied health professionals about my mom, and certainly pharmacy as well, but also other caregivers and patient advocacy organizations. So I think all of that just needs to be taken into consideration.

So there's like four beliefs and findings from our convening that I just wanted to convey really quickly. Older adults need and want easier access to their medications. The barriers I talked about, longer appointment, wait times due to shortages, limited pharmacy hours, pharmacy deserts, all fall the hardest on the people who can least afford them. And then geography also plays an issue in proximity to healthcare. There's significantly more older adults in rural communities than urban areas, and older

adults who are also more likely to face transportation difficulties. For the most part, older adults are ready for digital tools. They're online, they're on their phones, they're using QR codes, they're managing their health with apps, scheduling telehealth visits, and using digital tools every day. And thankfully due to advocacy efforts, more tools than ever before offer adaptability for disabilities. So the assumption that digital self-selection's too complex is outdated, and sometimes it borders on patronization. So I think that's important to keep in mind.

The current regulatory framework minimizes the benefits to patients that can be gained by increasing access to self-care. And I know there was some discussion around benefit risk and there'll probably be more in the Q&A as we go around, but I think it's important that high rates of under diagnosis and undertreatment, as well as other access barriers, should be factored into the benefit risk equation. We recognize the FDA's caution comes from a genuine commitment to patient safety, and we thank goodness for you, and we also thank you for your service, for sure. We are huge fans of the Food and Drug Administration and appreciate all you do. However, when the agency evaluates an OTC shift, we want you to keep the question in mind, that not only, what could go wrong if we act? It should also be, what may already be going wrong because we haven't? And so we ask you to rework the risk benefit framework to take seriously the cost of doing nothing, and also the desire and the dignity of letting people make informed choices about their own care.

Older patients also deserve a seat at the table when decisions are made about which medicines they can access on their own. The FDA's advisory committees have long provided a formal public space, and we have participated in multiple ones across many, many years, and we are so appreciative. That has definitely gone down in the last couple years. And we really want to encourage that with this switch enthusiasm, that that be reinvigorated because advocates and caregivers and patients can speak directly to advisors in the FDA about what a switch means in the real world, whether instructions are clear, whether risks are manageable without a provider present, and whether expanded access genuinely improves outcomes for the people it's meant to serve. And when the stakes are highest, when you have for first in class switches and not novel pathways like ACNU, patient perspectives are essential.

So unlike traditional prescription advisory committees, which mostly focus on clinical efficacy, the switch discussions are fundamentally about consumer behavior, how people understand information and assess risk and make decisions without a clinician present. So we really urge the agency to preserve a formal public consultation process from prescription to OTC switches. And thank you again for everything you're doing and for convening today's meeting.

Thomas Roades:

Thank you very much, Sue, for those examples from both your personal experience and some of the work that AAR has done convening different patient advocacy organizations. Really helpful. And then finally to round out our opening remarks, Shonna.

Shonna Yin:

I'll come to the podium too. Follow the trend. Hi, everyone. I'm Shonna Yin. I'm a general pediatrician and a researcher at NYU School of Medicine, and I've been working on research focused on health literacy the past 20 years, on the intersection between health literacy, health outcomes, and health disparities. And as a researcher focused on these issues, and listening to those who have presented before me today, I had some musings and thoughts before we dive into our full panel discussion. As mentioned in the, sorry, in the prior panels, it's really important to use a health literacy lens to think about these issues from an individual consumer's perspective. We know that... Oh, sorry, I do have some slides. Let's see if I can get to them.

We know that the typical older adult takes multiple medications. And in fact, the study that I looked at showed that one in three older adults take five or more medicines. So I'd love to bring this frame of health literacy back into view as we think about innovations to enable increased access to non-prescription drugs. How will consumers navigate access to multiple additional medications without a healthcare provider? How will they consider drug-drug interactions, side effects, risks, and benefits? It's not just about increasing access to any single medication, but we need to think about all the medications and individual needs and the intersection between those medicines. So it makes me wonder to think about this potential role or some level of role of standardization. For example, one area to focus on is, how does a consumer distinguish one medication from another within the same class of medicines? If each manufacturer uses a unique ACNU approach for their product, there's the potential for numerous different approaches even within a single drug class, and that can be overwhelming and lead to potential confusion.

