Defining "Candy-Like" Nonprescription Drug Products

Hybrid Public Workshop

Hosted by Dr. Brandon McClary

Monday, October 30, 2023

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Silver Spring, MD 20993

Reported by: Richard Livengood

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A P P E A R A N C E S

List of Attendees:

Dr. Brandon McClary, Host, Interdisciplinary Sciences with the Office of Nonprescription Drugs

Theresa Michele, Office of Nonprescription Drugs, FDA

Natalia Davydova, United States Pharmacopeia

David Tisi, Technical Director, Senopsys

Xiaoling Li, Thomas J. Long School of Pharmacy, University of the Pacific

Jeffrey Worthington, President/Founder of Senopsys

Swapan De, Senior Chemist, Office of Pharmaceutical Quality, FDA

Danae Christodoulou, Branch Chief of the Office of Pharmaceutical Quality, FDA

Rachel Meyers, Ernest Mario School of Pharmacy, Rutgers University

Catherine Tuleu, Professor in Pediatric Pharmaceutics, University College London School of Pharmacy

Judith Chin, Resident Program Director and Professor of Department of Pediatric Dentistry Nova Southeastern College of Dental Medicine

A P P E A R A N C E S (Cont'd)

Gilbert Burckart, Associate Director of Pediatrics, Office of Clinical Pharmacology, Pediatrics, FDA

Cynthia Connolly, Professor of Nursing, University of Pennsylvania, School of Nursing

Jennifer Lind, Epidemiologist and Captain, U.S. Public Health Service Commissioned Corps.

Maribeth Sivilus, Lead Epidemiologist, CDC Medication and Safety Program in the Division of Healthcare Quality Promotion

Christopher Hoyte, Medical Director, Rocky Mountain Poison and Drug Safety

Suzanne Doyon, Director, Connecticut Poison Control Center, UConn Health

Kristine Parbuoni, Associate Professor, University of Maryland, School of Pharmacy

C O N T E N T S

C O N T E N T S (Cont'd)

P R O C E E D I N G S

DR. MCCLARY: Good morning, everyone. All right. I am Dr. Brandon McClary, Interdisciplinary Sciences with the Office of Nonprescription Drugs here at FDA. So I just want to welcome everyone, and thank you for joining this public workshop on defining candy-like nonprescription drug products.

This workshop is a collaboration between FDA and University of Maryland CERSI. We have a great lineup of presentations today. I will be serving as the host for the workshop, which means I have the honor of introducing all of our amazing speakers.

But first there are some housekeeping items I just wanted to briefly cover. So as a reminder, this is a hybrid workshop. We have a number of folks participating via webcast today. So the agenda is available on the workshop webpage. Please also refer to the full biographical summaries of our speakers posted on the workshop webpage to learn more

about their amazing work.

Following the workshop, meeting materials including recordings, speaker slides, and also transcripts will be available online. So be looking out for that sometime within the next three weeks.

We have wi-fi availability for all of our in-person guests, and that information should be featured on the last page of the printed agendas, which also includes a QR code which will link you to some of the meeting materials. So additionally, refer to our housekeeping slides that will be displayed during the breaks.

We have food at the kiosk right outside of this room in the main hall, where you can purchase coffee, assorted beverages, and also snacks throughout the day. If you would like to order lunch, please do that and submit your order by 10 a.m. at the kiosk. Again, that's located in the main hall. And you can pick up your lunch during the lunch break. Lunch can be eaten within the room or at any tables at the main

hallway, or if weather permits, at one of the tables outside.

Restrooms are also located in the main hall, behind the kiosk. And if for any reason you need to leave the FDA building, just be mindful that you will have to go through security once you reenter.

And lastly, we have already received a number of public questions during the registration period, and many of those questions will likely be covered during the workshop. But if time permits, we will try to address any additional relevant questions to our speakers during the panel discussions, at the end of each session.

So with all of that said, I am now happy to introduce our first speaker, Dr. Terry Michele. Dr. Michele is the director of the Office of Nonprescription Drugs here at FDA, and she'll be delivering some opening remarks on today's workshop. Thank you.

DR. MICHELE: So good morning, everyone. Now it is just such a pleasure to welcome

everyone here, with many of you in the room as we get back to in-person meetings at White Oak, as well as all of the many people attending virtually. Just in time for Halloween, it's my pleasure to have you here at this workshop today on candy-like dosage forms.

So there's a natural tension in formulating drugs between creating palatable dosage forms that people, and especially children, are willing to take, and the potential safety and manufacturing risks that occur if you make those forms taste too good. So we're trying to figure out what that means today.

And candy-like dosage forms for nonprescription drugs aren't a new phenomenon. They've been around for many years, with even Mary Poppins singing about how a spoonful of sugar helps the medicine go down.

However, we've seen a proliferation of these products over the past few years, particularly in the dietary supplement market, and now it's starting to creep into nonprescription drugs as

technology provides increasing options for how we can formulate drugs.

So given this, we started looking at what information exists on these types of dosage forms, including what information exists on consumer understanding of the dosage forms and the potential confusion that might exist between these dosage forms and candy.

We realized pretty quickly that there's just not a lot out there. And with very little research, starting with something as basic as a definition, it's just not there. So since a first step in starting to gather data about this is defining the products that we want to know about, we realized that a "we know it when we see it" kind of approach just wasn't going to cut it. And so the idea for this workshop was born.

The number one goal for the workshop is to further define features of nonprescription drug products that could be considered candy-like. So to help us come up with a definition for what these

formulations are. And as such, we'll be exploring this question with each of our panels to get ideas on this from all the experts.

And in addition, we'll be exploring formulation and stability considerations, implications for adherence, the potential risks of these dosage forms. Things like accidental overdose, especially in children; misuse and abuse of these types of dosage forms; GI side effects; effects on blood sugar; dental issues raised by the high sugar contents and sugar substitutes in some of these products.

We are honored today to have an incredible lineup of speakers, with representatives from industry, from academia, from the U.S. Pharmacopeia, from State Poison Control Centers, and from federal agencies including CDC, as well as many of our colleagues here at FDA.

I'd like to thank all of our speakers today for donating their time and all of your expertise to this important effort. I'd also like to thank our collaborators from the Division of

Pediatrics and Maternal Health, The Office of Clinical Pharmacology, and the Office of Pharmaceutical Quality here at FDA for helping put on this workshop, in addition to our collaborators from the University of Maryland Center for Excellence in Regulatory Science and Innovation, without whom this workshop could not have taken place.

And last but not least, I want to give a big shoutout to Brandon McClary, an interdisciplinary scientist reviewer in the Division of Nonprescription Drugs 1, who you heard from already this morning. He is the mastermind behind this workshop. He's put in countless hours of tireless dedication, along with others from our group as well as others, for more than a year to bring this workshop together. And this is on top of all of his other work.

So it's a real testament to the dedication to public health to bring this together. So thank you, Brandon.

And finally, I'd like to thank everyone

in the audience for attending, for adding your voices to this important dialogue. We look forward to the thoughtful question that we already have coming in during our panel discussions. And with that, I will turn it back to Dr. McClary.

DR. MCCLARY: Thanks again, Dr. Michele, for your remarks. So we will now begin our first session, which is titled "Formulation Considerations for Solid Oral Candy-Like Dosage Forms."

And first I'd like to introduce Dr. Natalia Davydova, principle scientist with the USP, the United States Pharmacopeia. She will be starting off our first session, giving an overview of USP monographs for chewable gels.

DR. DAVYDOVA: Good morning, everyone. My name is Natalia Davydova, and I'm scientific liaison for dietary supplements dosage form, including chewable gels which represents gummy products. I am glad to have opportunity here to present USP activities in the developing of monographs for

chewable gels, marketed as gummies.

USP currently developing chewable gel monographs for dietary supplements only. Dietary supplement chewable gel continue to gain popularity in market in a wide range of the population, from children to elderly, utilizing a pleasant taste, attractive appearance, and ease of intake.

Based on the chart, the U.S. gummy market is expected to grow at a compound annual growth rate of 10.8 percent from 2022 to 2030 [ph]. It's important that dietary supplements manufactured produce high-quality chewable gel that are safe and effective, to deliver the intended nutritional benefits indicated on the product label.

In my presentation, I will provide some overview of chewable gel monographs, monograph components, and specifications given in the monograph which indicate USP quality attributes for this dosage form. Also, I look at potential safety issue and recommendations for consideration when developing the chewable gels.

We have currently four official monographs for chewable gels called a gummy product. This is ascorbic acid, cholecalciferol, cyanocobalamin, oil and water-soluble vitamins with mineral chewable gels. We also -- to publish -- non-chewable gels in the near future.

Also, we have more monographs under development. We're currently reviewing some needed documents from the manufacturers. Here are some of the examples of the monographs. Future monographs.

So the first component of the monographs is the title. And we were not able -- the title of the product, of the monograph covered gummies is chewable gels. We were not able to initiate the development of monograph before the definition of this dosage form was defined in the General Chapter 1151, pharmaceutical dosage forms.

Since it was -- I mean, it was quite questionable if this finished dosage form can be a good dose or acceptable dose for delivery, not only dietary ingredient but also drug compounds.

Finally, USP expert committee agreed to introduce the name chewable gels for monographs covering dietary supplements only called gummies. General Chapter 1151, pharmaceutical dosage form, has been revised and included information on chewable gels. A new dosage form for oral delivery of dietary supplements and drug substances.

Here is a partial definition, I could say, from General Chapter 1151. Chewable gels are used to deliver drug substance or dietary supplements via the oral route. In addition, those drug substance or dietary supplements, chewable gel can consist of all or some of the following components: gelling agent, sugar, water, sweeteners, and flavoring agent.

The sweeteners and flavoring are intended to enhance patient acceptance and mask the taste of the delivered labeled drug substances or dietary supplement. Chewable gel maintains their molded shape, are elastic, and yield to mastication. They are intended to be chewed before swallowing.

Chewable gels are also known as

"gummies" in the confectionary and dietary supplements industry, but that item is not used in official article title.

As soon this definition would be in the general chapter, we were able to develop the monograph. And the next component of the monograph is the definition. In definition, we present the content of the dosage form and limits of -- acceptance criteria for the elements.

In the USA, dietary supplements are expected to meet 100 percent labeled claims through the declared shelf-life under recommended storage condition. And the formulation of gummy products was additional challenges compared to the tablets or capsule preparation, due to dietary ingredient stability issue. Due to -- because the matrix is -- contain water and low PH, which affect stability of many dietary ingredients.

And due to stability issue in manufacturing process, manufacturers regular add an extra amount of the nutrients during manufacturing to

compensate the loss during storage, in order to achieve the declared shelf-life and still have 100 percent of labeled claim for each ingredient.

And establishing specification for the upper limit of dietary ingredient in chewable gels is challenging because the dietary supplements with wide range of doses are on the market and overage could be a safety concern.

Here's an example of two labels from different gummy products. And you can see that the content of ingredient is completely different. For example, one product has vitamin A with daily value of 133 percent, and another product can have vitamin A only 32 percent daily value -- for example, one product has 100 percent daily value and another product 166 percent daily value.

Therefore, manufacturers should be -- should be very careful when taking into consideration USP upper limits, which were developed based on the data available to us from different manufacturers. Stability data for each ingredient. Because for some

doses, its maximum level could be acceptable, but for higher dose it can be -- I mean, it's -- exceed upper limit.

Here, an example of acceptance criteria for the same ingredient in our chewable gels monograph compared to tablets and capsules monograph. So you can see that based on -- again, this specification was established based on the stability data presented from several manufacturers to us. So even for single ingredient, the stability in chewable gels are lower and require higher overages in order to keep, maintain, the suitable level of ingredient through the shelf-life.

Here, example of the same ingredient from multivitamins dosage form tablets and capsules compared to the chewable gels. There are some -- some ingredient is relatively stable. However, some ingredient completely unstable in chewable gels matrix.

For example -- based on the data what we receive from manufacturers, we found that

manufacturer report up to more than 600 percent overage for -- because it's completely unstable. For this reason, our expert committee recommended to remove the -- from the definition for multivitamin chewable gels, due to inappropriate stability. So this chewable gel cannot be used for -- delivery system.

Another quite unstable ingredient, a very important ingredient for dietary supplements, is folic acid. Folic acid is found sample, we found use even 400 percent of overdose -- many cases and more than upper limit.

So therefore, we produce quite high acceptance criteria for folic acid for upper limit. However, our expert committee requested to put particular message for this ingredient that any overage should not exceed the tolerable upper intake level.

Another component is the strength. These are all assay precision. We spent a lot of time to find out the good sample preparation for -- for

gummy product in order to get less variable assay results. And we found that -- that cryogenic frozen samples is the best way in order to get a stable and reproducible results. Therefore, all our monograph recommend cryogenic sample preparation just in order to take a representative sample -- can be different sample preparation like extraction -- but the ground and frozen gummy is what we proposed because it was showed to be suitable for reproducible results.

Another important parameter is performance test. And USP monograph recommend distribution test for all gummy products. Because due to instability, most chewable gel product contains stabilized -- dietary ingredient, including coating to protect some dietary ingredient from degradation or possible interaction. And protective coating can affect the release of nutrients. Also, gelatin agent may impair the release of nutrients from the matrix.

In the table, I show some examples of assay results. Vitamin A permeate and dissolution results in multivitamin chewable gels as percentage of

label claim. And we analyzed a lot of chewable gels on the market, but here just example of three product which show that not all the product can release -- I mean not close to completely amount of, for example, vitamin A from chewable gel matrix.

For this reason, it's confirmed that dissolution testing is suitable quality control tool for chewable gels.

Another performance test is weight variation. And we recommend the requirements of General Chapter 2091. Quite a long time -- claims that it is difficult to make weight variation because of -- the big variation. However, we did -- investigation. So we bought a lot of product from the markets and make more than 1,000 weights, measurements, different -- different lots from different manufacturers.

We found that weight variation relatively tied. So -- and our specification, it looks like tied for chewable gels. However, these specifications were developed based on the

comprehensive statistical analysis of almost 1,000 weights measurements.

Very important specific test for chewable gels. This is water activity and PH. We don't have this specific test for conventional dosage form. But for chewable gels, this is extremely important parameter of quality which allowed to have recommended stability through the shelf-life.

And we recommend water activity. USP recommend water activity not more than 075. However, this parameter may not be appropriate without a controlled PH value, which is not more than 4.5. And PH is another specific test which is also important factor for quality chewable gel product.

And we recommend PH value of not more than 4.5. But again, I would like to highlight that the effect of water activity and PH should be combined to control microbials more effectively. And each separate this, if it's PH 4.5 but different water activity, it's -- these parameters cannot work relatively well for quality assurance.

And a couple of thoughts about the potential safety issue. It is general concern that chewable gel dosage form may have potential safety concern because of risk of accidental overdose due to attractive candy appearance and pleasant taste. And eating dietary supplements, chewable gels, like candy is a common problem.

Nearly 50,000 instances of vitamin toxicity from dietary supplements are reported to the American Association of Poison Control Centers. Most report issue for iron overdose in kids and fat-soluble vitamins A, D, K overdose in adult.

Also, nutrient overage is not reported on the label. And for this reason, label actually mislead consumers about the amount of nutrient they consume.

And in my final slide, I would like to provide some recommendations which we consider important to take into consideration when manufacturing chewable gels. Manufacturer for dietary supplements. Manufacturer should consider the risk of

adverse effect from unknown degradation of products, as well as the uncertainty that is created with a presence of a huge amount of degraded vitamins or botanical [ph] because in dietary supplements we don't investigate this.

Stabilization process used should not compromise viability of the chewable geld dosage form to release dietary ingredient for potential absorption. Also, manufacturer should consider established safe tolerable level of each ingredient and try do not exceed this level even if overage are used.

And make sure that the manufacturer's product maintains its safety and ability to deliver the level of additional ingredient for potential absorption through its expected shelf-life.

So it was my last slide, and thank you very much for your attention.

DR. MCCLARY: Thank you again, Natalia, for your presentation.

Our next speaker is Mr. David Tisi,

technical director at Senopsys, LLC. The title of his presentation is "Drug Product Palatability."

MR. TISI: Thank you, Brandon. My background -- I'm David Tisi, the technical director at Senopsys. Food and sensory scientist by training. And when I told my kids that I was going to come to Washington D.C. to talk about candy, they were so excited they wanted to practically jump into my luggage. So hopefully everybody else had that too.

I wanted to talk about palatability in drugs, and flavor, really starting with some definitions. You can look to the dictionary to find definitions of palatability. Those aren't particularly applicable to drug products. You can -- the agencies have definitions that are not actionable as well. So really, we're fighting for those -- for those definitions.

But in terms of flavor, to a sensory scientist it's important to define flavor. And for a sensory scientist, it's everything that's perceived in the oral cavity, as the product is taken in the oral

cavity. You should be thinking about each of these as today's presentations go on, because flavor is comprised of four different areas.

First starting with basic taste, this I the perception of molecules dissolved in the saliva on the tongue and in the oral cavity by taste receptor cells, also known as gustation. You're limited to five: sweet, sour, salty, bitter, and umami.

Next is the -- next is olfaction. The perception of volatile chemicals in the sinus cavity by olfactory neurons that are located there. The products can get there through either orthonasal or retronasal olfaction, which is reaching the -- reaching those receptors either through the headspace or in the -- or after mastication.

But again, these are two completely separate areas of flavor. You have to think about taste separate from aroma, as different -- as sight is from sound. They're processed by different receptors, thought about in different points of the brain, and are completely separate from each other. It's just

that we're thinking about these together in terms of flavor.

The third element of flavor is known as feeling factors or chemesthesis or trigeminal irritation, depending on where it's -- where it's located. This perception, chemesthesis, is the perception of really the stimulation of thermoreceptors located in the epithelium that are -- they are generally to measure the temperature change of the oral environment. But in the case of chemesthesis, you are triggering those receptors via a chemical stimulation and not a physical stimulation.

So you can see that there's a number of different -- all different temperatures can be triggered physically, as well as chemically, to your brain. That signal is processed in the exact same way. So when you describe a chili pepper as being hot, that is a true statement as far as your brain is concerned. It's just that one way you're getting it physically; one way you're getting it chemically.

And then the final element of flavor is

texture. It's how a product deforms upon mastication. We as adults eat three times a day, so we're very adept at chewing and how these product deforms. Pediatrics that have not learned to chew products, they have a very different interpretation of what -- of what texture is and how it -- how it comes along.

But all of those need to be considered, and each are completely or very appropriate in terms of palatability and what a formulator has to deal with.

Moving onto what do drugs taste like. Well, this is some data. These were 150 new chemical entities, so this is not -- this is not OTC data. But new chemical entities that is really all over the map in terms of what are the aversive attributes that formulators have to deal with.

On the left side you're looking at the primary -- the primary attributes. These are, we'll call it 70 percent are basic [ph] tastes bitter is the primary challenge. But when you delve to a separate layer of that on the right, it really is all over the

map. These products -- just the active itself is bitter and it has an off aromatic or it's bitter and it has trigeminal irritation. So each of these -- again, flavor is a multifaceted challenge.

And that is not just the case for NCEs. It is the case, of course, for OTC monograph products. Here are some examples, not meant to be exhaustive by any means. But you take something like Ibuprofen which is -- has a bitter taste and it has a burning mouthfeel and it has a characteristic aroma that's -- that's part of it. So all of these have to be thought of and dealt with together by a -- by the formulators that are putting these products together.

The world of sensory science, how you can objectively measure flavor, is really divided into two separate buckets. One are analytical methods that use highly trained individuals that measure the intensity of -- quantitatively measure the intensity of attributes that are present. Any of those element of flavor. Versus effective methods. This is the Pepsi challenge. This is consumer testing that says

like or dislike.

You use that to make marketing decisions, but the development is really left to analytical methods due to its quantitative nature. These methods are published in various journals that -- so nothing really is proprietary here. As well as -- as well as industry organizations.

So some of these methods, like the ASTM, American Society of Testing Material's method of -- the flavor profile method, measure what flavor is. And it does this by identifying, number one, what are those aversive attributes -- excuse me, which of the attributes that are present. This could be any element of those flavors: basic taste, aromas, feeling factors, and mouthfeels, and measuring their intensity over -- measure their intensity on a calibrated scale.

Again, these are using highly trained individuals that measure the intensity -- the intensity of what there -- what is present there, calibrating much like you would calibrate a PH meter. This is how the food industry does it, this is how the

drug industry does it, in terms of defining what is present in a formulation.

And importantly, you're measuring these in the aftertaste as well. Not just -- not just initially. Many drug product linger for a long period of time.

You might ask where that scale came from and why doesn't this go to infinity. The answer is you reach receptor plateau. This is really the fundamental graph of the field of psychophysics, with the perceived intensity on the Y axis and the concentration of stimuli on the X axis that establish a sigmoidal scale.

Importantly, as you go up -- you march up through the sigmoidal scale, you reach a couple of thresholds. What is known as a detection threshold. This is the point at which the signal to noise ratio breaks through. You can tell that something is present there, but you cannot understand exactly what is being -- what is being perceived. This is, in the field of acoustics, this is you hear a noise down the

hall but you can't understand what's being said.

You then reach a recognition threshold. This is the point where that noise becomes a whisper and actually language is translated. And then you receive receptor saturation at the high end.

So what does that data look like? So this is an example of a flavor profile of an OTC product. This is really how the analytical sensory and -- sensory scientist breaks down what is present in a formulation. And just like a -- just like at HPLC we break down the -- what is present in the -- chemically.

So what is present here is basic taste sweet, then sour, then those positive aromatics, and then you get some negative aromatics and bitterness thrown into there. And of course you're measuring these in the aftertaste. So this very much is a quantitative measurement of what -- of what a product tastes like.

As I mentioned, a sensory scientist looks at a -- the -- the output of a flavor profile

just like an analytical chemist would like at the output of a -- this is illustrative, by the way. But they're looking at the individual peaks as the individual attributes that are present. The peak height or AUC as the intensity of those attributes, and how long those persist in the aftertaste is the illusion time. So again, just a very quantitative method of figuring out what the flavor of these products is.

So some examples of OTC actives at their clinical strength and how they persist in the aftertaste. Some go out very -- for a long period of time. And again, something like ibuprofen, basic tastes bitterness, yes, it's bitter but that's not its primary challenge. If I showed you the burning graph, that would go out much higher and look -- and look very different.

So tying this back to that threshold, recognition threshold, the point that a whisper down the hall becomes language, you're really trying to make a palatable drug product, not necessarily by

taking that -- taking the aversives down to zero. You're trying to take them to the point where a consumer is not saying that this is bitter and starting to have an aversive reaction to it. So again, that recognition threshold, not the detection threshold.

So to a formulator of what can they do, what are the tools that they have in their -- in their pocket to deal with those aversive attributes, really there's five that -- that a formulator uses, either OTC or NCE. The addition of a flavor system -- the addition of a flavor system. Number 2 is the addition of some type of encapsulation. This is either putting a barrier coating, a Wuster coating, or an -- resin, a film coat.

The third way you can deal with this is the use of alternative API forms. That could be in the form of a new -- a new salt moiety or a prodrug. Again, long development timelines associated with those.

Chemical complexation. This is -- this

is adhering the active drug product to a smaller -- to another molecule that will prevent the perception. Typically, beta cyclodextrin is used very classically. And then five is signal interruption. Really the early interruption of that perception of bitterness at the -- at the tongue or in the -- in the signal cascade responsible there. But really in the field of OTCs, number 1 and number 2 are the ones that are used most typically.

So that first one, flavor systems. What -- you know, really, to a sensory scientist, what is the flavor doing? You are -- we are really leveraging the concept of mixture suppression or taste-taste interaction.

So what we have here, I don't know what that second box is, but what we have here is the -- the -- on this first graph, this is some research out of the University of Oregon. This first bar is the intensity of quinine sulfate.

So what mixture suppression tells us is that when you add basic taste to other basic taste,

you're bringing down the perception of the target basic taste, the high one. You are blending that away. So if you start with the bitterness of quinine sulfate and then add sucrose, you get a reduction. If you add sucrose and sodium chloride, you get a further reduction. If you add sucrose, sodium chloride, and citric acid you get even a further reduction, even though these concentrations are there. That's what a formulator is doing from -- from -- with a flavor system.

And this holds true for if you have an adverse -- an extremely aversive salty product, like a colonoscopy prep, you would also add other basic tastes to drive down the target basic taste. Sweet, very rarely have, in my career, encountered a sweet drug. But if it was too sweet, you could add those other complimentary basic tastes to bring down the perception of sweetness. Same with sourness.

Again, taste-taste interaction. You've probably come across this when you were in the kitchen. This -- this concept at a very fundamental

level, by making lemonade. Right? So you take a very sour lemon juice and how do you make that less sour? That's your aversive attribute. Well, you're adding in, in the case of lemonade, putting in sucrose. Now is that changing the PH or is that changing the titratable acidity? Not particularly. But you're really leveraging that sensory -- sensory practice of mixture suppression.

So different excipients, of course, can be used to get there. Frequently sugar -- frequently sweeteners are part of that -- part of that mix. Though, this would be the same for acidulants and taste modifiers like salt.

So there are many different sweeteners that can be used. You may have seen a table such as this that talks about the relative sweetness of those different sweeteners, looking at all tied to the relative sweetness of sucrose, which is a 1, to things that are thousands of times as sweet.

The -- in the case of sucrose, for most concentrations you have a fairly linear response,

whereby you dump in more sugar and it gets more sweet. But this -- the numbers that you see on the table really are an over-simplification for things that have non-linear responses. Most high-intensity sweeteners have a non-linear response.

Something like sodium saccharin here, it's rated here at 300 times as sweet. That's mostly that this -- at these low concentrations, because you get that plateau so early on in the -- in the concentration. And in fact, something like sodium saccharin or most high-intensity sweeteners have, at strong concentrations, some bitterness that is brought into that.

If you are at a cafe or if you see a pink packet in the -- in the atrium outside, if you dump an entire packet of sugar into your mouth, it's going to be fairly pleasant. If you dump an entire pink packet, the sodium saccharin, it's going to be revolting because you have stopped being sweet and you are adding bitterness to that -- to your mouth.

So not only intensity is important, but

how long those persist in the aftertaste. Just that different sweeteners have different -- different times that they persist in the aftertaste. Sucrose is the gold standard and -- and has a strong onset and then fades very quickly, but other ones have different -- different time delays.

But starting to get to some data. What you're going to be seeing in the next couple of slides is the -- is the -- an overview of 97 branded pediatric products. These represent the pediatric cold, cough, and flu, and analgesic sections because we're really interested in what does a drug taste like. And this -- this is solution suspensions, drops, chewable tablets.

So what we have here are those -- again, the scale go from zero to three and how strongly each of these are in the -- how strongly these are in a histogram form. So what does your average -- what is the mode of pediatric drugs look like?

So we have most pediatric drugs have a

sweetness that are slightly below a moderate intensity. A bitterness that ranges between a moderate and -- a slight and a moderate. And aromatics, these are the positive aromatics, the cherry, grape, and orange, that go right at a mode right around moderate intensity.

So you have to think about, okay, so that's what your average or the world of drugs products taste like. What is the flavor of those?

What does a candy taste like? The world of confections, you can distill it in most broad senses down to about three different areas: hard candies or boiled sweets; chewable candies, gels; and chocolate-based confections. So what do each of those taste like?

From the hard candy side, you're left with -- you're left with the products that are extremely sweet, have no bitter, and have aromatics that are also particularly strong.

In the chewable candies, they have, again, very sweet, no bitterness. Maybe a little bit

less intensity in aromatic.

Now chocolate confections are probably the most disparate here. They have -- that they're fairly moderate -- they're more moderate in terms of sweetness. They do have some bitterness, and the aromatics are slightly reduced compared to the other -- those other sweet types.

So it's -- so if you're really comparing what a drug tastes like to what a candy tastes like, drugs are lower in sweet, or at least OTC drugs are lower in sweet as on the whole, they are higher in bitter on the whole, and they are lower in aromatic on a whole. So there are differences in the perception of flavor of -- between drugs and candies.

And that goes -- and that doesn't just stop at those intensities. That also is talking about -- I didn't even talk about sourness. Sourness, some -- some confections, Warheads, Sour Patch Kids, they're extremely sour almost to the point of novelty seeking. That is very different between drugs and candies.

Texture, texture, texture. I can't really harp on this enough. The fact that almost all confection products have a novel texture. The hard candy. If you were trying to replicate Everlasting Gobstoppers, have that sticking around in the oral cavity as long as possible. Chewable candies really play into the novelty affect of chewing a product, having it break down, squeeze between your molars, and reposition it. There's novelty in there.

The most -- the most impressive is probably chocolate in chocolate-based confections. You don't really think about the -- the -- you know, why do people talk about chocolate? They love to talk about the aroma. Really, it's the texture. Cocoa butter has a very sharp melting point, right at the point of body temperature. So you place a hard candy -- a hard chocolate confection in your mouth, it becomes a liquid, and then you have release, immediate release, of the aromatics and the -- the aromatics and sweetness that is there.

We love chocolate so much you can take

out the flavor and it becomes an enjoyable product. If you've ever had white chocolate, you have taken that cocoa flavor out of that -- out of that product, and it becomes a palatable formulation. You're eating plant lard. But we love that -- we love that texture change so much, that that's what we perceive.

Obviously, major differences in branding. Major differences in the packaging and the color intensity. Extremely vibrant colors. Again, you're just not seeing most of these areas in the field of OTCs you are in every commercial candy product.

Color has a big -- color has an effect on the perceived flavor intensity. So as you increase the color, that flavor intensity goes up, a does overall acceptability. So most confectionary companies are very interested in pumping up the color because of those -- because of those responses.

And of course these -- these questions that I brought up are not going to be limited to the more simple route of oral liquids, like in most OTCs.

If -- when these actives are placed into gummies, films, chocolates, you're going to have the same aversive attributes and the same need to cover those up.

So really, the question is have nonprescription drugs been developed specifically for palatability or to promote liking [ph]? And you can see that there's a difference in the -- their overall perception. So they're not exactly the same. But of course, it's a -- it's a balance on -- between rejection and overdose that we're going to be talking a lot about today.

Thank you. I just wanted to mention this. Fran [ph], from my panel, asked what should we call this formulation, this -- this -- call my talk. And she talked about, well, trick-or-treat has two meanings. I said, "What do you mean?" She said, "Well, there's treat as in to cure and treat as in a delicious substance." So I thought that was very interesting that treat has both those definitions that are appropriate here. All right, thank you very much.

DR. MCCLARY: Thank you again, David, for your presentation.

Our next speaker is Dr. Xiaoling Li, professor of pharmaceutics from the Thomas J. Long School of Pharmacy at the University of the Pacific in California. Dr. Li's presentation is titled, "3D Printing Technologies for Oral Drug Delivery."

DR. LI: Well, first of all, I would like to thank Brandon and Kevin for inviting me to give this presentation on the topic. I'm very passionate about it and have been devoting quite a few time onto it in the past eight years.

Yeah, since some of the content I'm going to talk about related to a company I founded eight years ago, so I -- I'm obligate to have this disclosure.

To put everyone on the same page, let me start with what is a 3D printing? 3D printing actually is a digitized process using the computer and design to create an object on the computer. Whatever shape or, you know, geometric structure you would like

to have, you will be able to create on a computer.

And then we'll convert that structure into an instruction. We'll be able to execute by the computer to instruct the printer to print the object layer by layer. So basically the -- several mechanisms you can use to build this layer-by-layer structure.

The first one is using -- that will involve the chemical reaction, and then we can start to play with the temperature. You increase the temperature, make the material flowable, and then you'd cool it down and solidify. And you can also have a bunch of small particle and then put an adhesive, bind this small particle together, in a layer-by-layer manner. The last one is going to be the extrusion injecting, and again, that would be used to build each layer.

In the biomedical science area, this 3D printing has been used in various areas, as I show in the slides. But today what we'd really like to talk about is the pharmaceutical products. How we use the

3D printing technology in this area. Specifically, I would like to talk about three aspect. The first one is the personalized dosing, the second one is the drug delivery, the third one is the manufacturing. How we can utilize the 3D printing technology to -- to achieve all these three aspect.

To give you a little bit background about the player and status [ph] of the 3D printing technology in pharmaceutical area, I put up a little bit history. To start with is when the 3D printing technology is invented. It's in 80s by Japanese. And then in the pharmaceutical area, the first appearance is in 1996 by Dr. Cima in MIT. He used this powder-binding technology to create solid dosage form.

And a year later, a company form, license these technology, called Therapix [ph]. And unfortunately, Therapix convert their interest into the -- device. But some of the -- pharmaceutical scientists spinoff company called Aprecia. The -- Aprecia later launched a first product in 2015. So we do have one 3D printed pharmaceutical product in

market right now, approved by FDA.

The personalized dosing representative would be FRX [ph], which is a UK company. The company I'm involved with, it's in -- in extrusion-based 3D printing technology. So we're powder binding, extrusion-based, and various technology use for personalized dosing.

From ASTM point of view, the 3D printing technology could be divided into seven category, and among these seven categories, those big checkmark would be the primary application of 3D printing matters in -- in the pharmaceutical area.

In the literature, one of the matter which is extrusion-based, it's called FDM, has been extensively published and studied because it is a very simple machine and easy to acquire. Low cost.

So we have using this type of technology to create RO [ph] tablets, captures, even, you know, in printable device and dermal patch like microneedle.

Let's first take a look of the

individual dosing or personalized dosing. This is a very good concept, but regulatory wise I think still it's not really mature. Okay? FabRX in UK is the company really tried to push this concept moving forward. The -- the implication in the cycle [ph], I think it's quite obvious. We can see a lot of benefit out of it; right?

They have used this printer created by themselves. It's basically FDM based. Okay? What FDM does is you make the material into a filament and then let the filament going through a printing nozzle and it melt and then build layer by layer. And they -- they have, you know, different type of the color or shape and try to test acceptance of the patient and its advocacy. Basically, they want to see how 3D printing technology will influence patient's acceptance.

And this is the first product approved by FDA. It's called Spirtam. And the technology is powder-binding technology. Basically what you do is you have the powder making into one layer, and then

selectively spray the adhesive to bind some of particle together. You put another layer, you bind them, so slowly you will build a tablet.

The characteristics of this product is it can instantly disintegrate. It's very fast. Utilizing the 3D printing technology, really what we can do or what we can achieve, is try to build a structure. Both internal and external structure.

So external structure is more appearance-oriented, but internal structure will offer a lot of advantage to have different mechanism of the release or mode.

So that lead to the technology I'm involved. It's called Melt-Extrusion Deposition 3D printing technology. In this technology, what we do, is try to continuously convert a powder material into molten or flowable material and then build the object layer by layer.

So this printer can be precisely deliver very small amount of the molten material and then build an object layer by layer. So compared to

the FDM, we don't really need to make the filament [ph]. And that would take a lot of restriction out of what kind of material we can use. What kind of API we can incorporate.

So if we multiple printer coordinate with each other, in this case let's say we have three different printer head and -- and handling three different type of material, we can build a very complicated structure. For example, we can -- with the coating or with the seal on the top, and they can serve different function. We can build different shares [ph] and we can build different compartment. And these different compartment can have a different API or same API.

So essentially what we did, from the software and hardware point of view, create a technology or instrumentation specifically for pharmaceutical application. And the material we're using, it's all pharmaceutical grade excipient GRAS material.

So we took about 206 GRAS material and

pharmaceutical -- and build a database. So we have a good understanding about its melting points, softening point, maximum daily allowable amount, and melting point, et cetera. Okay? Flowability.

And coupled with that, we also have the structure design for different dosage form. So let me quickly talk about this structure. Why do we want to talk about it and why it's so interesting for us.

Let me just take one example. Let's say I have a three-compartment tablet, which you will be able to control the components in there or API in there individually. And we can -- we can put three different excipient in there, and then you can add one immediate release, one zero-order release, and one delayed release.

And I keep using this example in my talks saying we can have the first compartment containing Zolpidem. And it's going to knock you out right away; right? It's a fast onset. And -- but it will not last too long because the half lives are very low.

So we can put the second compartment containing Melatonin to maintain your sleep over the night. But in the morning you really need to wake up, so we can put a third compartment using caffeine so you can wake up and have a normal day. Right?

So those will be what a multiple compartment can do for different API. But later I will give you another example to talk about with the same API we can also do a lot of things with individual compartment.

We can use different material. So here are the examples. We -- we can use a sugar-base material to build, again, different -- different compartment. And here's one example where the structures look like this. So it's one of our kind of like -- tablet. Okay? We have two compartments. One compartment we have apple flavor; the other one we have orange flavor. But they come at a different time.

So when people take this tablet in the mouth, first you're going to sense apple flavor, and

then later you're going to have orange flavor in two or three minutes' span. So how do we do it? Well, we put them into different compartment and let them release at a different time.

So essentially what we did is have this cover of the compartment using different material, and we can precisely deposit that material onto the surface and make it as a seal.

Well, in addition to, you know, multiple compartment, what else can we do? There are many pharmacokinetics profile, we have different clinical application. Right? So you may need to have something which has a zero-order release, and we can just have this tablet built with a shelf [ph] and cost [ph] structure because the layer by layer.

So you can build each layer with the same surface area. So each later is going to come up the same amount; right? But we can change the surface area of each layer. For example, in this case you're going to have small surface area to start with and then gradually become bigger, so your amount of

release as the time is going to increase.

And you can have it slow, fast, and then slow down later, and you can have low dose at the very beginning and a very quick release rate. By the way, if you look at the slope, you can see the release rate. And then you can slow down, and then toward the end probably absorption is not that great. You won't have more coming out; right? As we're coming down our GI tract.