So I wonder, can groups of manufacturers, for example, those marketing drugs from a particular drug class, can come together to work to create a seamless experience for consumers related to that class? Could there be a somewhat unified approach for uploading the blood work, verifying the age or verifying the presence of health conditions? Could there be a unified approach to supportive counseling on lifestyle or risk factor modification, especially for chronic conditions? Some medications require long-term use and monitoring to ensure appropriate continued self-selection, so can monitoring be standardized across medications in the same class?

I think that we can leverage technology to help us meet some of these challenges, as Mary Alice alluded to in her discussion as well. I wonder, can existing technology be used to help create a system within which a complete medication profile for each consumer is kept, pulling together information from electronic health records, since individuals may go to more than one health system for care, pulling together information from pharmacy software systems like SureScripts, pulling together information from records of medicines purchased over the counter at pharmacies, drug stores, or other non-pharmacy retail locations, or even medicines purchased online, and thinking about how information can be transmitted bidirectionally?

ACNU, there's a potential for consumers to be taking many more medications without healthcare provider involvement, so it'd be helpful to have a single complete medicine profile for consumers which would allow us to warn consumers regarding potential interactions, flag which medications consumers may not need to still be on, et cetera, look at the patient kind of holistically like healthcare providers do when they try to do medication reconciliation at each visit. As I'm sure we'll talk more about on this panel, how can web apps and newer technologies like AI, AI chat bots, et cetera, be used to support self-selection, appropriate use, and decisions regarding when to stop taking a medication due to adverse events or other issues.

And finally, as someone who trained in pediatrics, I'd like to ask, what are the implications for children? Will people take medications indicated for adults and give them to children? And I want to note that children are at higher risk when medication errors and adverse events occur given their smaller size, as well as the way medicines are processed in the body in a way that's different in children than adults, and remind people that children are not just small adults. So those are my brief remarks, and I look forward to the panel discussion.

Thomas Roades:

Excuse me. Thank you very much, Shonna, and thanks everyone for the opening remarks there. So I think with those opening remarks, we've got a very good sense of a couple of innovative tools or approaches that are under development that could be used to support access to products with an

additional condition. And then also got some great thoughts on some of the most important principles to keep in mind for implementation there from the perspective of feasibility from the point of view of a seller and also from more of a clinician and patient perspective, what's most important to keep in mind as we implement there.

So I think maybe I'll jump ahead here to think about what this might look like in different settings. Obviously, I think a chain drugstore or a pharmacy is one of the most common examples that comes to mind when we think about where consumers might be purchasing non-prescription drugs, but of course that varies beyond that as well. We have non-pharmacy retail stores, you can pick them up at a 7-Eleven, say, or online retail getting shipped directly to the consumer. So I want to talk a little bit about how we might implement across those different settings, how consumers are purchasing in those different settings. Let me maybe start first again with Dustin. I believe you mentioned you're envisioning this would be a case where the consumer verifies their kind of compliance with the additional condition online and then it would be a shipping direct to consumer. Is that kind of the primary route of access that you're envisioning for the tool that's under development there?

Dustin Little:

Yes, certainly in this case. I think that in medicine in many ways, the world has changed in the last, I don't know, decades, but we're sort of still doing things the way we've done them forever. And I was thinking, I really like to drink coffee and I'm away from my special coffee setup at my house for a couple days, but the way I get my coffee at home is I order it, it gets shipped to my house and it's really quite convenient. So I think where appropriate and where it makes sense, I think leveraging a model like that for non-prescription drugs makes a lot of sense. But I think what's important also is that there's flexibility and there's other ways as well. Because this is about increasing access to non-prescription drugs, so I think we need to have sort of multiple ways to do that.

Thomas Roades:

And on that point, Mary Alice, I know you mentioned potential for the tool that you described could facilitate your purchase through any of those different settings. Can you talk a little bit more about what that might look like in practice as you envision it?

Mary Alice Lawless:

Sure. A couple of things on that. So we started from that as a fundamental principle that we want mass access if it's possible. And so looking at the systems that are available to facilitate that, you sort of have consumers, which, still, I think the statistics are still 85, 90% go to retail pharmacies to pick up their drug products, whether they have them shipped or they pick them up in person. I think it's 75% of the people go in person and 85% of the transactions are retail pharmacy. So we don't want an abrasive experience for consumers, we want to try to go with the flow of where they are and how they're working. And in talking to retailers, they're pretty excited about that because they can certainly take an API feed to get a credential that can be used at point of sale. This is all front of store, very convenient and easy for consumers. They don't have to stand on the long lines.