So here you can see the theoretical model is one of the line and experimental -- is another line. And all these mathematically described. So you can see, you know, the prediction. It's very good; right?

In 70s, in mid-70s, for those in the pharmaceutical area, probably most of you have heard Iguchi's [ph] name. This is younger Iguchi, [ph] Bill Iguchi, [ph], and his -- one of his student, Bob Libbey. He later become VP of Squibb, but now is like BMS. Right? The S is Squibb.

They proposed a geometric shape which

would be able to control the drug release and offer a zero-order release rate. But for decades, no one can really achieve this because it has a very special geometric shape. With the 3D printing technology, using the 3D printing technology, we'll be able to build tablet with that compartment, with that specific geometric shape.

When we further get into this model and then build to study each parameter, the opening, the angle, the depth, and see how they will influence the release rate. So we have a wide spectrum of the release -- we can cover. Just use one of the geometric shape.

We can build other structures. For example, we can build structure with a delayed release mechanism. We have coat and shell, and by varying the thickness of the seal, we will be able to determine when this drug will start to release. And you can even have zero-order release built into the coat so you can have delay and kinetics release control.

And we can have multiple component in

there. In this case, we have two API. One is in orange color, and then the other one is in this teal color. So the teal color is going to be zero-order release, and the orange color is going to be multiple post-time [ph] release.

So eventually you're going to see the teal color is a straight line; right? Zero-order release. But the orange color you have first pulse nothing happen, and then a second pulse. And in the dark study you can see, you know, definitely you're going to have constant release, PK profile, and post-time [ph] PK profile.

By utilizing the multiple component, we can easily modulate the PK. And in this case, in this application case, we call Lego approach. So what we do is we have one compartment using the immediate release formulation and the other compartment use extended release formulation.

And first we would put these two formulation into the dark study to get -- animal or human, and get a parent PK. So we harvest those PK

parameter, and then we would do a -- do a simulation by varying the ratio of these two formulation. We'll be able to get the target PK profile. So with that you can see, you know, based on the simulation, we can achieve the target just in one formulation at hand.

So with all the example I just give you, I think I probably already give you impression these -- the 3D printing technology could help us to make the formulation development much more predictable. So we develop a plate formulation [ph] by design. Versus the current practice, most of the formulations are formulation by trial. Okay? Trial and error, you finally get to that formulation. So with this approach, it will be able to make a lot of things much more predictable.

So this 3D printing formulation by design approach will start from the target PK formulation and then convert it to in vitro release profile and then -- I think my time is almost up. I need to speed up. And then we pick the model and form the material, the database will pick the material to

build this structure, and then using the 3D printing instrumentation to achieve the structure and then have the in vitro and in vivo release.

So instrumentation wise, we build two type of instrumentation. One is for R&D or early clinical development, which it's a smaller machine, and then we have 3D printing system which is for full-scale commercial production.

So the production line, basically divided into three zones. The first one is material preparation zone, printing zone, and then packaging zone. So whole thing would be automatic. So I don't know if I can get this one going. Okay, yeah.

So this is small machine, and you can print one tablet at a time or print four tablet at a time. So as you can see, start from modeling and then handling different material using different printer head. And in this case, it's a four tablet printing at each -- at the same time.

And each layer we print is going to go through a laser scanner to measure the height. And

this is the production line. And material will come from the preparation zone. This is a material preparation. And then using this robotic mobile vehicle, put it into the printing zone. And after you get into the printing zone, it's a 32 printer head printing at the same time for each material. So you have multiple stations to handle different material.

And after printing, those robotic arm is going to take it and then put into the mobile robot and then put into the packaging zone. So the whole production line, it's automatic; okay? And each tablet will given a QR code. We can trace all the printing condition for each tablet. Okay?

So in a way, what we did, is we tried to use this by design concept to change the pharmaceutical industry common practice. So starting from the drug delivery, structure by design formula, in the product development area we have formulation by design. And in the manufacturing it's quality by design. Right? So the whole thing is by design approach. And what we'd like to achieve or what we

are achieving is a digital product development and digital manufacturing.

So with that, I think I will try to associate what I've talked with the candy-like. With a very limited knowledge about what a candy-like product would be, I give some feature or characteristics for the candy-like. And I may not be right because I think a lot of expert are here and too early in the day. I think I'm going to be learning a lot.

So limited knowledge, I think, you know, temptation is one of the factor. And then if we create the pressure on that. And if the use of this product will have some dependency or not, and the use of control will be another one of -- another important factor.

For example, with addict; right? It's a lollipop of -- it is a candy, it looks like candy, it tastes like candy. But I'm not so sure we should classify it as a candy-like drug, because it's highly controlled. It's not freely accessible for the user.

So with that, if you look at the left-hand side, you're going to see some of the feature we can use to give these product, the candy-like product, with all these features. Which, you know, may be very difficult to achieve, or may not be able to achieve in the past, and using 3D printing technology we should be able to achieve it now.

Well, I think I want to skip this time because this is ADHD and we have developed something to reduce the stimulants used to reduce the dependence. That's one of example.

To summarize, I think I would give this slide to cover some of the application of the 3D printing technology for pharmaceuticals. And usually I would say, you know, your imagination is the limit. A lot of things we can do using the 3D printing technology, and we just start. And it's a very exciting area. I hope, you know, a lot of people will look into it.

And although the example I'm using today, many of them is prescription drug, but I'm

pretty sure the technology can be easily trickle into the OTC or monograph drug. So with that, I would like to thank my team. Now it's about 140 people. One-third of them is engineer. And also would like to thank -- organization and on right-hand side you see the company received TCT healthcare award. TCT is a 3D printing community. The annual award, it's considered Oscar in 3D printing. So we are very proud we received that award.

So thank you. I think I'm going over my time.

DR. MCCLARY: Thanks again, Dr. Li.

So that brings us to our first panel. So in addition to our previous speakers, Dr. Natalia Davydova and Dr. Li, who will be serving as panelists, I am also happy to introduce Mr. Jeff Worthington, president and founder of Senopsys. Additionally, I'd like to introduce Dr. Swapan De, senior chemist with the Office of Pharmaceutical Quality here at FDA.

Our first panel session on formulation considerations for solid oral candy-like dosage forms

will conclude at 10:30 a.m. And just as a reminder, if time permits, we'll try to take questions from the online Q&A chat. In addition to that, we have a microphone set up at the center of the aisle for our in-person audience. So at that time, again, if time permits, we'll invite you up to the microphone to ask your questions.

But with that said, it's also my pleasure to introduce our moderator for this session, Dr. Danae Christodoulou, branch chief of the Office of Pharmaceutical Quality here at FDA.

DR. CHRISTODOULOU: Good morning. The first question we have for our speakers is regarding your definition of a candy-like dosage form. So from your professional perspective, how would you define a candy-like drug product, and what characteristics contribute to this definition? And we can start with Dr. Davydova.

DR. DAVYDOVA: As I have mentioned in my presentation, that we have definition for gummy product which is candy-like. And it's available in

General Chapter 1151. And partially a definition I already presented.

And yeah, I can -- actually, I have this general chapter and I can just briefly read what it's -- you know, how USP define -- define gummy products.

So it's under -- this definition came on the gel dosage form. And these consider, like, chewable gels. Again, I mean, it's only like chewable gels. It's much more of the candy-like product. This actually -- it's actually chewable gels are used to deliver drug substances and dietary supplements via the oral route.

In addition to the drug substances or dietary supplement, chewable gel can consist of all or some of the following components: gelatin agents, sugar, water, sweeteners, and flavoring agent. The sweeteners and flavoring agent are intended to enhance patient acceptance and mask the taste of the delivered labeled drug substances or dietary supplement.

Chewable gels maintain their molded

shape, are elastic, and yield to mastication. They are intended to be chewed before swallowing. Chewable gels are also known as gummy in the confectionary and dietary supplements industry, but that term is not used in official article title.

Also we have definition for preparation of this finished dosage form. Chewable gels are formulated with one or more gelatin agent such as gelatin or starch, sugar such as sucrose, fructose, or corn syrup [ph], flavoring agent, sweeteners, colorants, and water. The ingredient are blended and heated to form a -- solution that is poured into mold. A corn starch mold. After cooling, the individual units are separated from the mold.

This is what we have in USP, and this is nothing more I can --

DR. CHRISTODOULOU: Thank you.

DR. DAVYDOVA: And this came after a lengthy discussion with our -- with FDA, including liaison which participated in our dosage form expert committee, nomenclature expert committee, and dietary

supplements manufacturers. So this definition is acceptable by dietary supplements manufacturers for gummies.

DR. CHRISTODOULOU: Thank you very much.

And just continuing with the formulation, I'd like to just pose the same question to Mr. Worthington, if you can add anything from your perspective in what constitutes maybe a candy-like dosage form.

MR. WORTHINGTON: My pleasure. First of all, thank you, FDA, for inviting me today, and M-CERSI for organizing the meeting and facilitating travel.

Candies are very complex. There's thousands of them. Our children will be coming home with them tomorrow night. And as my colleague, David, indicated they differ in all kinds of dimensions.

We approach the development in terms of what is necessary to make a product palatable. We don't set out to say how do we create a candy. We set

out to say how do we create a palatable drug product.

And so to do that, as my colleague, David, presented, unlike most dietary supplements, drug products tend to be extraordinarily bitter or have other aversive taste. The taste-masking challenge is orders of magnitude greater than most dietary supplements. Of course there'll be the random exception to that statement.

So as such, we follow the approach which is really used in the drug industry that FDA would look at for a new drug application for an investigational drug, in that you need to propose every ingredient in the drug product, as well as its usage level in terms of what is its functionality.

So from a palatability standpoint we say, okay, which ingredients are necessary to reduce the aversive bitterness or mouth irritation or whatever it happens to be, and only look to include those excipients that have a measurable impact in the reduction.

And as my colleague described, it's

taste-taste interaction. So you add sweet to reduce bitterness. By doing that, you're reducing the perceived sweetness. So you come to the point where you have reduced the amount of bitterness to the greatest extent possible, adding more -- sweetener has no positive benefit, so it's -- it's really a propose and justify from building the formulation from the ground up.

Same goes for the flavoring aromatics. The cherry, orange, and grape are -- typically you add them to get to the point of patient recognition. You're not trying to create more flavor, as in terms of the aroma, than is really necessary unless you have an aroma-masking challenge.

And then texture, it's the wild wild west of textures. That's what makes candy so -- so wonderful. From our standpoint, we typically view texture as do you need it to deliver a sustained release, as in through -- you know, through chewing as an example, or by building viscosity to suspend the active. So our view is we create a drug, not a candy,

nothing more.

DR. CHRISTODOULOU: Thank you.

And, Dr. Li, you touched upon shape and the stability of the shape and how that is formed and what happens after chewing. Can you also tell us, from your perspective, what do you think a candy-like dosage form could be defined as?

DR. LI: From dosage form point of view, I think immediately probably we think about lozenge, you know, like a pastille. But I would like to think if we want to define something as candy-like, there's also a psychological factor.

DR. CHRISTODOULOU: Psychological factors, yeah.

DR. LI: If a patient or user, not necessarily patient, really want to come back to have more; okay? So I think that's part of the feature of a candy. You know, the kids get a candy, they get sweetness, they like to have more. So that should be another factor to be considered.

Although, you know, the topic probably

would be more in -- in the area of the OTC or monograph, but some of the prescription drug probably have abuse tendency, could be in that category, too.

So that bring to another issue, is the control, accessibility. So if we have, you know, the external chip or the taste, it's one factor. And the other extreme probably would be the accessibility. And in between, probably, would be the psychological factor.

DR. CHRISTODOULOU: Thank you.

DR. LI: Of course, the dosage form could be able to contribute to all these factors.

DR. CHRISTODOULOU: Yes. Dr. Swapan De, would you like to comment?

DR. SWAPAN DE: Yeah, may I ask you some question? I think this is very interesting, this 3D technology. Because the drug is forming layer by layer; right? So is that excipient -- excipient solution and active solutions. Do the excipient solution, is they are definition separate or each excipient is -- is going in there?

DR. LI: Yeah, we can -- depends on the design. We can have a layer of excipient, a layer of -- of the API-containing formulation, and we can also just have the homogenous one. So it really depends on the release mode, on what would be our target profile.

For example, you want to have a mini pause. Then we can just create what you just described. You know, it's a very small interval and one layer, and then just very short period of delay, another layer. And we can also just have all layers.

DR. SWAPAN DE: My next question is since this is a -- we are talking about candy, do you see any issues if you use sugar or that type of excipient in this --

DR. LI: No. Actually, the sugar is one big category we're using, especially for oral cavity dosage form. Like a menthol, sucrose, mannitol, you know, all those polymers [ph], we study them and understand how fast they will dissolve and what is the softening point, melting point.

So we have a good study about this material, and it really depends on the application. And if you want to have an application with a relatively slow dissolution, it would be similar to the hard candy. Right?

So if we want to have something dissolve much faster, probably we'll make a more porous structure than --

DR. MCCLARY: I'm sorry. Just to quickly interrupt. We're having some trouble with our online participants hearing. So if you could speak closer to the mic, that would be great. Thank you.

DR. LI: Okay, thank you. So it really depend on the structure, and that is the advantage of using 3D printing. For example, if we want to -- using the sugar-based product, if we want to make an oral disintegrate product, we can have hard candy -- which will hold the structure, and inside you can have thin threads. So it would be just like a cotton candy. So when you put into the mouth, that cotton candy is going to melt instantly.

DR. SWAPAN DE: So you think that chewable gels or gummy-like product can be created by this technology?

DR. LI: Yeah. But just from the manufacturing point of view, if it's a gummy I probably would go for molding instead of 3D printing, because it doesn't have a lot of structure requirement. Yeah.

DR. SWAPAN DE: Yes.

DR. CHRISTODOULOU: Thank you. So moving into the second question. Can a candy-like dosage form be made such that it's very distinct from candy? For example, there are regulations about debossing, embossing, imprinting, and is this possible to be achieved on the candy-like dosage forms just as we would have it in a capsule or a tablet?

So what would be some distinction factors for a candy-like dosage form with -- with a candy? How can we distinguish these two, if possible, to be on the market? Go ahead, please.

DR. DAVYDOVA: Yeah, just again, I

mean, I just would like to share just what situation with the dietary supplements. If you take, for example, very popular gummy bear for children, so we have actually you can distinguish them on the -- in the store, because they have separate packaging. So it's in bottle, dietary supplements, and candy -- candy have different packaging.

And also the label. The dietary supplements and candy. However -- and they are located in different places in the store. However, when you come home, it's can be stay in the safe shelf, for example, for children. But if you take them out from container, they are not -- not different at all.

And here's the problem that possible overage, if the children have access to the dietary supplements. Because if they came from school, they are hungry, they just take candy and say, okay, I will take two dietary supplements, okay, then two, and then two, and then it's possible overages.

From actually possibility of the

printing, of course, I mean, what we saw on the market, you cannot maybe use exactly that technology of the printing, but some -- some printing on the chewable gels is possible.

Because we saw very advanced, for example, chewable gels which contain, for example, different portraits on the -- on the surface. Which I can conclude that some sort of printing with notification actually for drug is -- it's exist, actually. They can hold and be visible, based on the dietary supplements, what is available on the market.

DR. CHRISTODOULOU: Thank you. So we have some possible imprinting on these chewable gels.

DR. DAVYDOVA: I believe so, based on what is -- what you saw on the market.

DR. CHRISTODOULOU: Thank you.

Mr. Worthington?

MR. WORTHINGTON: Yes. I'd kind of like to take a little bit of a different tact. You know, hear a lot about gummies so far today and probably more so. My viewpoint is it's a technology

looking for a solution.

What is it that gummies would deliver for a drug active? Are they providing something that a gum, you know, a medicated gum wouldn't? That a solution wouldn't? Or a -- you know, is it -- is there an effective release from the chew characteristics that's unique and different from an orally disintegrating tablet, from a chewable tablet?

I think there's lots of things that I can point to of a -- of a gummy that I would rather not see in a drug product. I don't think the shapes should be consistent. Things like rings and worms, cartoon characters, et cetera, and a lot of the iconography that goes along with gummies and a lot of other dietary supplements.

There's a reason that dietary supplements have a different regulatory framework than drugs do, and I think we should recognize and appreciate and adhere to those -- to those boundaries.

So you know what a candy is when you look at it. It may be very hard to define, but I

would advise or just recommend that we kind of continue to -- we're trying to deliver a drug active in a safe and efficacious manner, and some of these forms are a means of delivery, not a means of delight. Thank you.

DR. CHRISTODOULOU: Thank you. So you're suggesting that some boundaries, if we set some boundaries in shapes --

MR. WORTHINGTON: Absolutely. I would not allow, as I indicated, shapes. I would eliminate lentil shapes. So lentil looks like most candies. Probably not supposed to mention names, but they look like M&Ms, Reese's, et cetera. So I would not allow that shape.

Given -- I would not allow, you know, characters and anything -- you know, stars, diamonds. That's not the purpose of a drug product. I would not have drug products in bags, et cetera.

So I think there's -- there's clear ways for us to define what the boundaries are, even if we can't actually define what a candy is. I think we

might be better served defining what a candy is not.

DR. CHRISTODOULOU: Thank you.

And, Dr. Li, did you want to comment?

DR. LI: Yeah, I think I agree with what Jeffrey say. It's really -- there are two steps. The first step is we need to define what is candy-like drug or what belong to the candy-like drug. And then we can, probably from regulatory point of view, you will be able to give some definition and then some of the shapes, those attractive factor, may not be used for the drug.

DR. CHRISTODOULOU: And is the 3D printing technology amenable to some shapes that may not be confused with candy?

DR. LI: Definitely, definitely. From technology-wise, I don't think that's an issue. The 3D printing technology is a big advantage. It's not mold related. It's -- if you can imagine it, you can draw it, you will be able to make it. So any shape, as long as you define or you can draw it, you can even take a picture and then convert it, digitalize, and

then using the conversation, making into the machine to print that shape. You just imagine a draw. There's no barrier in that.

DR. CHRISTODOULOU: There's no barrier. Okay.

Swapan De, do you have any comments?

DR. SWAPEN DE: Since this is a manufacturing ideas, I think it would be probably very beneficial all those things that I explained, but how about just the look of a drug product? It may be candy. Chewable gels, gummies, even hard lozenges. Based on my experience, I think manufacturing of this type of dosage form is challenging. The reason it is done in many different ways, either by molding or by direct compression.

But the point is, when you directly compressing this gummy-like powder, then the dosage form can come up in between hard lozenges and chewable gel. So how do you control this type of dosage form?

And then -- then applying to the -- to the pediatric and -- persons, having the palatability

and test, I think one of the things can come to my mind that is it possible to make the shape and color in such a way that it doesn't look like candy, but the taste will be like that.

And something more direct. I know this is challenging, but this is the things probably we need to think about.

DR. CHRISTODOULOU: Great. So we can just --

MR. WORTHINGTON: Can I --

DR. CHRISTODOULOU: Yes.

MR. WORTHINGTON: Can I add an item on?

DR. CHRISTODOULOU: You have a follow-up comment?

MR. WORTHINGTON: Yes.

DR. CHRISTODOULOU: Please go ahead.

MR. WORTHINGTON: You know, in terms of color, for most in the prescription drug product because of color regulations internationally, it's extraordinarily complex. The tendency is to avoid the use of colors. The opposite is true for candies. You

can't make them more intensely colored. I would advocate no colors for OTCs.

DR. CHRISTODOULOU: That's actually a very good comment, because there are some -- there is a CFR regulation about the colors that can be used in drugs. And colorants are different than other excipients. So we can take that into consideration as well.

And this actually brings us to manufacturing challenges for candy-like dosage forms. And we talked a lot about the sugar content. Excipients such as a mixture of glycerin/gelatin may affect the bioavailable of drug products. Could you comment on some technical challenges on the manufacturing of the dosage forms and just give us your own perspective?

DR. DAVYDOVA: Again, I can talk only from what you can see on dietary supplements, and you can see the stability issue. And the manufacturers put a lot of overages in order to keep -- sort of in order to keep reasonable shelf-life. You know?

Because they try to put at least two, three years. And in -- from logistic point of view, two years may be not quite suitable, because it can be -- stay on the shelf completely a short time.

So the manufacturer tried to go with, like, three years shelf-life. On expiration date, I meant, from manufacturer to the -- to the end of shelf-life. So -- and, yeah, it's -- ingredients, because of particularly I talking about chewable gels, that because of high moisture and recipe [ph] it's just not many ingredients is there.

For this reason, I mean, the main ingredients in chewable gels are protected. They use coating -- protected coatings in order to stabilize the ingredient. But this then it's another problem that because it's -- some coatings are like a rock and they cannot release dietary ingredient at all.

Again, different from the -- from the drugs. Dietary supplements do not have any clinical study. So we cannot have any -- profile in order to see. For this reason we just recommend dissolution as

a must quality control test, in order to -- at least to show that ingredient can be released even you use, you know, stabilizer and -- to be available for potential absorption.

So this is two -- two problem. I mean, it's stabilization which can affect release in dietary ingredient or maybe drug ingredient, and overage. Because in drug, you have to keep 100 percent of the -- from only the product, 100 percent of ingredient and dietary compound. So, I mean, it's can be challenges maybe because it's difficult to -- to formulate 100 percent without overages, due to stability issue.

Maybe this dosage form, it's can be only suitable for certain -- certain drugs.

DR. CHRISTODOULOU: For certain drugs.

DR. DAVYDOVA: Yeah, I mean, it's maybe even very limited.

DR. CHRISTODOULOU: Thank you.

Yes, please.

MR. WORTHINGTON: Yeah, manufacturing

is way outside my wheelhouse, but I would just build up on one thing that was just mentioned. In terms of the flavorings, this is the aromatics, the grape, orange, et cetera. Those are typically complex mixtures of aroma chemicals, and they're the more labile ones. So they decrease upon storage, stability. So typically you put more in initially so that you have some flavor left at the end of the expiration.

DR. CHRISTODOULOU: Shelf-life.

MR. WORTHINGTON: And there's generally no analytical methods. You can't use accelerated testing because they're labile molecules and they degrade.

DR. CHRISTODOULOU: That's very interesting.

Any comments from you, Dr. Li?

DR. LI: Probably I should just focus on the topic I talk about, 3D printing technology. I don't think it would be a very challenging issue using the 3D printing technology I'm talking about. That's

solvent-free, so usually you're not going to have that high content of water.

And also if you use pressure technology, it's powder binding base. So it start from dry powder. The water content also very low. And that platform will be able to create a system where instantly disintegrate in the mouth.

So the material or the formulation we're using probably is quite different from traditional gummy-type of the formulation. The gummy-type of formulation, probably one of the important ingredient is gelatin; right?

So gelatin, if you have the water content below ten percent, it become quite hard. The hard gelatin capsule, probably it's a six to ten percent of the water content, and that's already, you know, kind of hard. And if you want to have a chewy feeling then, you know, water content got to increase.

In my opinion, probably that water content is really the problem of causing the stability issue, yeah.

DR. CHRISTODOULOU: Okay. So I think that -- shall I go to the one more question for the panel? It's actually a very quick question. Using the differences in methodologies involved in assessing palatability in children versus adults. Maybe do you have any comments?

MR. WORTHINGTON: Sure, I'd be happy to address that. I think my colleague, David, included that in his presentation. Really there were the two types of analysis methods. Analytical, which is to measure the product, and what are called affective tests, which are -- measures human response to the product. And it's things like liking and preference. For children you can't use them to develop the product, because they can't give you the language to describe what's wrong with it.

So really both from a development perspective, it doesn't matter whether it's adult or children. If you were using affective methods such as "I like it" or "yuck" or "yum" or smiley face, et cetera, it's not helpful for development. But

typically for children, you have to use liking with, you know, a facial recognition scale. With adults you have a bit more flexibility.

But we all have the same perception. It's just that we don't have the language skills to be able to describe it.

DR. CHRISTODOULOU: Thank you. So do we have time for one question from the audience in the room? Is there any -- yes. Can you come to the mic, please?

MR. MACKAY: Duffy MacKay, CHPA. I noticed that -- does dissolution include mastication when you're trying to figure out if a candy-like form is absorbed? I noticed the USP monograph does not.

DR. DAVYDOVA: So actually, all our monograph, as I mentioned, recommend dissolution testing for quality control. Because we found that -- first of all, what we found that many ingredient, for example, cannot release from chewable gels like similar -- using the same dissolution procedure as for tablets or capsules for the same

ingredient.

We have to develop specific dissolution procedure for the same ingredient in chewable gels because they -- especially, for example, vitamin D. The formulation, the chewable gel formulated that vitamin D practically cannot release -- so you need to develop specific factors, specific condition in order to suspend or dissolve the vitamin D dissolution media.

And because of stabilization, a lot of ingredient just use stabilizing coating. So -- and again, for this reason, we analyzed a lot of product from the market in order to show that they are not consistent. Some -- some chewable gel can release ingredient practically the same like assay -- our specification is 75 percent from label claim.

So -- but usually when we analyze, we analyze assay procedure which is usually, for example, 150 percent for vitamin A or 160 percent.

But what we found, that only a couple product, chewable gel product, can -- using

dissolution procedure, develop dissolution procedure, can release almost assay value. But majority case, they barely can meet 75 percent of label claim, which is -- shows they can release only 50 percent from assay value.

So there is some -- yeah, we found that it is -- dissolution test is extremely important for chewable gels, especially without clinical study. You know, we would like to be sure, at least USP, because our monograph is just voluntarily because we have plenty products on the market who just don't use our monographs.

So we just would like to be sure that at least the -- the manufacturers who would like to meet USP requirements, I mean, it's -- can be -- I mean, can be relatively -- I mean, I could say high quality, but quite -- have decent quality in order to be sure that their product not only tasty but also can release and provide some benefits for consumer, in agreement with the label claim.

DR. CHRISTODOULOU: Thank you.

And we have a very interesting question for Dr. Li from the audience online. So from -- are there any special packaging considerations for 3D printed drugs? And also it was mentioned that the tablets get individual QR codes. How would a consumer track which tablet was taken if there was an adverse event, since consumers don't always take the product in a systematic way, and could report one tablet as the cause when it may not be the case?

There is another part to this question, but maybe you can take the first part.

DR. LI: The -- part. Let me just take the last part I remember to start with. It's about the QR code and how would patient track it. And of course, you know, from backend we harvest a lot of data, including the manufacturing data and QC data.

By the way, this production line I show you, there are seven PAT point. So those are all taking the data at real time.

But from the patient side, it really depends on what information they needed. Probably

the -- some of the QC data or manufacturing date. But I'm not so sure the purpose of the question is. If there's adverse effect --

DR. CHRISTODOULOU: You no longer have the QR code because you consumed the product; right?

DR. LI: It's on the packaging.

DR. CHRISTODOULOU: It's on the package.

DR. LI: Yeah, so you can go back to track that one is you don't threw it into the garbage can.

DR. CHRISTODOULOU: Okay. And are there any special packaging considerations?

DR. LI: Currently, we're using the aluminum blister packaging. Yeah. I believe Aprecia is using the blister packaging too, yeah. They have a new technology, you know, have a pre-formed cup and you can have a powder in there while the printing, and it's a very neat technology too.

DR. CHRISTODOULOU: And how could the OTC industry utilize this more individualized tracking

to enhance the adverse event reporting? I think you already touched upon this question.

DR. LI: So just same thing, yeah.

DR. CHRISTODOULOU: From the packaging, yeah.

DR. LI: Right. There are probably some concern about the cost of manufacturing, which I probably will add into it. The current manufacturing cost is at a -- if you take API out of the picture, the excipient and the manufacturing cost is a cent to tenth of cent. So it's not like a lot of people think, you know, creating a 3D printing product is going to be extra expensive. It's not. Yeah.

DR. CHRISTODOULOU: Okay. Can we take one more question or we're out of time?

DR. DAVYDOVA: Could I add?

DR. CHRISTODOULOU: Sure.

DR. DAVYDOVA: Because it was question involved mastication. So yeah, I know that some manufactures, when cannot meet the dissolution requirements, they said okay, it's supposed to be

chewable so we just can cut them and then put -- solution.

So actually in this case, we follow FDA guidance for chewable tablets. So there is no -- any recommendation for -- for cutting or -- in order to -- because we cannot -- the number of biting is not standardized, you know? So it's impossible to standardize any dissolution procedure by using cutting on chewable gel.

So we recommend to dissolution of whole piece. I mean without any cutting, which stimulate the sort of chewing. So thank you.

DR. CHRISTODOULOU: Thank you. I think we're out of time. Back to Brandon.

DR. MCCLARY: Thanks again, Danae, for moderating. So that will take us -- oh, also we need to say thank you to all of our panelists for that informative discussion.

And that takes us to our break, our first break of the day, which will go until 10:40 a.m. So again, just a reminder that there's coffee, tea,

and snacks available at the kiosk right outside of this room in the main hall.

(Off the record.)

DR. MCCLARY: Dr. Meyers will be speaking on the impact of candy-like characteristics on medication adherence in pediatric populations.

DR. MEYERS: Okay. All right, thank you so much, Brandon, and thank you to the FDA for inviting me to come here. Again, my name is Rachel Meyers. I'm a pharmacist by training, specifically a pediatric pharmacist. I'm faculty at Rutgers, but I spend most of my time in my hospital, where I practice in the pediatric ICU and also the general pediatrics floor. So that is my background. I've been in this position for 16 years now.

Just as a quick disclosure, I am a consultant for CNP Pharma and also for Wolters Kluwer.

So today I get to talk about something I'm very passionate about within pharmacy, and that is giving medication to children. I should also mention as my background that I'm also a parent of two

children, so I have lived the life. I know what it is like to have your child spit medicine at you, and yeah, the difficulties that we have with dosage forms.

I also work with our transplant clinic. We do -- we have a very large kidney transplant center at my hospital, and I see all of our pediatric patients on the day they come to be listed on the transplant list. And we go through all of the medications that they're going to need to be able to take.

And my basic summary for them, their homework from me, if they do not know how to swallow a solid dosage form, that is their homework. To figure that out before they get called with a transplant. Because some of the medications that we have for our younger kids, the liquid formulations are just very difficult to take, and transplant patients have to take those medicines every day. And so if they can swallow a solid oral dosage form, their life is going to be so much easier.

So we're going to talk about some of

those alternate dosage forms. We're also going to talk a little bit about toxicity. I know there's some speakers later in today that are going to really focus really into that, so I won't get too much into that.

I want to give just sort of my take on what candy-like might be. My -- as a mother and a -- and a pediatric pharmacist. And talk about some adherence issues and some things that we can do maybe outside of the candy realm.

So as we know, the issue with giving medications to kids is that quote/unquote inability to swallow that solid oral dosage form. And I'm going to sort of bring that into question a little bit, because I think we need to think a little bit out of the box when we think about giving medications to children.

However, this has led to -- this idea that we can't swallow solid oral dosage forms has led to the development of more and more liquid orals. And that's sort of the classic way that manufacturers make medications pediatric-friendly.

Now liquids, though, sometime the

thought is, oh, it's liquid so you can give it to a child. Well, I think as most people in this room have realized who have seen -- had children and given medication to children, that is not always the case. We have a lot of taste issues, as we talked about earlier today.

That is my number 1 complaint. This last month I got complaints from nurses more and more. "Our Prednisolone tastes terrible. They're spitting it all over the place. Can we please change the brand that we're ordering?" And I talked to my purchaser, and she said, "I don't know what they're talking about. It's the same brand. I've been ordering the same brand for five years."

So something must have changed, because the number of complaints I'm getting are rising. So these taste issues are a big problem.

Volume is huge. The volume that some of the medications come in is extraordinary what they think a child can take. In one case, there's a particular steroid on the market, the volume needed to

dose our children would be 50 milliliters and up. And so we're just not going to do that, so we give the IV formulation orally because we found workarounds in pediatric medication. This is what we do. It's part of the tricks of the trade of being a pediatric pharmacist is finding the right workarounds.

Texture was mentioned earlier. Even in liquids texture is a problem. Augmentin is my classic example. It is very grainy and highly objectionable to children, including my own. Smell is also a big problem. We have lots of medications who have very poor smell. Liquids.

So what has happened is we have this development of alternative dosage forms because some of these liquids are still so objectionable.

So just looking around on the market, I was looking for pictures of things and what's out there. Again, most of the candy-like ones are these gummies, but you might even define a chewable tablet as a candy. Right? It depends how we decide to define it.

I was looking, just as a side note, into sugar content of some of these. Now the OTC ones all have the sugar content on them, but I reached out to the manufacturers of Tylenol and asked them what is the sugar content of the tablets, and I was told that that was proprietary information and I was not allowed to know. So I don't know what the sugar content is in that, but that would be good information to have even in this OTC product.

Also remember that there's compounding pharmacies that are out there that are compounding things, and gummies are something that are being offered even in the compounding space.

One that concerns me and one that we have seen cases of is chloral hydrate, which is no longer on the market as a drug, but you can actually buy the powder. Compounding pharmacy can still produce this. But we have seen adverse events from this product. And so just because it's not on the market doesn't mean it's not still out there and coming from these compounding pharmacies. So that is

a concern of mine as a pharmacist.

So the risks that I see with candy-like medicines is, as we've touched on already, the idea of overdose. Again, it being too desirable.

When I was in my training, I went and did a poison prevention talk to a group of elementary school children. And we had, you know, our examples of, you know, what's a poison. You know, we have the Tide Pods, that kind of thing to show them and talk about what's a poison. And we talk about how medicine, while it may not be a poison, it's something that you don't take unless you have a grownup with you and a grownup telling you what to do.

And I remember I was holding this bottle of gummy vitamins, and at the end I asked the kids, "Does anybody have any questions?" And one child raised their hand and I said, "Yes?" He said, "Can I have one?" So it's that idea of that desirability factor that we're not seeing it as a medicine; we're seeing it as a treat.

So I would like to focus -- and my

thoughts on candy-like is that idea of the sugar content. And a lot of these gummies just -- I quickly scanned around and I found they were anywhere from one to three and-a-half grams of sugar per gummy. And some of those products, you know, depending on your age, your dose may be two gummies, so therefore you're going to have double the sugar dose. Which is up to ten percent of that recommended daily allowance for sugar.

And so when we're getting that much sugar from a medicine or a supplement, we have the risk for dental carries, right, and also just added sugar in your diet. And remember that these vitamins and supplements are something that children are generally taking every single day. This is not an antibiotic with a ten-day duration; this is a daily therapy.

And so when that's just part of their regular diet, that's a concern to me as a healthcare practitioner.

And then I know our colleague from the

USP mentioned this, but that ingredient consistency, for me as a pharmacist, I like things to be very exact. It needs to have in it what it says on the label. And I -- I'm not thrilled with the idea of the stability of gummies and their ability to give patients the amount of supplement that we need.

I know we think of vitamins as sometimes not necessary, but we have had patients -- actually, a few in the last couple of years with vitamin deficiencies come in. I've -- we've had a case of scurvy, we've had a couple cases of rickets that have come in. And I practice in New Jersey. Right? This is the suburbs. This is not, you know, a third-world country. But we have cases of these.

We send patients home, and I want to know that the vitamin dose that I'm calculating in helping the pediatricians send the patient home on, I want to know that it's the right amount that that patient is getting.

Because when I have a kid on IV vitamin C for a week and then I'm sending him home on an oral,

I want to make sure it's going to provide the amount that it says on the -- on the label.

So of course our overdose risks, again, touched on a little bit earlier. But the biggest thing we worry about in children is the iron overdose. And of course, you can see that pretty quickly when large volumes of vitamins are consumed at once. Generally, that 16 mgs per kg is considered that toxic dose.

And then of course calcium and overdose also can be quite toxic. Those are kind of the two that I worry about the most.

When I was scanning the literature, I found this interesting case actually out of Philadelphia. This was a 21-month-old child who was chronically overdosed with Little Critters calcium and vitamin D3 gummies.

This was a mother with a -- she had some mental health issues and she was chronically giving multiple vitamins to her child daily, and it was very unclear from the history how long this had

been going on, but for a very long time and the child came in very, very ill.

And so the case report really emphasized that this was obviously medical neglect and a very unique form of it. But this is something that if -- if that medication hadn't tasted that good, maybe she wouldn't have had such an easy time to administer this medication multiple times in a day. But because it is such a desirable and treat-like dosage form, it was able to be given for a long period of time.

So what are the alternatives? We talk about chew tabs. You know, to make a long story short, chewable tabs don't taste that great either. And then of course we talked about liquids already.

Here is my issue that I've encountered and sort of been mystified by just as a parent. My kids are 10 and 12. My 12-year-old has been able to swallow a tablet since she was about seven or eight. And there are no swallowable -- is that a word -- swallowable tablets, multivitamins, on the market for

children. It's either a chewable tablet or a gummy. Or at least I have not been able to find one as a parent. I've searched on Amazon, I've looked in pharmacies.

They're not out there, because there's this idea that if it's a child, a child cannot take an oral solid. And I just want to challenge that, because my daughter complains about it to me. She says, "I don't like the gummies. They're gross. I don't want to chew on this candy in the morning." And the chew tabs she finds disgusting also. So, and if it was a swallowable tablet she would much prefer that.

So what if we simply made solid dosage forms that kids can swallow? Why does it have to be candy-like? For me, again, as a parent and as a pharmacist, I think we have to get away from this idea that all kids can't swallow oral solids.