To Michelle's point, when we talk to any retailer with the pharmacy in the retail setting, they're worried about those long lines, they're worried about the reduced hours. Like, what are we going to do with all these people coming in the front door looking for these new products? Now that's a future state, obviously, but the idea is to let this activity sit in the front of the store, but let the data run through the back of the store. So between the POS, which is the front of store system and the pharmacy management system, that's where that data transaction happens that then routes that data back into

the consumer's record. So there's really no limit on where the transactions can take place. I think Dustin, to your point about statins, I mean, if it's a daily drug for the rest of my life to maintain or prevent heart attack and stroke, maintain cardiovascular health and prevent heart attack and stroke, I'd probably like to have it delivered to my house, maybe after the first one, right?

You might buy a few at first and then say, "You know, why doesn't this just come as an automatic subscription?" So I think consumers will weigh in and they're going to tell us what they want by their actions.

Thomas Rodes:

And building on that, Michelle, I know you talked about the importance of standardization in your opening remarks. Any additional thoughts you would want to add about what works well for implementation from kind of a perspective of standardization or how consumers are shopping in your stores? I know oftentimes you have the purchase online, maybe pickup in store option versus the traditional shopping experience. How does all of that play out and how might we fit these new tools into that paradigm?

Michelle Cope:

So I was kind of thinking about this. I mean, I think that regardless of where you're obtaining the drug, unless it's like direct to consumer, but I think you're going to see there are going to be common issues across whatever the setting is, whether it's a retail setting that does not have a pharmacy or whether it's a retail setting that has a pharmacy because you are going to... I would fully anticipate that the vast majority of retail settings with pharmacies will still have this as a front of store thing and while they're... So that being said, it's the point of sale system is going to need to be the same, have the same sort of functionality that you would see at a non-retail store. So I think they're going to have a common need for standardization or they're going to have a common need for something that's workable.

So whatever the mechanism is, the item is, whatever, that presents to the retailer that says, yes, this patient has completed the questionnaire, the online questionnaire, whatever, and they are eligible for this purchase, there's going to be a common need across retail types for that to be something that's similar and that whatever the process is for the sales transaction, that's a similar process so that they're not having to adopt something that's different for every different product. So there's that. And then the other piece is, and I know this is, again, a little bit outside of the purview of today, but it's still very important, is coverage. So that's still going to be an issue for a non-pharmacy retail setting, right? And so how do we support coverage in those settings?

Maybe the solution there is there's the debit card type thing where your insurance gives you the card for non-prescription drugs or whatever, and then you can have it covered that way. So those are, I think, the kind of commonalities. And I wouldn't necessarily say there are distinct things that have to be worked out. I think that's something that we all need to solve together.

Thomas Rodes:

Well, and if I could just follow up with Michelle real quick on that point, actually, as you said, it's kind of a challenge that we all need to solve together. Is there an opportunity maybe for developing standards that associations like NACDS or potentially FDA or industry could collaborate on some sort of standard of what additional conditions could look like and how they are implemented?

Michelle Cope:

So I think that the additional conditions are just... That's different by every product because it makes sense. Statin is going to have a different additional conditions than potentially some other medication, an ED drug or something. But in terms of the processes for operationalizing that, I would hope that there is a forum where everyone can come together. And I would welcome the opportunity to work through FDA or another government entity that could help that, help us bring us all together to work that all through.

Thomas Rodes:

Sue, go ahead. I saw you wanted to jump in there.

Sue Peschin:

Yeah, I mean, I agree. I do think that consumer education and provider education are going to be important in the mix of all of this, just to understand the implications of the switch and drug to drug interactions and all of that, and pharmacy is obviously a critical component of that. But I agree with everything you said about just making sure that there's consistency. And with the coverage issue, we're particularly concerned about long-term care settings, and nursing homes in particular. And we've been really, I think, encouraged by this administration's tendency to work across agencies. So the interaction between the FDA and CMS has been good to see, and I do think that there's an important place for dialogue, looking at the Medicaid program. There are some things in place in Medicaid that are offered to residents in terms of a card and all of that.

But I do think that understanding what coverage looks like is important for just availability in those settings, because you just want to make sure that there aren't whole settings where the switch products might not become available due to coverage concerns.

Thomas Rodes:

Yeah. The importance of collecting data to understand coverage gaps. But then also I wonder if there might be opportunities for data collection to support expanded coverage if we see that these maybe new products are having a real impact on public health outcomes. Go ahead. Yeah.