So can children swallow tablets? This is an idea that in the prescription space has been explored by a lot of companies, and there's a lot more

stuff coming out. There are studies out there showing for the mini tablets, which again have specific definitions and -- they're having their own issues with defining what exactly a mini tablet is versus a granule. But there are studies out there down to two days old, giving these mini tablets to basically newborn infants.

And children as young as four have been shown to swallow tablets that weren't necessarily mini tablets, but up to ten millimeters. They did a study looking at what kids can actually swallow.

So I guess sort of outside the realm of what is a candy-like, my kind of outside of the box question is why do we have to have medicines that are candy-like?

Now of course we live in the United States, it's very consumer-based driven economy, and these are OTCs and a consumer is going to pick what they like. But I think we need to shift the perspective that we have to make medications desirable.

Okay, sorry, I'm not able to advance my slide. There we go. Okay. So how would I define candy-like? In my opinion, it's about the sugar content. To me a gram or greater per dose unit, like an individual gummy, is candy. And that that is too much, both for the dental carry issue but also for dietary reasons.

Again, I want to just wrap up by saying that kids can swallow oral dosage forms. Not 100 percent of kids, but I think we also need to get in the habit of thinking that if a kid can't then maybe we need to train them and make that part of -- part of growing up. That swallowing a tablet is something that you need to learn to do.

I do also want to emphasize that we always encourage our consumers to choose products that have ingredient quantities verified by parties such as USP. That, to me as a pharmacist, is extremely important that we're picking products that are reliable and that have in them what it says on the label.

So again, there's that delicate balance between making medications acceptable and desirable. I really like the idea of limiting that sugar content. And also to touch on, we need child safety packaging, of course. Again, the case report I gave you was about a case of a mother who had a mental illness, so obviously when an adult is helping you with this that's not going to help. But I think child safety packaging, again, needs to be stressed.

And then clear directions about correct dosing. I think it was brought up earlier, too, we also need to say on the labeling the dangers of overdosing, right, and what is the dose limit for a day and why consumers should not consume more than is recommended. And that needs to be more clear, especially when we have dosage forms that are this desirable. Thank you.

DR. MCCLARY: Thank you once again, Dr. Meyers.

So next we'll hear from Dr. Catherine Tuleu, professor in pediatric pharmaceutics at the

University College London School of Pharmacy. Dr. Tuleu is joining us virtually, and her presentation is titled, "International Perspectives: Appropriate Pharmaceutical Design of Oral Medicines in Pediatric and Geriatric Populations."

DR. TULEU: Good morning, and thank you very much for the organizers for my invitation to talk at this workshop on defining candy-like nonprescription drug and to give you international perspective on appropriate pharmaceutical design of oral medicines in pediatric and geriatric population.

My name is Catherine Tuleu. I'm professor in pediatric pharmaceutics at UCL School of Pharmacy, and I have been working in the field of pediatric drugs for 20 years now, which has led me to pave the field of sensory pharmaceutics. I founded EPTRI, the European Pediatric Formulation Initiative, in 2007 -- to the enforcement of the EU pediatric recommendation [ph]. And it is a consortium, working in a very competitive way on pediatric drug formulation.

And I have a vested interested in pharmaceutical sensory evaluation that led me to my company senCeuTics Limited that offers a full spectrum of pre-clinical, clinical, and pediatric formulation services.

So as I'm starting, I just want to give a little map of my talk, and maybe that will act as a disclaimer. So I'm going to touch upon the similarities and differences between pediatric and geriatric-centric drug product design, and we're going to talk about target product profile within the regulatory framework. So within the guidelines or guidance that we've got.

I'm going to talk mainly about prescription drug products because this is what I'm working with. And although obviously I'm international, I'm mainly -- citizen who lives in UK. So my perspective is mainly from England.

And I just want to point out that in Europe we've got a very fragmented market. We've got multiple jurisdiction, multiple languages, as you can

see on the map. We are culturally very diverse, so very diverse consumers, and we've got different prescription habits in between countries, which further complicates the -- the landscape.

And that means as well that although in America you've got one FDA, in Europe many food and many drug administration are often two very separate entities, which again complicates the OTC markets.

Talking of which, I also want to point out that on the top, this is shelves of OTC products in America, and the equivalent in UK, for example, would be that we've got much, much, much less choices in over-the-counter products. And again, I want to highlight that this is -- the topic I was given.

So we're going to talk about patient-centric drug product design, considering the three entities, and we're going to start with the patients. And as my brief stated, we're going to talk about the young and the old.

So developing children medicines is not child's play. And children are defined by the ICH 11

topic as newborn, so zero to 28 days; infants and toddler from 28 day to 23 months; children 2 to 11; and adolescents 12 to 18. It's mainly driven by their developmental age. So how they're going to handle the drug and the excipients. We're going to go back to that.

However, this category 2211 kind of -- consideration around physical and behavioral age, which is driven by tremendous changes in that children population. And that's really what we consider as formulators.

So the various consideration -- so we've got a moving target, and the various consideration for each pediatric subset. The root of administration, the dosage form including the excipients, the dosing, the acceptability of the dosage form, and how it's going to be administered. Is there any food/beverages included and/or devices?

We have a guideline in Europe on pharmaceutical development of medicines for pediatric use, and it's a good resource to get some information

on what to consider when you're developing an -- product. And which would have to include age specificity, the condition of the patient, the duration of the therapy, the dosing regimen, et cetera.

And the areas I want to highlight, specific part on excipients in the formulation and on patient acceptability, and I will talk about that a bit further. And -- because acceptability is in fact a key binding element in the pediatric investigation plan, which are the equivalent of your PSP in America.

And acceptability is defined as the overall ability and willingness of the patient and caregiver to use the medicine or product as intended. So from the moment where they unbox the medicine, they are in contact with the leaflets, then there is the primary packaging, and then there is what they do with this primary packaging until they administer the dose.

So really, you know, this is a very organic way to look at the acceptability from the documentation that comes with the box, but as well the

complexity of the administration -- it. The dosing. The dosing volume, the number of tablets, if the tablets can be broken and -- for administration. But as well, ending up with obviously, you know, what the product itself looks like, its appearance, its palatability, and of course its swallowability.

And I would like to point out there's two guideline. One from the MEA that I've already mentioned, but as well there is a very good WHO guideline development on -- of pediatric medicines. And again, it's a key binding element, so companies have to demonstrate acceptability of their product.

The geriatric population, it's a little bit less simplistic. So the age proposed by the ICH [ph] is early old, 65/74-year-old; middle old, 75/84-year-old; and late old, over 85. However, this often does not reflect the biological age, and there is a further physiological approach that uses the classification of fit, of frail, old adult.

And compared to children, this is very complex because obviously all the adults have

comorbidities. They've got sensory deficits, like issues with swallowing that increases. Cognitive impairments and/or physical frailty. And there is no guidelines. However, the MEA had proposed a geriatric strategy in 2011 that is framed on the same topics that have been discussed for children.

And I borrowed that slide from a very good colleague, Dr. -- who is a professor in my department. And I really like the way to compare the young and the old. So starting from the packaging that on one hand needs to be -- but on the other hand needs to be geriatric-friendly and simple.

In terms of compliance, we know that palatability is a big issue in kids, and dysphagia is more prominent in adults. PK -- in kids considered to be mainly due to body weight, which is not necessarily true for the very young. So up to two years old. And it's complex in older adults because of the comorbidity.

In terms of the carriers, [ph] for the young it's mostly -- caregivers where for the older

adults, the other caregiver might be another older adult. So that can further complicate this aspect.

In terms of adaptation of the dosage form, often for kids we liquidized the formulation, whereas for older adults we try to mitigate the -- and of course we talked about the immaturity and frailty in the population.

Okay, so now if we move onto the other aspect of our product design, it's the drug acceptance. And of course, what is important to consider is the dose. It's -- of the API, but as well the quantity of the API in each dose and the pack size. And in fact, in the guideline, the applicants who are going for -- submission needs to consider the dosing recommendation and duration, but as well accidents or dosing error. Specifically, the risk of tenfold overdosing, accidental ingestion of the full content, linked with patient acceptability.

So it seems that really there is more safeguard around prescription medicines. First you need to abide the five routes. The drug is prescribed

for a specific patient, at a specific, for a specific administration, and for a specific duration. Whereas for OTCs, there are products that can be bought by consumer without a prescription at the pharmacy or another retail outlet, and usually these products are to treat minor ailments.

However, we know from the past as well that there have been withdrawal of, for example for children, many cough and cold medicines for children under two because they were containing -- that could have led through to other safety issues.

So now let's move on, on the drug product. Probably more relevant to the discussion today. And I just want to point out that adherence is quite complex, as you probably all know. And -- but for children, medication and -- medication factors are a major challenge.

So this is the result of an EU study where it was 700 -- sorry, 652 children were asked, "Why do you find some of the medicines difficult to take?" And as you can see, most of them answered the

taste. So palatability is the number 1 issue in children. And as you can see, difficulty in swallowing tablets and capsule comes not too far down, but is certainly probably more prominent in older adults that need to take multiple dosage forms.

Now in terms of palatability, going back to my guideline on pharmaceutical development of medicine for pediatric use, in the palatability section there is a segment, even though it's asking the applicant to really give example of how to improve the palatability of the pediatric preparation, there is a segment that says as well that it must not become too attractive to children, candy-like, as it is known to increase the rate of accidental poisoning.

And so really, it -- it's tricky then to find a definition of candy-like prescription dosage form. Because on one hand we're asked to make the dosage form more desirable, more palatable, easier to handle, easier to dose, but of course for prescription medicine, under the EU regulation and the guideline provided, you really need to have a rationale for your

excipients. So, you know, and it's especially stated in this document that you really need to consider the colors that you're adding, the flavors, and the sweetening agents. So really there is a limit to keep that within a safe -- safe boundaries.

And as well, I think what we've got in Europe is different commercial pressure, especially for prescription drugs. First, there is no advertisement at all. It's a much more fragmented market, as explained before. But in terms of pricing of medicines as well, and it is less governed by private insurances. So that's a really big difference.

So I feel that the big differences between prescription versus nonprescription, potentially candy-like dosage form, is that one is consumer-led whilst the other one is much more patient and prescriber led.

Okay. So we talked a bit about palatability. Now let's talk about swallowability. So again, this graph borrowed from this paper showed

that palatability is more -- good appearance, good palatability, is more prominent for medicinal product for pediatrics, whereas as you can see, swallowability becomes more important for medicine products for the elderly. Also present, obviously, for pediatrics.

And in fact, when you look at some medicines that look like candy, they all have in common that they are made easier to swallow. And I've put this example here of the Fentanyl. People call them Fentanyl lollipop. However, they are just lozenges. So, you know, sucking type of dosage form of -- of Fentanyl, so very strong opioid.

But there is as well some other lozenges such as for ibuprofen, lemon lozenges. And of course another good example is the whole product range of nicotine. So for example, this example here goes from a mouth mist, to a gum, lozenges, nasal spray, or patch, and then later -- and as well, micro tab. So a small tablet that is to be administered sublingually. And the whole government, at least in UK, under different type of medicine.

And it's interesting to see that in kids, in fact, there is a big trend in UK to try to train kids as early as possible to swallow solid dosage form. So -- and in fact, those programs that are implemented in hospitals use sweets to train kids to -- to take solid dosage form as early as possible. So -- tic-tacs, Smarties, and they need to play with that to train themselves to swallow.

And again, interestingly, in 2008, WHO had an initiative called Better Medicines for Children Project, and really what they were advocating is flexible solid dosage form, meaning solid dosage form that behave like a liquid at the point of administration. So solids that do not need to be swallowed whole. So that would cover dispersible tablets or -- tablets or digestible films, or even sprinkle capsules that you can mix with a swallowing aid, such as food, soft food, or beverages.

And as well, the big trend was around pushing -- particulates. So really getting the drug in a number of discreet units. So that covers

granules, pellets, and mini tablets.

And in fact, I've taken that from a big -- landscape on innovative delivery system for pediatric medicines. And as you can see, in terms of the future of kids' medicine, all the -- the new medicine are -- have been inspired by these candy sweets-like dosage form. So film, we've got mouth fresheners, films that are on the market, or even the flying saucer that tend to disappear in the mouth when you take them.

In terms of multi-particulates, the hundreds and thousands are good example of that. And that children are very familiar with and that are easy to swallow.

And as well in terms of mini tablets, we have for years, you know, those very small sweeteners, which is really, you know, people are trying to use now to deliver drugs.

But on that list, I would like to single out 3D printing. In fact, 3D printing, you know, has seen a trend and rapid progress, opening

many opportunities and really bridging the gap towards personalized medicine. And it's, I think, especially interesting in compounding. When we think of products for rare diseases or who do not have pharmaceutical treatment we are using, for example chemicals.

And one paper has been published. It's a Spanish survey on very few children, four, but it's interesting that this printed -- age, weight, and measured the blood levels to treat maple syrup urine disease, a very rare type of disease. And as you can see, the kids could choose their color, their flavor.

And looking at the blood concentration, they showed that the printer gave really very good results compared to the standard of care, which was just putting the -- in a capsule. And in fact, a tighter blood level result.

However, there are other products that are heavily inspired from the confectionary industry. And I did a very quick search and found a few candy-like list -- so you've got this first one is a soft chew. And they're offering to print it in any

shape. They are, you know, containing -- then there was this interesting paper where it was some 3D printed cereals containing ibuprofen and -- and then this one and there is one more paper on using chocolate as a base.

And this one was containing -- and I think to me that's really a reflection -- we're entering a complex ecosystem where we want to make the dosage form more acceptable, if not desirable, but we don't want to jeopardize the safety. And that's a difficult exercise, a balance exercise.

So just to conclude or, you know, conclusive remark is that for sure, you know, therapeutic success goes with better adherence. And of course, I hope I've demonstrated whether it's palatability and swallowability, but if you increase acceptability you're certainly on that way towards better therapeutic outcome.

And, you know, the consideration around sensory pharmaceutics, so how can we play with formulation dosage form design factors and

administration factors to facilitate that is certainly very interesting. But I think we need to keep in mind, and as it's stated in this APPI [ph] poster for the Association of British -- Industry that the message needs to be clear for the user that medicines are not sweets. And it is not that simple.

So I'm really looking forward -- thank you for listening, and I'm really looking forward on all the discussion of today's workshop because I think it's a fascinating topic. Thank you very much. Bye.

DR. MCCLARY: All right, I want to thank Dr. Tuleu once again.

Our next speaker is Dr. Judith Chin, resident program director and professor of the Department of Pediatric Dentistry at Nova Southeastern College of Dental Medicine. The title of Dr. Chin's presentation is, "Use of Sedative Gummy Bears Compared to Oral Syrups in Pediatric Dental Patients." Thank you, Dr. Chin.

DR. CHIN: Good morning, everyone. I am a board-certified pediatric dentist, so I treat the

kids that no one else wants to treat. And I wanted to give this presentation. This is with conjunction of everyone else on my team who's helped over the years.

So disclosure, I have no conflicts of interest to disclose. I do have to say, although I am a board-certified pediatric dentist and I sit on several of the committees for American Academy of Pediatric Dentistry as well as the American Board of Pediatric Dentistry, this presentation isn't a representation of either of those national committees, national organizations.

So a little bit about decay. We've come a long way with improvements over the decades, but there's still quite a bit of work to do. As a pediatric dentist, I have job security. I will always be busy. There is a lot of decay in the U.S., as well as internationally.

It has changed, but with U.S., with the dietary habits of the children and as well as the parenting habits, we still have a lot of decay.

So just a few notes. 50 percent of

kids from ages 12 to 19 have a cavity in at least one of their adult teeth. Many phobias come from our childhood experiences. So if it's a bad experience in a dental office as a child, that traditionally carries on the rest of the life of that individual.

With autism being 1 in 36 people in the United States children, a significant number of my patients are patients who have autism. I do have to say as a pediatric dentist, we don't see the majority of children in the United States; our general practice dentists do.

So we're referred the patients. Traditionally, our best patient referral source is from our general practice dentists, where they feel it's out of their training or scope or ability to treat them in a safe manner.

As a pediatric dentist, I also see -- in the State of Florida, we see up until age 21. And the I'll see special needs adults.

Safety is our number 1 concern. If we can't do it safely, we're not going to do it. We're

just not going to do it. We follow guidelines and recommendations from national organizations. Not just pediatric dentists, but anesthesiologists and pediatricians as well.

We have to really take a lot of things into consideration while we're treating -- when we want to treat a patient. How old is the patient? Are they neurotypical or do they have cognitive concerns that we have to be aware of? A four-year-old patient is much different than a ten-year-old patient or a 16-year-old patient. How are we going to treat them?

Family preferences are significant. The parenting style of that child. We only get them one day, maybe three days a year. They're in the house the rest of the life. We can't undo some parenting behaviors. We can't do that, but we can help modify it while they're in our office.

We will always start with non-pharmacologic procedures. When this patient, when this child needs something, we're always going to go non-pharmacologic. Watching a TV. I'm a horrible

singer, but I sing. I do that in order to distract them from what I'm about ready to do to get them into a better state of health.

But sometimes we have to do more things to make this procedure safe and comfortable for a child so that we don't create that phobic. So that's when we go into pharmacologic options such as laughing gas or nitrous oxide. We can do that, we can do that safely with all national safety measures.

Sometimes, though, if that doesn't work we need to go to the next level. Whether we're doing oral sedation, whether it be moderate sedation, mild sedation, or deep or general sedation.

So for the United States, a lot of people are like, just take my kid to the operating room and get everything done. If they have state insurance, if they have Medicaid, or whatever that brand is in your state, it's traditionally at zero cost to the family. Which is a very nice thing in the United States for kids. After they age out at 18 or 21, nothing is free. Everything costs. So cost can

be a big concern.

But even when it's free, for us to get into an operating room and to see this patient in the safest environment, there's a wait. There's a long wait. So we're telling our three-year-old, four-year-old medically healthy patient, yes, you have a mouth of decay. You have 20 teeth and of your 20 teeth, 18 out of 20 of those teeth have cavities on them. We'll see you next year. We'll see you next year.

And if something happens, you need to go to the emergency room if you develop extraoral swelling or a fever. Until then, the only patients who get moved up on that waiting list are patients who need transplants or patients who have cancer. We assure the families, thank goodness your child doesn't have that, but you will need to wait.

So when it comes to sedating children, there's really two things which have been talked about often. Often this morning and throughout the presentations. They don't like the taste. And it is

difficult to administer on a child. Tablets, they're not as good as tablets. And there's actually been studies showing that if they could take a medication, the outcome for the sedation will be better. If they're willing to take it, the outcome will be better.

So any child who we might sedate, it's because they've failed everything else. We've tried every other game that we can do, and we can't -- we're not there.

So we'll follow national safety sedation standards that are out there, free to see. At our clinic, we -- the two drugs that we traditionally use are Midazolam and Hydroxyzine. Midazolam is incredibly bad tasting. Hydroxyzine is slightly better. But you need a lot more volume for us to make it effective.