Mary Alice Lawless:

I'll say one thing on coverage, because as my friend, Joe, likes to say, it's a diabolic word. It means a lot of different things. So we're talking formulary coverage here, I think, right? Don't forget the prescription drug is still covered on formulary. So really, those long-term care settings should not be disrupted in any way. I'm sure all of those residents would be still covered under their Medicaid benefit or whatever formulary benefit they're living under. What we're really talking about is, and the whole rationale for the ACNU rule is the undertreated, the lack of compliance and the undertreatment of these common and chronic conditions. So those people are not opting in for the prescription drug...

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Mary Alice Lawless:

So those people are not opting in for the prescription drug. And so we're trying to give them another access route so that they can come into treatment, they can raise their hand, they can say, "I'm worried about my cardiovascular health," or "I'm worried about some kind of symptom I'm having." And I think that's a really important distinction is that there's formulary coverage and then there are all those other mechanisms like the FSAs or the debit cards that you mentioned, Michelle, or HSAs or health

reimbursement arrangement, et cetera. And we've had a lot of payer perspectives around our work. They're very well aware of this and they do see it as two aspects. One is the formulary with the prescription drugs and the other is other mechanisms for making sure that there's some subsidy, let's call it, so that folks don't feel like they've got to figure out, is it more expensive as an RX or is it more expensive as an OTC?

Sue Peschin:

Yeah. I just want to respond... Thank you. I just want to respond to that because we're very close to the long-term care provider community. And it actually is a concern. I just talked to NCPA, the community pharmacist-

Mary Alice Lawless:

Pharmacist.

Sue Peschin:

... and ASCP before I came here, the consultant or long-term care pharmacist. And they were the ones who, because we work with them on a variety of nursing home issues. And there is a limited stipend that are offered to residents via Medicaid, but it is small. And I'm with you. We wouldn't be here if we didn't want to see expansion. So we're with you on that. But that stipend right now is small. So all I'm saying is the FDA and CMS need to coordinate and have dialogue on this so that if changes need to be made to make sure, because otherwise nursing homes will just say, "We just won't offer these products." And you want there to be access in all different types of settings. That's all I'm saying.

Mary Alice Lawless:

Yeah. And the stipend is for the non-prescription.

Sue Peschin:

Yeah.

Mary Alice Lawless:

Yeah.

Sue Peschin:

Yes.

Thomas Roades:

Well, maybe a great topic for a follow-up meeting. I think that interagency coordination and the importance of ensuring coverage and access as things develop here. But I want to bring us back to the topic of developing and implementing these innovative approaches. And maybe I'll go to Shonna here to help us think a little bit more about striking the right balance between this kind of flexibility of different approaches versus standardization, the importance of for feasibility and also for consumer understanding, standardization can be very helpful. But then on the flip side, flexibility obviously will be very important to make sure that we're hitting the most important clinical risks and conveying those messages to consumers specific to each product. How do we strike that right balance and what are some maybe thoughts on top of your mind in terms of how we approach that?

Shonna Yin:

Yeah. I worry a lot that people will be overwhelmed by having too many different ACNU approaches out there. And I think, Mary Alice, your system seems to integrate multiple different ACNU approaches into one system, one central system. Is that-

Mary Alice Lawless:

We're just saying there's an awful lot of firepower in healthcare already today that we can leverage and use to create a very synchronous experience for consumers. All the marketing, all the messaging, all the product positioning, all of those cool slides that Russ Bradford had up, that will still be done by the sponsor. But you're right. In terms of going through this, taking this extra step, let's call it, it should be as expedient as possible. It shouldn't seem overwhelming. Most of the heavy lifting should happen on the backend. The consumer will interact with whatever the dialogue is, the additional labeling that is determined as appropriate. But other than that, they don't have to know how David's slide works that he put up at the beginning of the day, that all this stuff is going on in the back. We can use all the firepower of that and all the technology, the interoperability and the systems and the data without having to burden the consumer with that exact experience.

Shonna Yin:

Yeah. And how do we leverage what's existing that we have? Like electronic health records and how they're trying to make that more interoperable between different health systems. How do we leverage pharmacy software systems and leverage of all the different places where that... I think it's really important though that there is this bi-directionality. So once someone does buy one of these medications that it goes back somehow to the electronic record or some record central place so that there's one place where all the information lives about a person's medication history. And that'll be really helpful in terms of being able to keep track of people who are taking medicines, especially chronic medicines, et cetera, et cetera.

Mary Alice Lawless:

So the interoperable systems that run healthcare can take any data back and forth. For us, I think what we want to think about is what is population scale and valid? So like EHRs, there are a level up there of still inconsistency, right? Somebody was talking about EHRs today, but there are others like the Surescripts database, which is the pharmacy database and runs all the DURs that is providing a gold standard service 6.7 billion times a year as these products are transacted. So that's a stable population-level set of data with lots and lots of fields that we can start with. But yeah, over time, as EHRs perhaps actually come to a standardization that we could plug into and know we're getting enough of the population that it delivers the benefit, as the risk benefit panel talked about, then the type of data is nothing we have to compromise on. We just want to make sure it's valid and good data to serve the purpose.

Thomas Rodes:

Well, Shonna, I feel like you're kind of taking over for me as moderator there.

Shonna Yin:

Sorry.

Thomas Rodes:

That was a very nice segue to our next question. That was exactly where we wanted to go with this discussion, I think, was to think about how we incorporate different pieces of health information that might be important for self-selection there. And I think that was a great example, different pieces of health information that might come from the health record. Do you see that as a challenge that there obviously interoperability is a major priority, but still a major challenge when we think about bringing in different pieces of personal health information, like, say, a lab test that might be needed for diagnosis, but maybe there's also another factor about a patient's health from the EHR that goes into the calculation of whether the drug is right for them? Do you think that's doable to integrate that data?

Mary Alice Lawless:

Again, case by case.

Thomas Roades:

Yeah. Sure.

Mary Alice Lawless:

I hate to say about this world that we live in, but it's very case by case. If there's enough data for the target population in a dataset, then we can use it. If it's not, then it's not going to deliver the benefit. And that's why we're looking at these population scale sets to begin with. I don't have the number off the top of my head because it's not my area of specialty, but I think there are tens of thousands of fields in the medication history record. That gives us a lot of information that we can work with in terms of identifying risk in specific consumer profiles that would trigger a decision to send that consumer to seek some care. So let's use what we have that is very validated and that is being used really for a very similar function on the pharmacy side today and use it at the fingertips of the consumers and then add onto it as other databases.

Labs, that's an interesting one. We have two major national networks with Quest and Labcorp. In a certain situation, the benefit may be delivered if the prompt says, "You're going to need some labs for this. Do you want to register at Labcorp or Quest?" Now we know we can get it because they're already online. If they want to go to NYU, to the outpatient lab, that's a little bit of, and only one person is going there, that's a different issue. So we really have to look at each case and say, "What do we need to have happen here?" AstraZeneca now has proven that consumers can transpose their lab values into an interface, so that also works.

So there are lots of different ways, and that's why taking the issues, the challenges that in the translation from the prescription label to the drug fax label, and pulling those out and really deciding how can we solve those and what technologies, data, et cetera, do we need? At least the infrastructure can facilitate whatever that is.

Thomas Roades:

Yeah. Well, appreciate you thinking big picture, future state there with us. Even if not all of these challenges are solved today, helpful to think about how we might approach them. And Dustin, maybe can I come back to you here? I know the example that you walked through, as Mary Alice just mentioned, involves inputting some lab values from the consumer. Maybe if you were to think broadly about potentially other products, I know this is more hypothetical, but would you envision this web-based consumer input screening could capture a bunch of other sorts of information, as I just mentioned, that might be useful for self-selection? Or how might you think about going about that?

Dustin Little:

Yeah. I suppose, and I was just reflecting on the labs and I feel like in medicine we do a lot of gatekeeping and I think labs is one of those areas. I think lab testing is getting democratized a little bit. In our program, some of the participants had had their cholesterol and their lipids tested at home. And so I think as we make lab testing, for example, more available, that brings us more opportunities to utilize those lab results. But somehow I get a little bit torn because we talk about these big ideas that I think are really important, but we also have to start somewhere. Like Dr. Murray, you talked about a paradigm shift, I thought, in non-prescription drugs. I have a headache, so I take some ibuprofen. That's kind of obvious, but should we consider switching some non-prescription drugs that are prescription drugs that are used more chronically?

And I think that's a total paradigm shift and it opens up the possibility of people's lab results being on the cloud and there being communications between the EMR and other things. But to really be able to do that, we've got to start developing or converting these drugs to non-prescription status and democratizing the access, right? So we have to sort of start at square one and then we can leverage all this technology as well.