I am not a pharmacist, but I will talk a little bit about Midazolam. Why do we use it? Why do we use it? We use it because it's a quick onset. We use it because they actually do have an oral

medication. Midazolam can come in different forms. It can be via IV. Kids don't like IV. It could be inhaled intranasal. They don't like anything wet going up their nose.

So if they're not able to take a medication by pill, which most of our patients can't, we use this. Versed; it has reversal. That's why I love this drug. It has a reversal. So if a patient goes from moderate to deep sedation, we can reverse them in a timely manner so that our procedure still remains safe.

Hydroxyzine. Hydroxyzine, we add that when a procedure is going to be longer. Midazolam doesn't last that long. So just as other presenters, when one drug is going offboard we need another drug on. That's why we will use Hydroxyzine for some of our patients, when we know that the procedure is going to be long.

A kid who fractured their front tooth and they're eight years old and it's their adult tooth and now they need root canal therapy. Root canal

therapy is hard on adults, let alone on a second grader. It's very challenging. So we need enough time so that we can do this safely. There's no reversal to it, and the amount, the volume, that they need to take is significantly higher than it is with Versed.

So after a long day, I was meeting with someone a couple of years ago and we were having an institutional luncheon, kind of a meet-and-greet, and it happened to be a pharmacist across from me. He was like, "How's your day going?" I go, "Not good." I literally had puke on me in the shade of Versed because they had just spit up and I didn't have enough time -- and it was a bad week. The whole week was like that.

And he had said, "Hey, have you ever thought about maybe doing it in a different form?" I'm like, "What forms?" Because I know there are some out there. Fentanyl, the lollipops. That's nice, but it takes a long time to consume the lollipop.

He's like, "Well, what about a gummy

bear?" I'm like, "Gummy bear?" That -- tell me more. So he actually designed -- he said you can get a gummy bear, I can create a gummy bear for you, in Hydroxyzine or Versed. I can do that and it will work. It will work.

I was a sceptic. You've got to prove it to me. He was right. He was right. We had prescriptions made, individual prescriptions for the patients. And after we saw that I'm like, I think we need to evaluate this in depth a little bit more because this might help our patients.

So we actually came up with three aims. Developing these gummy bears, seeing if the kids like them, and seeing if it actually sedates the patient to a level that we need it to be.

So on the picture, you'll see the forms that we used when they were compounded in the local pharmacy, in Inova [ph] Pharmacy. We had independent variables and dependent variables. We love faces. Truly, the hedonic scale, it's been used many times for children. It's also great for stats because it's

1, 2, 3, 4, 5. We can use that. It's a solid number.

The effectiveness. How well did it sedate the patient? Mild, moderate, deep. How long did it sedate the patient? How much time did it take to sedate the patient from going from mild to moderate?

All of that we looked at. We looked at age, we looked at gender. We evaluated. And so this form that you see, it's a completed form on a patient, modeled off of what the American Academy of Pediatric Dentistry has for monitoring sedation. By law, it must be evaluated every five minutes, but we're continuously monitoring. We don't wait every five minutes. We are continuously monitoring these patients as we're doing our dental treatment.

We received IRB approval. We had a total of 80 subjects. The liquid versus gummies. Patients with autism and patients who were neurotypical. We tried to match as much as possible, the procedures that were done to equal out as much as possible. One kid is not getting a root canal while

another kid is just having a simple little filling done. So we tried to match it as much as possible.

The study is still underway. It's still going. But we'll talk data for most of the patients. Most of the study subjects that we had, we're able to get data for them.

So here are the results. We were able to do it. But we really had to take in some cultural society influences. Gelatin, traditionally, is pork-based or beef-based, and we had to make sure in our population that it was halal or that didn't have pork in it, or if it did we had to disclose it. And we do disclose that. It is -- so in our gummy formulation, it was bovine, it was beef-derived. We chose that intentionally.

It lasts 14 days because it's compounded. We use sucralose because as a dentist, I'm not putting sugar in there. I'm a dentist. That's what -- they're in my place for a reason. But also, sucralose is much more concentrated than sugar, as others have said in the past. So we don't have to

use as much to get the effect that we need.

Our flavors, yeah, we taste-tested them without the prescription medication in them. What we thought the kids would use or not. And we had standard dosage sizes for each gummy.

You can see that the gummies were clear. They're clear for a reason. Because we don't want kids saying, "I want the green one. I like the red one. Where's the pink one?" No, it's clear. It's a clear gummy. Isn't it cute? That's what it ended up looking like. It's adorable. With Hydroxyzine, the Hydroxyzine gummy was a little bit less clear than Midazolam gummy.

Our results. Anything in shades of red or pink are happy. They're joyful. So our shades, our patients overall, our study subjects, liked the gummy. They preferred the taste better than the liquids. It was nice to see that. Very nice to see that.

One subject spit the gummy out. I'll talk a little bit about that, because it was an

unexpected surprise. With these patients, it's not unexpected that they're going to spit something out. That's why they're being sedated. They're needy dental treatment. We've tried everything else.

As far as the onset time, the onset time for a moderate sedation was actually quicker than the syrup. So when the original dissolution studies were done for this particular gummy, fully dissolved within 15 minutes. The PH of Midazolam and the PH of Hydroxyzine is very acidic. Yay. Our bodies, our stomach acid, is very acidic so it was dissolved very rapidly into the system, which made it quite effective.

And although it was not statistical significant for the time on that last slide, when you're talking to a four-year-old there is a ginormous difference in time between 16 minutes and 18 minutes. Two minutes is an eternity.

For the sedation levels, the levels were the same. And in fact, it was more consistent with our gummies as moderate sedation. Not too deep,

not too light. Not mold conscious sedation, but moderate conscious sedation. So there was less variability for our gummies when they were used.

We've had no adverse reports for this particular presentation and for this particular study for use of any of the gummies.

So a little bit of discussion. It does seem like our patients like -- and I say "patients" because they're my patients. I love these special kids. They are my special friends. They did like them. They had no idea that it was a drug. That was very intentional.

With the syrups, kids know you're getting a syrup, and we all know it, they sniff it, they swirl it around like a glass of wine. They want to see what it is. A gummy, game on. I haven't had anything to eat or drink for the last eight hours; I'm ready to eat. And this dentist is giving me a gummy. They didn't even do the math that that would never work. They took it as quickly as they can.

And how quickly did they consume a

gummy? Gummies, they -- it was one or two seconds per gummy. It's actually in one of the previous slides I had a lozenge. It's not a lozenge; it's a chewable gel. It is the chewable gel. It used to be classified as a lozenge. They eat it as quickly as they can. It's like a race. They don't let it dissolve and luxuriate throughout their mouth. They eat it as quick as they can.

The one time that we had a patient spit it out, they did not spit out an ear. They did not spit out a paw. They spit out the whole entire gummy. So we knew exactly how much they spit out. That never happens with oral medications when they spit it out, liquid medications. You have to guess how much they spit out.

But because of that, you can never readminister. For pediatric dentistry, we can never readminister. Oh, I think they spit out 4 MLs. Let's put -- no, we just have to roll the dice and see if this patient is going to get sedated so that we can do the work safely. So it was kind of nice that they

spit it out, because I never would have thought that that would happen, but it was a nice thing to see and to consider.

We still have -- when I submitted this presentation in, we had 13 subjects. We have nine subjects left to go. We hope to be done with all of the data gathering by the end of December, and then analysis by February.

Future clinical trials. That's a little bit harder to get everything compounded and picked up by the pharmacy. The parents -- we don't allow the parents to pick it up. We pick it up. We don't want somehow that it magically to disappear. We're in South Florida. It's hot; it's really hot. They melt. Gummies melt, whether it's in a hand or a car or something else.

So we have these individually made, compounded, prescribed for each and every patient, and it works.

Here are my references. And thank you to everyone for participating in this particular

presentation, but also to everyone who helped me with getting this underway.

DR. MCCLARY: Thank you again, Dr. Chin.

So that brings us to our second panel session. This panel discussion will go until 12:25 p.m. So our in-person panelists will be, again, Dr. Rachel Meyers and Dr. Judith Chin. And additionally, Dr. Catherine Tuleu will be serving as our virtual panelist.

So it's also my pleasure to introduce our moderator for this session, Dr. Gilbert Burckart. Dr. Burckart is the associate director for pediatrics in the Office of Clinical Pharmacology here at FDA, so welcome.

And just a quick reminder. So for our panelists, for this session, in session 3, I think we've had some issues with these microphones. I don't think there have been too many issues catching the audio online, but just to make sure everyone in the room can hear, we ask you to please just speak up

closely to the microphone. Thank you.

DR. BURCKART: Great, thank you. Those were three excellent presentations, and I'm now convinced that I want to get all of my dental care from Dr. Chin. Maybe not the gummies, but the dental care.

Okay, well let's get to the real heart of things here, which Dr. Worthington, I think, started, and our three speakers here kind of jumped in on.

And so let's ask the question of what's the place of these candy-like dosage forms in drug therapy? And so beyond the use in supplements, dietary supplements, and our USP colleague this morning kind of indicated there maybe even some problems there in standardizing what's in them.

But beyond the dietary supplements, if we talk about drugs now. I deal with mostly with prescription -- you know, prescription drugs, new drug approvals, NDAs, BLAs in the eyes of clinical pharmacology. But even for OTC products, if you think

about toxic drugs, think about acetaminophen. You know?

So is there a place for putting drugs in these candy-like dosage forms? So yes or no, Dr. Meyers?

DR. MEYERS: I would say only in very -- a very small number of circumstances. I guess the toxicity concerns are a big concern to me, and I think it's a very fine line that we're walking.

And again, I think Tylenol is a good example. You need the child to be able to take it, but it can't be so good that it becomes desirable. So I think that's a very fine line.

I think in general, when I talk to formulators in the drug industry, particularly about prescription products, when they talk about taste masking, there seems to be this -- they would rather there be no taste; right? Because even when we give things a taste, if it's a -- if it's something you need a child to be able to take, not everybody has the same -- likes the same flavors. Right?

Like, I've had kids bring in -- they don't like our Tylenol, so they bring in their brand from home. So if you can get away from taste at all and just make it something that it just has to take, I think that works better in general. That would be my opinion. I just worry about toxicity and overdose.

DR. BURCKART: So that was a no. Okay.

Dr. Tuleu, let's go to you. I really liked that slide about the future dosage forms, because those are the things I see when you talk about dispersible tablets and -- we needn't perhaps talk a little bit more about mini tablets, but you had a lot of dosage forms up there that are kind of on the horizon for pediatric patients or patients who have difficulty swallowing.

But I didn't see candy-like dosage forms on there. So what is your vote? Should drugs be in these candy-like dosage forms?

DR. TULEU: If I had to give one answer, it would be no. Or like Rachel, in very limited number of drugs. It's true that phrase

candy-like, but they are very much inspired by candy. If you think of dispersible films or tablets that melt in the mouth, you know, it's to overcome this -- to increase the acceptability of it.

So I think what the -- to really overcome the -- incentivize the kids or the elderly person in terms of the willingness to take it and including ability to take it, if we're just talking about the sensory aspect of the dosage form.

But I think it's dangerous if it's outside of a less regulation environment. And so for example, I can see how the medicine gummies works. I mean, within the context of a dental practice where, you know, it's a one-off and it's given by the prescriber.

However, the same thing at home. I would be extremely concerned about putting that in the home. Or you connect with packaging, warnings, storage, and however we know -- we've got the same issue in UK with the -- that kids love it.

And so, I mean, it's taking a huge risk

when you've got an active that is, you know, as a therapeutics window, a safety and therapeutic window that is not absorbed with other products.

DR. BURCKART: Okay. So we have two no's, Dr. Chin. Did you invest in this company? No. That's making these gummies? No.

DR. CHIN: No.

DR. BURCKART: Okay, okay. You get to jump in here. I was speaking primarily about commercial products, but please.

DR. CHIN: So no disclosures. Big pharma has patents on every form of delivery that you could ever envision for a type of medication.

I would like to say cautiously yes, yes. If it is better for the patient, if we can make sure that they -- I work with the transplant team as well. If we can take that medication and take it on a consistent basis, that would be good.

And I would flip the scenario just a little bit. In the United States, just say no to drugs, just say no to pills. For kids, to say, "I

want you to start taking these pills" and take them very easily and take them very young, I'm not sure that's also what we would want to advocate for, due to such high misuse of prescription medication.

So there has to be a balance, but I would say yes. I would take a gummy any day for my practice versus the oral medication.

DR. BURCKART: Okay, well, let's talk about the scenario you gave us. Because in the Office of Clinical Pharmacology, dose is job 1. And you are individualizing the doses of those gummies for your patients; right?

DR. CHIN: Correct.

DR. BURCKART: So if you were making them in a different situation, in other words if you just had whatever gummy, you know, you had to standardize the dose or maybe they had to take three gummies, does that defeat your scenario?

DR. CHIN: So I wouldn't say it defeats our scenario. So for my particular study, there were different weights, different ages. So some of the

study subjects had to take two gummies. Some had to take five. Some had to take one of one and one of the other.

Any medication has to be dose-driven. So whether it's in the gummy form or liquid form, any medication has to be dose-driven. So I don't think that banishes the option of using something that would be candy-like.

DR. BURCKART: How about other options for sedation? Because this brought back to mind a study I did at Le Bonheur Children's Hospital in Memphis in 1978. Computerized tomography was a new thing, but the kids had to be very, very still, right? While you did computerized tomography.

So we did rectal Thiopental. So I have a publication in 1978 on rectal Thiopental. Why aren't you using rectal Thiopental?

DR. CHIN: Great question. Not in my purview. But, you know, there are medications that can be inhaled, can be rectally given. There's so many different options. I think it's a tool in the

toolbox. It's one of our tools. Not the only tool. But one very legitimate tool that could be used for delivering safe healthcare in the U.S.

DR. BURCKART: Okay, well, that -- Rachel, go ahead.

DR. MEYERS: Yeah. So I know Dr. Chin mentioned intranasal briefly, that kids don't generally like it, but it is a dosage form -- and this is what I tell my students. This is the up and coming dosage form for us in pediatrics.

Especially in our epilepsy population, where we were doing rectal Diazepam for many, many years, but now we have a couple of different brands of intranasal benzos out there. And they are extraordinarily popular.

Because if you are eight years old and you have a seizure in your classroom, where do you want to get your benzo from the school nurse? And generally they're unconscious, of course, at that point, or a lot of times they are. So that's been very popular.

And the other is in our emergency room. We give benzos, we give Fentanyl, we give Ketamine, we give Dexmedetomidine intranasal pretty routinely. And also, I practice at the burn unit for the State of New Jersey, and we use intranasal there as well for procedural pain. So intranasal is big.

Oh, and the other example I would give is for Glucagon for our patients with diabetes. In the past there's a pretty unstable dosage form. You had to mix it and then give it, you know, sub-q, which isn't the greatest, and now we have an intranasal form. So compared to a sub-q dosage form, that's a lot better for kids.

DR. CHIN: If I may follow up on that. So for dentistry and medicine, once we go intranasal it's considered an IV administration, a parental [ph] administration. And every state has laws specifically regarding that. And that would be considered more of a deep sedation.

So for the State of Florida, I won't even be allowed to do that. I would have to have an

IV sedation permit. I would have -- must have treated many patients, have many more hours in the hospital during my training. I did six weeks of training, and that's the current regimen, for six weeks of training. For IV you have to have six months of training.

I do see patients in the emergency room, and that's where we use, when we're wonderfully supported by our emergency room physicians and our respiratory therapists. That's when we actually will use intranasal Versed. But not really an option for almost every pediatric dentist. Maybe oral surgeons. They are regulated. Almost all of them have that training and expertise to do parental [ph] administration.

DR. BURCKART: Okay. How about dispersible tablets? You know, I think there's some limits in terms of what's available versus dispersible tablets. But using a dispersible tablet even in a young child is, you know, immediately dispersible. And maybe Dr. Li wants to comment on -- you know, because he talked about it immediate dissolves. And

so you put it in the child's mouth; it's immediately dispersible. I'm not sure if it tastes good. Have you tasted any of your preparations, Dr. Li?

DR. LI: Well, you can make it taste good.

DR. BURCKART: You can make it taste good. Oh, okay. See that? Whatever you want. He's ready. Okay. But there certainly are other things. And you mentioned mini tablets. I do worry about mini tablets. I guess they're used in Europe more.

Dr. Tuleu, are you familiar with the use of mini tablets in pediatrics?

DR. TULEU: Yes, yeah, because there's lots of work around safety and tolerability of those small dosage form. The added advantage, I mean, whether -- you know, because we talk about mini tablets -- you know, it's just another process, manufacturing way, but it's the same principle. They're full solids, and in -- so, you know, it's in a liquid in that way.

However, it requires a device, and that

adds further complication. You know, lots of people have been doing research on device, adjust the dose -- with liquid or you play with the packaging to have different strengths.

So I mean, it's probably the least candy-like. I mean, if we're going back to the candy world. Because, I mean, it's supposedly easier to swallow because it's smaller, but you bring another -- you know, then there is kind of like an alien mouthfeel issue. A bit like you would have, you know, with -- but you can make it taste neutral because you can coat them.

So you kind of, you know, answer one challenge, but then you kind of open another one. And I don't think it's very -- it's the most candy-like dosage form. But again, it really depends on your indication. It depends, you know, of the need for fine tuning in dosing. It depends on so many things.

But certainly, you know, a consideration for some projects. You know, the development projects.

DR. BURCKART: Thank you. I'm on the organizing committee for a workshop, an FDA PQRI, Product Quality Research Institute workshop that's going to be held at the end of February on pediatric formulations. And there are several of the people from industry on there. Particularly the ones from Europe are very intent on switching over to mini tablets.

And I understand that from a stability standpoint and dosage flexibility standpoint. You know, that make sense. So that looks like an up and coming way to approach this particular problem, although we are worried about aspiration; right?

DR. MEYERS: I guess at first glance, I would be worried about aspiration. But again, there are studies out there already showing -- not showing any risk of choking. Now again, these were controlled studies, so what would happen in real life we have to see. But yeah, there isn't enough, I think, clinical experience in the United States with them yet to determine, but we'll see.

DR. BURCKART: And mini tablets, by the way, are not listed on the official dosage forms. Maybe our OPQ colleague wants to comment. But I don't think there is -- it's a pellet; is that right? Maybe it's a pellet. But yeah, it's not official yet.

Okay, well, let's talk about sugar, because sugar was mentioned. But, you know, when I think about the amount of sugar kids get in everything else, does it really matter that there's sugar in these dosage forms if they're taking their vitamins with gummies? From a dental standpoint?

DR. CHI: So from a dental standpoint, if their source of sugar is a gummy, if the gummy had sugar in it, honestly, I don't have a problem with it as long as it's consumed breakfast/lunch/dinner. Because when it's being consumed, masticated, our salivary glands are going, so the mouth is cleaning everything. It gets cleared.