Thomas Roades:

And I'll bring in an audience question here that someone flagged earlier for us in the day, actually, but I'm going to bring it in now, about kind of the increasing development of diagnostic tools that are also more consumer facing in the over-the-counter setting. So I don't know if this is more complicated or less complicated than the lab testing example, but what if we have an opportunity where the consumer can run that test themselves? Say, I don't know, some examples that I could think of, a non-prescription product where the consumer shouldn't be pregnant when they're taking it that's a test that's available over the counter right now. Or for example, I had flu in the past month. Really, really not fun. Seems like most of DC had it, really. But I found out that I had the flu and I got my treatment because I took an over the counter test.

I didn't go to the doctor to get the test. What do we think about examples like that? Sue, you mentioned the flu example as well. Do you want to talk about what that looks like for potentially older patients testing and treating for the flu?

Sue Peschin:

Yeah. I think we all became intimately familiar with the home tests over COVID. And there were combo tests that were developed for COVID, flu and strep. And it is ironic that you can get these results at home and then you have to go back. And there were waivers during the pandemic in terms of being able to get the antivirals, but those waivers were lifted in terms of the pharmacist. And it makes sense. People have familiarity with it now. There are things that you have to keep in mind. So there would be probably falling under ACNU when it comes to COVID in particular for people with renal conditions, but I do think that at this point you have to sort of look at population experience. And there's so much with that and the risk is so high to not get on the antivirals soon enough.

And that happens more than we like to think about where you just don't get access to the medication in time, so it can't help you. And older adults in particular at highest risk of hospitalization and death from those two respiratory diseases. So we would welcome that for sure.

Thomas Roades:

Any thoughts from others about the opportunity to integrate all of this information? Yeah.

Michelle Cope:

Just that. I'm sorry. I'm just [inaudible 03:57:06] this microphone. Yeah. So I'd just add that it kind of varies on a state by state basis because you can, there is test and treat available. You can go to the pharmacy, but it still can be challenging. So we have an example right there of how it is working. And I do think the availability of OTC testing can be helpful. Sure. Sorry. I don't know. I probably said all I just need to say.

Thomas Rodes:

No, please go on if you have more on that point. You were talking about examples of test and treat that you were working to facilitate there. Is that where you were going with that?

Michelle Cope:

Yeah. So depending on what state you live in, we do have potentially access to test and treat services in your pharmacy. Now, you don't have access to test and treat services at a non-pharmacy retail location. So I guess that could potentially work for something like that. And I would absolutely defer to the expertise of FDA, whether or not an antiviral would be helpful or the appropriate medication for a drug with apnea.

Thomas Rodes:

Shonna, anything you would want to add?

Shonna Yin:

I think the appropriate ACNU approach, I think it could work, but I think we just have to be cautious that people are able to self-select and know that there's certain restrictions about when medications stop being effective. So for Tamiflu, it's within 48 hours, you have to take the medication, et cetera. So otherwise, there's not a point to taking it. So I think we just have to approach with caution, but I think that it could be possible to move towards that direction.

Thomas Rodes:

Yeah. Well, you're right on track with my moderator talking points here again with the example of when a medication stops being effective. I wanted to shift us a little bit in our last few minutes here. So far, I think most of the examples that we've been talking about are about the self-selection piece, which is one way that an additional condition can be used. It can be to help a consumer decide if a drug is right for them. But then additional condition for non-prescription use can also be used to determine or to support appropriate use or to ensure appropriate use. So over time, is this drug still right for you? Do you need to change the way you're using it? Do you need to change something else? So the example that Shonna just raised, I think is on many, many drug facts labels, "Stop use and see a provider if X happens."

So I think that's another likely case that might come up with additional conditions or just a challenge that is really important in the non-prescription space overall, is to ensure that people are following through on appropriate use in that ways. We might have follow-up testing. For example, you could want to check whether your cholesterol is actually improving, whether you need a different dosage perhaps, or you might want counseling on lifestyle or risk factor modification, other interventions beyond the pharmaceutical intervention that could be really important. So anybody feel free to weigh in on this one. Thoughts on how we fit that in as well?

Mary Alice Lawless:

I'll start just to say that use is just as important. And of course, once a consumer has opted into this interaction, this conversation, the questionnaire, whatever, it presents however it presents itself, one of the requirements could be, I agree, to take messaging or get prompts or something. And that again, that's a very common convention in remote patient monitoring, longitudinal care that is used in many situations. So it's familiar to us and it's relatively easy. So now what matters is, what is the message? Is it if your symptoms haven't resolved after seven days, if you're not getting better, you should see your doctor, or something along those lines or something different? That's really what makes it a case by case. But in terms of the functionality, that's also something that once there is a, if you will, a digital relationship, and I should say that this can also be facilitated through interactive voice systems and so on.