Two gummies a day will not cause a cavity, whether it has five milligrams of sugar in it or 15 milligrams of sugar. It's the constant source

of sugar throughout the rest of the day, the duration, the frequency. I don't have a problem with gummies having sugar. In our gummies we use sucralose. It was a sugar-free sweetener, just so that we could try our best to make it as less of a cariogenic environment as possible.

DR. BURCKART: Oh, sugar-free. What did you use?

DR. CHI: Sucralose.

DR. BURCKART: Sucralose, okay. How about Sorbitol? We just did kind of an analysis of products that have Sorbitol because there's some very well-documented problems with children and the amount of Sorbitol they get.

So for new products, bioequivalence is tested in adults. It's not tested in children for ethical reasons. And so we've had experience with one particular product in which the levels in children, although it was bioequivalent when tested in adults, when we gave that product to children the levels of this anti-HIV drug were actually much lower than

expected. And so we actually had to adjust the product labeling.

But we're looking at the amount of Sorbitol per dose, and that includes generic products. We're working with some colleagues in the Office of Generic Drugs because generic drugs, remember, don't have to have the same -- although they have to have bioequivalence, they don't have to have the same excipients, you know, because that's proprietary.

So generic products can have lots of Sorbitol in them, and perhaps the original product did not. And so we're setting limits on Sorbitol and I don't know about the other --

DR. CHI: So we did consider pretty much all the sugar alcohols. Erythritol, Sorbitol, Xylitol. You name the "tol," we kind of looked at it. Common knowledge for any of the sugar alcohols, it can have an effect of diarrhea. And that's the last thing I want in my office for a patient who's undergoing a dental procedure for a long period of time.

And again, it depends on how much of

the sugar alcohol may be consumed and how that might affect each individual patient. So that's why we really tried to stay away from any of the sugar alcohol sweeteners. Specifically for that reason.

DR. BURCKART: Okay, thank you.

DR. TULEU: If I may?

DR. BURCKART: Yes.

DR. TULEU: Use issues will decrease because you give more in volume and you're probably more likely to be exposed to -- in solid dosage form, where in generally, you know, the amount you're ingesting is lower.

DR. BURCKART: Yes, good point. Thank you. Okay, so I wanted to mention about dissolution, because dissolution of these products was mentioned by our USP colleague, I believe.

There was actually, if you go back and look at the -- we had a workshop that was sponsored by FDA, and it was over Shady Grove on October the 12th. And it came out of the Office of Generic Drugs. But we had a very nice full-day workshop on modeling --

well, it was on drug absorption in children and modeling drug absorption. But dissolution is a critical part of that.

And so dissolution testing, when you're thinking about pediatric populations, has to be very specific for the pediatric population of interest. And so I just wanted to mention that.

Okay, let's talk about adherence. And, Dr. Meyers, do you want to talk about whether you think these dosage forms, candy-like dosage forms, would actually be positive for pediatric adherence? I assume we're talking about a long-term therapy; right?

DR. MEYERS: Yeah, I guess that would be my first question, because I think a little different in your situation where you need them to take it and they have to take it right now in a one-off procedure.

But when we're talking about a medication that needs to be taken daily, of course adherence is very important. But again, I think that we need to get away from the idea that it has to taste

delicious for the patient to take it. I have had patients in the hospital where -- one in particular I can remember, where the mother said, "No, I can't take him home," this was her 15-year-old who was sitting playing on an Xbox, "because he can't take oral medicine. He's going to need to stay in the hospital to take his IV antibiotic for pneumonia." To complete the ten days of therapy.

So I think we need to -- you know, there's issues. Again, we talk about parenting styles. So we have those kinds of issues. But we need to get away from the idea that we need to make it taste absolutely delicious for a kid to take it. It needs to just be acceptable.

And again, I think that solid oral dosage forms are a great way to go with that and try and teach more children how to accept those oral solid dosage forms, because you get away from taste completely.

DR. BURCKART: Dr. Tuleu, do you want to mention -- because you talked about training kids

to take solid dosage forms.

DR. TULEU: Yeah, I mean, that's what Rachel talked about. It's a big thing in England where -- because it's been shown that, you know, for very -- like say they need important medication, for example HIV medication that has a tendency to be extremely -- you know, you can train the kids very early on to -- even to quite a large solid dosage form, that capsule.

And I mean, there is a push. There is an economical push that way because those dosage form are cheaper than liquids. And if they exist as a solid dosage form, you know, why not training the kids to do it if they can do it safely.

I believe as well that it's early habit forming for possibly adults later on that we have to take dosage form, because we do have -- we have a lot of adults that are struggling to swallow solids. So I guess, you know, if you kind of start early on, that would be a very longer positive outcome, I guess.

So yeah, we've got those resources that

can be used -- but they don't leave any, necessarily -- professional, you know, if resources are available for the ward, [ph] I guess, to train the kids to transition to solid. If there is -- of the medicine.

DR. BURCKART: Yes, thank you. And I'll read one comment we got online. It says, "As a clinician and problematic drug use specialist, I would like to know why it should be preferable for kids not knowing what they're taking is a medication. We have responsibility to educate children to differentiate between a medication and something that is not."

So that would fall into that same category of, you know, if the kid's going to be on medication long term, then we have to really educate them, train them, and maybe that doesn't mean covering up something and giving them something that's really good to take.

DR. MEYERS: I would absolutely agree with that on both as a pharmacist who counsels patients and also just with my own children. I always

explain to them why they're getting what they're getting.

Of course, then my favorite example is my daughter when she was about six and she was going for her flu shot, and I was telling her about what the flu is and how terrible it is and this is going to help prevent you from getting it or at least not getting as sick. And when the nurse came in, she just starting screaming that she would rather get the flu.

So, you know, you have to explain it but make sure that they're still going to make a rational choice.

DR. BURCKART: Okay, thank you. My world revolves around pediatric patients, but I want to be openminded here. Are there other patient populations, in fact, that could benefit by these other candy-like dosage forms?

And I have to -- so I have to admit that my wife likes to take her vitamins in the morning as gummies. You know? She likes gummies. So are there other patient populations? Anyone in the

audience or panelist want to mention beyond pediatrics?

DR. TULEU: Companion animals, if you're considering them as patients, and, you know, making treats for cats or dogs.

DR. BURCKART: Okay.

DR. TULEU: Or masking pellets for fish or whatever. You know, that's --

DR. BURCKART: I don't think Brandon invited our Center for Veterinary Medicine, but that could have been one of our centers here.

DR. TULEU: It's a big market.

DR. BURCKART: Yeah, okay. All right, so sounds like --

DR. MEYERS: I just want to mention my father's a veterinarian, so I was taught to give medications to animals from a very young age. And it is a very difficult population, and there's a lot of parallels with pediatrics.

DR. TULEU: Yeah, there is.

DR. BURCKART: Okay.

DR. CHIN: I would like to mention also I think for our special need adult population, that is a definite population that is usually underserved and overlooked. So I appreciate even the question of that.

But I know there are more sugar-free gummy vitamins catered toward the adult population than the pediatric population. Like a lot. Wherein the pediatric population, when it comes to chewable vitamins, I think there's two maybe available on the U.S. market.

So those patients who have insulin-dependent diabetes, regardless of age, I think that's something to be considered.

DR. BURCKART: Okay, good. Thank you. Are there any other questions from the audience?

DR. MEYERS: Can I just add onto that? In terms of sugar content, I was actually thinking about our diabetic patients when I inquired from the company that makes Acetaminophen chewable tablets, how much sugar is in there. And when they told me they

couldn't tell me, all I could think was, well then how are my patients with diabetes going to account for that in their insulin dosing?

So I think we need to make sure it's very clear how much sugar is in the product so that we can account for that. We also have patients on ketogenic diet who need to know this information, and so we need to be open in our labeling.

DR. BURCKART: Okay, we'll get our labeling people working on that. Maybe our lawyers. We have lots of lawyers.

Okay, we're the only thing standing between you and lunch. So thank you very much. I really enjoyed -- oh, we have one more comment. Please come to the microphone.

DR. DAVYDOVA: Yeah, I would like to comment about chewable gels for dentistry. I think this is the trick here, that if I understood correctly, this is compounding with expiration date 14 days.

So this is the trick, when it's only

for ten days. So the possibility that you can formulate very precise dose and it will be stable for ten days, because we don't talking about three years or something like this.

Another case, what did I think? Regarding the dissolution, for example. So we recommended for dietary supplements, because dietary supplement are not regulated and we don't have any clinical data.

So we liked that -- the release during certain amount of time. I mean, using dissolution is quality control. In order to be sure that it's released when it's orally taken for potential absorption.

So in this case, I don't know if we can extrapolate for this case. Again, I mean, we are not dictate USP, like, one drug to another prescription drug. Because here they have clear clinical effect. That they measured the sedation and -- so finally -- so I think it's completely different story compound and chewable gels for easy taking for some medical

needs. From the, for example -- I mean, it's like with -- which is three years expiration date on the shelves. So this is just my comment.

DR. BURCKART: Thank you. That's an important point, actually. Extemporaneous formulations is a big part of what they do in a pediatric hospital. Every pediatric hospital has their extemporaneous formulations recipes, and they're just for short-term lease.

And often, stability is not tested, absorption is not tested. You know, they're problematic. You know, we'd like to minimize the use of those. You know, obviously there is a place, you know, in helping patients, but we'd like to see the use minimized for extemporaneous formulations, which is what this would be.

Yeah, there's a comment in the back?

UNIDENTIFIED SPEAKER 1: Yes, I have one. Well, several comments. But the whole thing about Dr. Chin's formulation is she's a pediatric dentist, gummies made by a registered pharmacist, it's

given one time, and the final conclusion, it works. That's it. It works.

DR. BURCKART: Yes. So your point is there's a place for this in treating patients?

UNIDENTIFIED SPEAKER 1: Yes, because it works.

DR. BURCKART: And we wouldn't deny that. Okay. Well, thank you very much. We're standing between you and lunch, we'll be happy to see you after lunch. Same starting time for session 3, which would be 1:30. So you get a couple extra minutes for lunch. Thank you very much.

DR. CHIN: And I should say as a dentist, I know how to have fun. So there are gummy teeth in the back. Anyone who wants any teeth, they can have it. My kids know on Halloween they can have as much candy as they want, and on November 1st it's gone.

DR. BURCKART: All right, thank you.

(Off the record.)

DR. MCCLARY: All right, everyone. It

is now 1:30, so we'll go ahead and get started with our third and final session. So again, welcome back from lunch.

The title of our third session is, "The Assessment of Accidental Pediatric Exposure to Candy-Like Nonprescription Medications and Potential Overdose Mitigation Strategies.

So to start off our third and final session, I'd first like to introduce Dr. Cyndi Connolly, Rosemarie B Greco Endowed Term Share [ph] for Advocacy and professor of nursing at the University of Pennsylvania School of Nursing.

Dr. Connolly will be presenting, "A Case Study of Unintended Consequences: Children and 'Candy" Aspirin in Twentieth Century America."

DR. CONNOLLY: Thank you so much, and I'm thrilled to be here. I want to thank Brandon, everyone in FDA, for inviting me.

Unlike my colleagues who have presented thus far today who've talked about present and the future, I'm actually going to be talking about the

past.

So I was asked to sort of give some overview of sort of how we tried to make drugs palatable for children in the past. And as Dr. Michele said this morning, that has always been important. From the nineteenth century of soothing syrups that led -- that helped create the FDA, through the elixir sulfanilamide scandal in the 1930s to many other attempts.

And of course it's very laudable for all of us. I don't think anyone likes to take medications that don't taste good. But most of us who are adults have the wherewithal to understand why it is that we're taking those drugs, but kids of course don't.

And while I'm coming to you today as someone who studied history at the doctoral level, I've also been a pediatric nurse for more than four decades. And so I'm one of those people, I think it was Dr. Meyers this morning who was talking about frustrated nurses with trying to get small children to

take Prednisolone that was coming out of their mouth.

I was one of the -- I'm one of those people who would be calling her in frustration. I've probably spent thousands of hours trying to get children to take medication over the course of the past 40 years.

In my book, I go through a series of cases where I talk about the legislative and political and social history of medications for kids throughout the twentieth century, both prescription and nonprescription, and nest it into what we know about the history of children's healthcare, pediatrics, and the changing ideas of childhood and parenting in the United States.

I also -- and taste has always been -- so taste has always been important. This is a slide that is the cover of my book that Eli Lilly generously let me use for the cover of my book. This was from their 1953 juvenile board of medication taste tasters. My guess is that this one did not make -- pass. But it was let the kids decide for themselves what flavor

of medication they want to take.

For my book, I was able to conduct lots of oral histories and travel to archives all around the United States to look at materials to sort of generate this narrative. I was particularly fortunate to have funding from the National -- from the NEH, as well as a generous grant from the Robert Wood Johnson Foundation, as well as a few others.

And I want to particularly thank the FDA History Office here, and especially John Swann, because they helped connect me with materials that I didn't know existed and also really helped me understand them and unpack some of what it was that I was seeing.

So the chapter I'm talking about here today uses children's Aspirin as a case study to look at twentieth century over the drug market for children. It's a rise and fall story that shows some of the unintended consequences and what can happen when you have a weak regulatory apparatus to address them.

So in 1948, pharmaceutical entrepreneur Abe Plough of Plough Pharmaceuticals, successfully reformulated a long off-patent product, Aspirin, into a flavor of small dose chewable tablet, designed to children's palate. And I'm thinking he probably used rudiments of some of the techniques I heard some of you talk about this morning and learned so much from.

So Plough had purchased St. Joseph's Aspirin back in 1921, but no matter what he did he was unable to make it profitable. But just after World War II ended in 1945, he noticed the explosion of births and sent his chemists to work, and the new orange-colored, sweet-flavored St. Joseph's Aspirin debuted in September of 1947.

Plough had hit the zeitgeist [ph] perfectly. You know, there was an explosion of births in the early post-war era. The numbers of baby food companies, for example, increased fivefold in the first five years after the war. The first three years after the war, the numbers of commercial baby food products increased. The numbers of toy companies

quadrupled. The numbers of other mass-produced children's furniture increased.

And so in line with these new products, there was now an antipyretic tablet formulated first for children. While he advertised it in 1947/1948, this is his first big ad campaign. I scoured all kinds of periodicals for -- in the popular press for this era, and this is his first big one.

And so like, of course, all advertisements in this era, it's presenting this very gendered middle class white family, marketed for that population. And it's trying to convince parents that children have specific and unique needs through this sort of, "That gown doesn't fit, honey," or, "Those trousers don't fit," in St. Joseph's ad.

So this was the first one. Unlike most of the other ones in magazines at this time, this is in color. It's much more sophisticated. And it's in every single issue. So he's really spending a fortune on this.

There are also, at the same time, there

are also -- I don't know if these are real testimonials or not that were written to Plough, but there are also letters purported to be from mothers. And then also importantly from physicians endorsing the product as well.

And so within a short period of time, St. Joseph's Candy Aspirin, as it's often called, is the blockbuster number 1 drug used in children, even far outstripping Penicillin, which -- and that was really the heyday of when we were using Penicillin for virtually everything.

Until the 1980s and the warning of Aspirin's link to Reye's Syndrome, it could be found at the bedside of millions of sick children. So here's my, I guess, disclosure for this. I couldn't find a copyright-free picture of a child with Aspirin at his bedside. This is my brother in 1968, and I took that picture.

I was then, I guess, eight years old, and I don't know why I thought that would be such a fun picture to take. So that's the only picture I was

able to find with a child with Aspirin at his bedside. And my brother is actually somewhere on the Zoom because he wanted -- very excited to see himself out in the world in this picture.

So in the wake of success of St. Joseph's, Bayer also rushes to introduce their own pediatric formulation. They're directly advertising it as tastes like your children's favorite candy.

Other companies would follow, but nobody could compete with Plough. By 1955, they owned 81 percent of the market. It's so -- it's bringing such big business to his company, that he's being -- that, you know, he's being promoted as a big business built for little customers.

Plough of -- sorry, shares of his company, his profits are going through the roof throughout the 1950s.

But there's an unintended consequence to this candy Aspirin, which some of you in the room and on the Zoom call probably know about. In a few year, the incidents of Aspirin poisoning in young

children increased dramatically.

Before World War II, only about 20 percent of the annual fatalities from Aspirin in the United States occurred in children under the age of three. If you've ever tasted Aspirin, that's not going to surprise you.

But by 1951, this group accounted for 80 percent of the deaths from Aspirin. In the seven years alone between 1947 and 1954, the American Academy of Pediatrics estimated the incidents of Aspirin poisoning in young children had increased by 500 percent.

The FDA, public health activists, pediatricians, and pharmacists start raising the alarm very quickly, and the new anti-poisoning campaigns for newly-created Poison Control Centers, and Aspirin is prominently featured in those. I think this one is from 1954.

And so the -- and we have all these same groups begin to approach the Aspirin industry alone and together in the early 1950s, with concerns,

with data concerning Aspirin over ingestion in young children, and poisoning. In the book, I go into great detail about a lot of the back and forth. I'm just going to give an overview here.

Despite the mounting evidence, the Aspirin industry, because most likely the huge profits involved, denied that there was any safety problem in children's Aspirin. In a letter to the American Academy of Pediatrics, which was copied to the FDA where I first found it, a Plough executive challenged the data documenting that there was any problem at all, saying that they sold 35 million packages of St. Joseph's Aspirin and they had no documented incidences where there was a problem at all.

With additional prodding in 1955 about the problem from the AMA's powerful counsel on pharmacy and chemistry, the FDA convened a hearing. The agency asked aspirin company attendees to consider a number of recommendations, such as putting -- such as safety packaging and to undertake dosage standardization across companies. The lack of which,

people argued, meant that some parents accidentally overdosed their own children.

The outcome of hearing was only that the industry would consider standardizing dosing and creating warning labels for parents. They rejected out of hand the idea of safety packaging.

Duke University pediatrician Jay Arena, who has strong interest in pediatric poisoning and was an early leader in the field, was so disgusting with the lack of an outcome from the hearing, he picked up his phone and called Abe Plough himself.

After giving him an impassioned description of the course of the candy Aspirin-poisoned child he had just treated, he appealed to Plough's marketing sensibility that it would be a major public relations coup if the company figured out a way to prevent young children from opening the bottle.

Plough agreed. And so even as Plough formally is fighting the idea of regulations, besides the scenes they are working to create that first

safety cap, which when it comes out -- this is the first ad that I can find, and it's being advertised anywhere that's being advertised in Parents, and clearly they're talking about the safety advantage of it. And pretty soon, in fact, Bayer and all the other Aspirin companies followed.

But unfortunately, the incidents of Aspirin poisoning continues to rise. By the 1950s, 20 percent of all poisoning in children comes from children's Aspirin. Again, sales continue to go through the roof. And calls in the early 1960s to do something about the problem go by the wayside, in the wake of Thalidomide and efforts to forge major new FDA law regulating prescription drug safety and efficacy.