But as Sue, as you're saying, really, most people are perfectly happy ordering their coffee on their phone in the morning, and so this is not going to be a heavy lift.

Thomas Rodes:

Who else wants to jump in here? Dustin, is the appropriate use piece something that you've been thinking about for the example that you talked about, or potentially for other products?

Dustin Little:

Definitely. I think I blew through it in the example, but one of the co-primary endpoints in our main actual use study had to do with appropriate continued use of the non-prescription rosuvastatin. And so for folks to be able to reorder, they had to go back to the web application and complete a few questions to ensure that their health status hadn't changed in such a way where they were no longer an eligible candidate. And because I have the floor for a second, Mary Alice, you made a really important point about ACNU. And Dr. Murry, you did as well. But I think if we're talking about treatments where the goal is to increase access, I think it's really key that with ACNU, we're not taking away the prescription option, we're adding to this with a non-prescription option. And your question made me think of it because some people might make the decision to see their healthcare provider.

They've been using a medicine on a non-prescription basis and they may either be directed to see their healthcare provider based on the drug facts label and the ACNU, or they may make that decision themselves. And that's an option for them with ACNU. And I think that's something that's really low-key, one of the most important aspects for public health.

Thomas Rodes:

Yeah, it's... Go ahead, Sue.

Sue Peschin:

I actually just want to, I completely agree with what you're saying because when it comes to older adults, the likelihood is they're not just taking a non-prescription medication and the importance of interaction is so important. And so getting a regular check-in is going to be important and they will have that exposure, which is good. And that gives us comfort knowing that with multiple conditions likely in those types of scenarios, there will be a check-in.

Thomas Rodes:

Yeah, that touchpoint is really valuable. We did hear earlier though that sometimes the non-prescription medicines sort of fall through the gaps in a provider visit where the focus is more on prescription and either the provider or the patient might think that a non-prescription medicine is not something that they need to mention or input. What do we think about a paradigm shift there and what could be done to advance maybe some consumer or some provider or other education to change the way we think about these products if we're talking about new classes and new approaches to non-prescription treatment?

Sue Peschin:

I think that's where the partnerships are so important and with the specialty societies and other provider organizations and all the patient advocacy groups as well, that there be education across the board. Because there are checks in the Medicare annual wellness visit, for example. And I think there's other opportunities when you have that interaction to talk about anything new that's been added on a check-in basis, but we need to amp up provider education, consumer education if we're going down this path, and we will advocate for that strongly.

Dustin Little:

I think it's a big challenge in the prescription setting as well, to be honest. Sometimes I feel like we're a little bit harsh on non-prescription setting because it almost is like we think that the seeing patients in the clinic and the prescription setting is perfect. And I still have a clinic I see and it's still not perfect. I sometimes really struggle to make sure I have a handle on my patients, the medicines they're getting from other providers. And so I think it's important for non-prescription, but also for prescription all across medicine to do that medication reconciliation.

Sue Peschin:

Yeah.

Thomas Rodes:

Shonna, Michelle, any reactions to those last few points?

Michelle Cope:

So I'm thinking about the med history on the prescription side of it. And I know I'm kind of thinking about my own experiences as a patient. I feel like that's very helpful when I go in to see my doctors. They're like, "Oh, I see that you have taken this and this and this." I'm like, "Well, yes, I have." And I wonder if you were talking about using the med history as a way to facilitate that information if at the point when the patient is completing the ACNU online or whatever, that program or whatever, that online tool can then link back into the EHR. And that would then be very helpful in the same way that on the pharmacy side now, like pharmacy records go through Surescripts and are shared and then become the med history that's available through EHR. So I wonder if that does sound like a very helpful solution to filling that out.

And this is also... Right now, we're at a point where you have so many... The OTC market is really about to explode a little bit, right? So this is almost a point where this is like, we're here and we need to start thinking about this and talking about this. So this is the perfect time to... We just need to start having those conversations. And yeah.

Thomas Rodes:

Shonna?

Shonna Yin:

I think just one reaction that I've been having in thinking about the ACNU approach is, how many web apps are too many web apps? Do you have your separate one for your statin and then your separate one for your blood pressure and your separate one... And then somehow you need to be on each of those to monitor things and upload your information, et cetera. I worry about that and I think that's going to be a big thing that we need to hurdle that we'll need to jump through.

Thomas Roades:

Yeah. Coming back to that standardization point that we've come to several times, I think. We're just about at time here. I'll give everybody a real quick lightning round. I'll just go down the row starting with Mary Alice and going down just super quick, 30 seconds or so. Final thoughts. Easy, right?

Mary Alice Lawless:

I like what Michelle just said, which is we may as well start.

Thomas Roades:

Mm-hmm.

Mary Alice Lawless:

We may as well start. No time like the present to just really think about, how do we use the resources we have and the need that exists that needs to be attended to and to start down this road? Nothing we've talked about today is so outside of the scope of either safety, risk management or consumer friendliness that we have any reason to hold back.

Thomas Roades:

Shonna?

Shonna Yin:

I think for me, just thinking about health literacy issues and centering the patient, thinking about the patient experience will be really important. And yeah, I think we'll end with that.

Michelle Cope:

If you walk away from one point from me today, I would just hope that it is the importance of standardization in supporting patient access broadly, because that's going to make it feasible for retailers to operationalize and offer a broad variety of products.

Sue Peschin:

I am under the understanding I'm the only patient advocate here today. And I just want to emphasize, have more patients, have more family caregivers at the table, real ones, not just from a big survey that you did and reported to the agency. And just want to, again, emphasize, do more of the ad comms and do it in this space. That voice, I think, sometimes is the most compelling voice you all hear in these meetings.

Dustin Little:

I've got this screen in front of me and it's got where all the panelists are from. And I'm not sure there'd be any other setting where you'd get all of these different groups together. NYU, the National Association of Chain Drug Stores, Alliance for Aging Resource, et cetera. And so to me, it's just really gratifying that we have this group here that's clearly focused on public health and want to thank... I know we have time to go still, but I want to thank Duke Margolis and FDA for putting this together because I think it's really gratifying.

Thomas Roades:

Yeah. Well, thank you all for coming together here and thanks to this panel. And now I will close this out. You all can take a seat. Thanks again for this great discussion. All right. So thank you again to all of our participants throughout the day today. I'll just give some very brief closing remarks here so you all can get going. We will have all the materials from today's meeting will be posted on the Duke Margolis website and a summary will be forthcoming as well. So I'll just be very brief in summarizing some of the main points of the day.

We started with an overview from Dr. Murry with FDA about the landscape of prescription and non-prescription drug regulation and some of the pathways to non-prescription status. Then some discussion on what expanded access to non-prescription drugs may mean for public health and individual health. How do we approach benefit risk assessments focused on that incremental benefit that non-prescription status could provide and developing rigorous evidence related to consumer behavior, then followed up on those points in our discussion about evidence generation, thinking about some new opportunities for enhancing that process, making it more efficient, bringing in real world evidence, all of the work that goes into consumer behavior studies to demonstrate safety and efficacy for the non-prescription setting, as well as what that evidence generation process might look like under the additional conditions for non-prescription use for products that will go down that pathway.

And then be very brief. On this last panel that we just had, appreciated the panelists helping us think about what a new state of non-prescription drug access might look like, what sort of innovations could enhance access and ensure appropriate self-selection and use and all of the other considerations related to how patients will approach that process, how it'll be operationalized across different points of sale, and what really needs to be done to maximize the potential benefits there and minimize the risks. So I'll conclude this event just by thanking everyone who made it possible. Lots of contributors to thank you today. First of all, to everyone who spoke up here today, really appreciate your contributions and sharing your expertise with us. Like Dustin said, it's been a really varied group of perspectives and that really provides so much value to us to have everyone come together like this.

So thank you all for dedicating the time to prepare and to speak to us today. I'd also like to thank our colleagues on the FDA planning team, all of whom were excellent to work with. I'll give a special thanks to the incredible Fong Pham, who was our project manager on the FDA side. And of course to Dr. Murry who spoke earlier this morning, thank you for your contributions. And then a thanks to everyone on the Duke Margolis team who we worked with to plan this event. That includes Matt Dambrosio, Brian Cantor, Valerie Parker, our excellent events and operations team of Luke Durocher and Hannah Vitiello, Marianne Hamilton Lopez, our senior research director who spoke this morning, and Alyssa Wong. And then lastly, we'll say thanks to the staff here at the National Press Club. Always keeping things running very smoothly for us. So we always appreciate working with you and all of your hard work.

And finally, I'll give a thanks to the attendees here today. And also one ask for you as you walk out. Please stop by the registration desk where you picked up your badge, your name badge, and you can

drop it back off there. We will recycle and reuse those. So thanks all for attending and for doing that one last thing on your way out.

PART 8 OF 8 ENDS [04:13:48]