By the way, it wasn't just parents who loved the product. It was health professionals as well. You can see that in the venerable Baby and Child Care by Dr. Spock. Because the first -- the early editions do not mention children's Aspirin, but his later 1957 edition below does talk about the importance of children's Aspirin for pain and for

fever in children.

Finally, in 1965, in response to an Aspirin overdose of one of his staffers and in a neighbor, South Dakota Senator George McGovern, introduces his own Aspirin legislation in terms of safety packaging to minimize morbidity and mortality. The Children's Aspirin Amendment of 1965.

The bill is considered along with a number of others related to child safety, under the umbrella of the Child Protection Act of 1966.

The Aspirin industry planned to ignore them. They talk and some of the trade journals say. But they very quickly had to pivot when President Johnson issued a statement. Not just a strong support for the proposed statute, but he calls out the need to limit children's Aspirin available in retail packages.

Industry is absolutely stunned. They call a quick -- they have a quick meeting, and they decide that this is going to be their line in the sand. The if they don't do something, that the regulatory, sort of the -- the regulatory power that

has hampered, they say, their prescription -- that their colleagues who develop prescription drugs, is going to come for them. They call it their rendezvous with destiny.

Debate surrounding the need for more federal oversight and packaging, labeling, and marketing of children's Aspirin become the focus point of five days of riveting testimony and interchange that spanned from June to September of 1966.

I'm going to spend a minute on this because it shows really the high water mark of industry strategy. First, there's the FDA's crusading new commissioner. He's the first to testify. He presents all kinds of data on escalating morbidity and mortality in children from Aspirin.

Got a wealth of evidence. He says every three days in the United States, a child dies from an overdose of children's Aspirin.

Congressmen seem riveted by his testimony and ready to act, until the Aspirin industry, supported by the glass and packaging

manufacturers that would be impacted by any kind of mandatory safety closures changing and packaging changes and sort of the way in which the drug was sold, testified.

And basically, they -- this was their response. That -- I'm distilling it for you here. They continue to say that there's absolutely no problem with Aspirin poisoning. It doesn't happen. But if it does, which they don't concede, it's bad parenting or children who are psychologically disturbed. And that regulation will harm children's interests and American business and is unpatriotic.

So they do such a good job that the Aspirin Amendment is tossed from the Child Protection Act. There's a call for another FDA hearing. It takes a few more years for stakeholders to finally get a poison prevention packaging act that covers medications in 1970.

Aspirin is the first product covered by the new law. And between 1971 and 1976, Aspirin mortality rates in children in the U.S. decline by 50

percent, according to the Public Health Service.

So first of all, why does any of this matter to people who aren't historians? Which I'm assuming is most of all of you.

I want to acknowledge that there aren't any lessons that we can easily map to today's concerns. History doesn't work that way. But it can help us understand unintended consequences and offer clues to avoid making some of the same mistakes.

I don't think anyone intended for this to happen, but the money just got so big it was very difficult to think about how to rein it in, in ways that were not going to hurt business.

I think it's worth remembering for a couple reasons. First of all, it's so quickly forgotten. So I think this is 1977, the American Journal of Public Health publishes an article that talks about the use of safety closures as a model for other areas of accident prevention because it's a model public/private partnership.

And really, a deep dive into the data

shows that that's not the case. That it really took a lot of effort on a lot of different people to bring industry to the table.

It's also worth remembering, because we were asked to think about in preparation for this workshop, some questions. And again, I'm thinking of this in a historical case study. So is there data available to suggest that candy-like features accelerate a trend toward their use.

So absolutely, thinking about sort of children's Aspirin, what we now call low-dose Aspirin in the twentieth century. Before we had that, it was a drug not widely used in children at all. Sponging, medicated baths were what were primarily used for fever. You see that in pediatric, medical, and nursing textbooks until the late 1950s.

After its introduction, Aspirin becomes even more popular than Penicillin, and the most widely used drug in children. So the answer to that is yes. Do adults perceive more palatable medications safer? Yes. The colorful ads and candy advertising leads

pediatricians to begin to suggest in their writing in the 1950s and 1960s that parents believe that these drugs are safer than, say for example, a colorful cleaning product which they know is not -- is poisonous. But these drugs, because they look and are marketed like candy, seem like they might be different.

And was the candy dosage -- if there evidence that it shaped consumer behavior? In this instance, again, absolutely. This product was not profitable. It became really the anchor of a major pharmaceutical firm's product line, and -- and sort of it is etched into baby boomer consciousness.

Actually, you can find, if you go online to YouTube, the character who -- Ken Osmond, who played Eddie Haskell on the TV show Leave it to Beaver, in 2012 did a low-dose Aspirin re-marketed to older baby boomers. Remember the drug that you loved as a child? You can now take it again; it's good for your heart.

And then finally, you know, this is a

little harder one to answer. Right? It was ubiquitous in homes. Was it to blame? I think it was ubiquitous in homes. It certainly tasted good. It was widely advertised, and it's undoubtable appeal to children certainly all contributed to its increase in usage.

So, you know, the challenge is how to reconcile, as we've all talked about today, right, issues surrounding child protection with innovation that benefits them and other people who can't swallow pills. And to know that there's always going to be those unintended consequences for enormously profitable products.

It's naive to expect that industries are going to be able to police and monitor themselves. For decades the FDA, pediatricians, public health and consumer activists, and even Congress were no match for the power of the Aspirin industry.

So I think an important lesson of this case study is it needs to be baked into a sturdy regulatory apparatus so that there will be tools to

address those unintended consequences, even if we don't know what they are right now.

So thank you very much for listening to me take you back to the past.

DR. MCCLARY: Thank you once again, Dr. Connolly.

So for our next presentation, I have the pleasure of introducing two speakers joining us from the CDC, the Centers for Disease Control and Prevention. First we have Captain Jennifer Lind, epidemiologist and captain in the U.S. Public Health Service Commissioned Corps. Captain Lind serves as the partnerships and prevention lead in the medication safety program in the Division of Healthcare Quality Promotion at CDC.

Joining us virtually, we also have Ms. Maribeth Sivilus, lead epidemiologist in CDC's Medication and Safety Program in the Division of Healthcare Quality Promotion. And the title of their talk is, "Preventing Pediatric Medication Overdose: Strategies, Challenges, and Innovations."

DR. LIND: Thank you, Brandon. And you placed us well after Dr. Connolly. I think we are a good follow up, as we talk about pediatric medication safety, the history if it, but then also some of the strategies, challenges, and innovations that we're using to try and address some of the issues.

So in the Medication Safety Program, we work to protect patients and members of the community by leading CDC surveillance activities for national tracking of adverse drugs events, and other drug-related harms and translating data into targeted prevention actions through collaboration and communication.

So how do we do adverse drug event surveillance? Pretty much the old-fashioned way. So for the adverse drug event study, it's called the NEISS-CADES, which stands for National Electronics Injuries Surveillance System - Cooperative Adverse Drug Event Surveillance Project. It's a mouthful, but it is a collaboration between CDC, FDA, and the U.S. Consumer Product Safety Commission.

And for NEISS-CADES, what we do is it's an active population-based surveillance system. Currently, it's based on a national probability sample of approximately 80 hospital, and the stratum includes one children's hospital and stratified by size. And then the data are weighted so that they can generate national estimates of ED visits and subsequent hospitalizations of adverse drug events.

So this is our case definition for NEISS-CADES. An adverse drug event is an injury or harm from the use of a drug. The injury is the ED visit, often precipitated by an action of manifestations. Attribution to the drug is based on clinician diagnosis. Our pathognomonic drug system symptom combination.

And then prior to 2016, only adverse drug events resulting from therapeutic drug use were included, but then after 2016 the system was expanded to include adverse drug events following the use of -- for any intent. And that's shown in the box to the right. And then drugs include prescription or over-

the-counter medications, supplements, and homeopathic products, and vaccines.

And so if you take a look at this chart here, it's from an analysis that was published just after we began doing adverse drug event surveillance using the NEISS-CADES data. Here you can see the population rates of emergency department visits for adverse drug events by age group.

And so as you might expect, we saw that there was an increasing risk by age. But something we did not expect to see was that the rate for the youngest age group was actually similar to those of the older adults, which was something we weren't expecting.

And so when we look at these data a little bit more closely, we found that most of the ED visits in the youngest children were from unintentional medication overdoses.

And so in the early 2000s, we saw that the number of young children being brought to emergency departments for unintentional medication

overdoses and exposures was rising rapidly. And it increased by about 40 percent from 2004 to 2010.

To put these numbers in perspective, a child born in 2007 had approximately a 1 in 54 chance of being brought to an emergency department for an accidental medication overdose or exposure by the age of six.

And so that's where PROTECT comes into play. And so in 2008, we actually convened a group of individuals working in this area and we created The Prevention of Overdoses and Treatment Errors in Children Taskforce Initiative, otherwise known as the PROTECT Initiative.

PROTECT is a CDC-led public/private partnership that uses a collaborative, data-driven approach to reduce the harms from unintentional medication overdoses in young children.

Partners include public health agencies, private sector companies, healthcare professional organizations, consumer patient advocates, standards organizations, and academic

experts.

And for the PROTECT Initiative we actually use a three-pronged approach. So first we not only focus on improving safety packaging to reduce unsupervised ingestions, we also work on standardizing the labeling to reduce medication errors, and then also updating educational messages on safe use and storage.

And so how can we prevent adverse drug events among young children? So as mentioned earlier, most of the emergency department visits for adverse drug events in young children were for unsupervised exposures. And despite the requirement for child-resident packaging for most medications in the U.S., around the time of the PROTECT activities, when they began, there were still over 60,000 ED visits annually for unsupervised exposures by children under the age of six.

We know that child-resistant packaging works when used appropriately. And this is a technology that has not actually changed much since

the 1970s that we heard in Dr. Connolly's presentation when it was first implemented.

And so PROTECT partners have begun exploring how to create safety packaging that might be improved. We began by focusing on prevention of oral liquid OTC medication exposures. PROTECT partners came up with the idea of using a bottle adapter as a flow restrictor to act as a secondary barrier that would always be in place to limit the amount of medication that young children could access on their own. They use -- they are designed to be used together with child-resistant caps.

And then here you can see an announcement from Johnson & Johnson in 2011, stating that flow restrictors would voluntarily be added to pediatric Acetaminophen products, and other manufacturers of pediatric Acetaminophen make similar commitments at that time.

Since flow restrictors were introduced, we've tested them in young children and they've actually proven to be effective. And so studies using

Poison Center and emergency department data have found that they are both effective. They are also effective in reducing the number of exposures overall, and the number involving potentially toxic amounts of Acetaminophen.

An American Society for Testing and Material Standard test method was developed to assess flow restrictors use mechanical test -- for mechanical testing. And then FDA also released a draft guidance in 2020 that recommended broader use of restricted delivery systems, such as flow restrictors, to help further reduce the risk of unintended oral liquid drug ingestions.

And so preventing ingestion of solid medications is actually a little bit more challenging. So as you would expect with liquid medications, they stay in the original bottle, typically, that they come in until it's time for use. On the other hand, solid dose medications are sometimes removed from the child-resistant packaging intentionally or unintentionally prior to use.

And so what we wanted to know was what were the containers that most young children were accessing for solid medications, and whether it might differ by medication class.

And so what we did was we partnered with five poison centers to ask additional questions when they receive calls about an exposure to an oral liquid medication by a child age five or younger.

And for most of the prescription medications, many of which can cause toxicity in small amounts, in at least half of these calls to Poison Centers, the child accessed the pills that were not in the original container, and that's signified by the blue bars, and that were intentionally transferred to a non-child-resistant container or that were intentionally transferred to a non-child-resistant container, which is signified by the green bar shown here in the figure.

And so it was clear that we also need to address these exposures in adults, where they're removing the medication from the original container

prior to the child accessing them.

And so this is one unfortunate real example of how one pill can kill that was recently featured in one of CDC's safe healthcare blogs. In the blog, our PROTECT partner, Adam and MaryBeth Gillan, actually shared the tragic story of how their nine-month-old daughter Maisie died after ingesting a single methadone pill that was found at a neighbor's house on the floor.

And the perspective that the patient and family representatives offer when they share their personal experiences highlights critical pieces of patient safety that we may not always see in our data.

So through PROTECT, we are actually continuing to encourage innovations in packaging, both of the primary containers which is the packaging that the medication comes in when you receive it from a pharmacy or a store, but then also the secondary containers which are the containers that adult might transfer medications to intentionally.

And so the top two images that you'll

see show interventions for primary packaging, so different types of flow restrictors for liquid medications, and then also unit dose packaging. And then the bottom image actually shows a design of a locking pill organizer that's on the market. But please note we do not, to our knowledge, believe that it has been tested for child resistance yet.

However, several companies that are members of the PROTECT initiative are actually working on different types of child deterrent or locking pill organizers, and we expect some to come to market soon.

And so as previously mentioned, emergency department visits for adverse drug events are relatively common in children less than five. And the vast majority of them are for unsupervised ingestion.

However, there is a small portion, and that's signified here in red, of emergency department visits that are due to medication errors. And so these errors are more common among the smallest, most vulnerable children, children less than one year of

age.

I won't read through all of the different examples, but this table actually illustrates how administration mix-ups can lead to multiple [ph] medication overdoses and underdosing errors. And so I want to note also that when multiple different units are used, such as milliliters, teaspoons, tablespoons, and other units, it can be confused and these mix-ups can cause overdosing or underdosing.

And so one of the things we focus on through PROTECT is that clearly and consistently showing milliliters only on liquid medication packaging labels and dosing devices can actually minimize errors when measuring and giving doses.

And so PROTECT partners have initiated and led a number of activities focused on improving labeling of medication bottles and dosing devices and have participated in related activities by partner organizations.

So through PROTECT, partners have

encouraged not only education of prescribers to increase the use of milliliter only on prescribing and dispensing oral liquid medications, but then also education of parents and caregivers to use a dosing device that comes with the child's medicine and to make sure that they get the right amount.

We also have worked with PROTECT partners to encourage production of milliliter-only dosing devices to minimize errors when measuring and giving doses.

And then shown here is an example of how we've worked with PROTECT partners in terms of encouraging adoption of these recommendations. So in this particular example, a large retailer revised their standard operating procedures for oral liquid medication dispensing to promote safe dosing best practices.

And so what they do with all of their oral liquid medications is they dispense flow restrictor, a milliliter-only syringe that is an appropriate size for the prescribed volume, and then

they also have packaging that has messaging to encourage parents to keep medications up and away and out of sight and reach of young children. And we hope to be partnering with other retailers in the coming years to encourage this practice.

And so then lastly, the third prong in our three-pronged approach for PROTECT is focused on safe storage education. Back in December of 2011, we launched the Up and Away and Out of Sight educational program to update and disseminate educational messages nationally.

In addition to the tools and resources and materials available online at upandaway.org, we also have rallies throughout the year to extend the reach of our messages about safe medication use and storage in a variety of media channels. We have print and online articles, social media, advertisement, radio, and video. We also encourage our PROTECT partners to help us reach broader audiences by participating in the rallies.

And then this is an example of some of

our core Up and Away messaging which has historically been centered around very simple, data-driven actions that parents and caregivers can take to prevent medication overdoses in children. I won't read through all of them, but you know, it really shows that, you know, telling parents again, keep your child safe, keep medications up and away and out of sight. And so some of this advertising looks very similar to what Dr. Connolly was showing in her presentation.

And so the question is with all of the interventions mentioned, have we seen any improvements in emergency department visits among young children. And so I'll now turn it over to my colleague, Maribeth, who's on the phone, to discuss some of the recent trends.

MS. SIVILUS: Thank you, Dr. Lind, and good afternoon, everyone. I'm going to start by sharing some recent data from the NEISS-CADES surveillance system that Dr. Lind introduced earlier.

So in recent years, we have seen overall declines in national estimates of emergency

department or ED visits for unsupervised medication exposures by children aged five or younger. So from approximately 76,000 ED visits in 2010 to about 36,000 visits in 2020.

The next slide. When we looked at trends in ED visits for unsupervised medication exposures by medication class, we found estimated visits for many classes from the period of 2009 to 2012 to 2017 to 2020. And the table shows trends and estimates of ED visits for pediatric medication exposures. The solid dosage form medication.

And so the green arrows on the right indicate classes for which there was significant decline, and the red arrow indicates a class for which there was a significant increase during this period. And that corresponds to herbal products and alternative remedies.

And so when we look more closely at the medications within this class on the next slide, we found that the increase was driven by a substantial increase in ED visits for Melatonin exposures. An

increase of about 400 percent from 2009 to 2020.

The next slide. And so we looked more closely at these ED visits for unsupervised Melatonin exposures by young children, and we compared them to visits for unsupervised exposure that involved other medication.

And then on the next slide, you see we found that the ED visits for unsupervised Melatonin exposures involved slightly older children than the visits for exposures to other medication.

So over half, or 53.5 percent of visits for Melatonin exposure involved children ages three to five years, whereas only 25.9 percent of the visits involving other medications involved that age group.

So nearly three-quarters of the visits involving exposures to other medications were made by children age two or younger. And so that includes the developmental stages when children are gradually increasing their mobility, they're learning about their environment by putting things into their mouth. But as children get older, we know that they become

more selective or at least, you know, relatively so about what they put into their mouth. And they may seek things that interest them.

And so in our surveillance activity, we see narratives indicating that children in this age group or the somewhat older toddlers, they sometimes climb to reach medication. Sometimes they even move a chair or stool to help them access the medication. I think we saw some graphics of that earlier from Dr. Connolly's presentation.

And sometimes we see narratives, too, in which multiple children are involved. And so maybe a slightly older toddler opens the -- you know, gets into the medication and shares it with their sibling.

We also found that about 46 percent of the visits involved female children, both for the Melatonin exposures and the exposures that involved other medication. So there really was not any difference there.

And an estimated 94 percent of ED visits for unsupervised Melatonin exposures, the child

did not require subsequent hospitalization. But for visits involving exposure to other medications, approximately 81 percent did not require hospitalization. And so the visits for the unsupervised Melatonin exposures appear to be less series.

For ED visits involving exposures to Melatonin and also for those involving exposures to other medications, about 87 percent involved only access to a single medication. And so that means that for 87 percent of the visits of Melatonin exposures, the child only accessed Melatonin and no other medication or supplement.

We're currently working on an analysis for identifying circumstances from the case narratives that might help with targeting interventions. So for instance, although we know that most of the Melatonin exposures involved solid dosage forms of the product, we're working to characterize the specific dosage form that was accessed.

So for instance, what prevented the

exposures in soft gummies? That's something that we're -- that we're currently working on.

Okay, next slide. We know that many medications might look like candy. So again, this is a timely reminder with Halloween being tomorrow. I know that my kids are very excited about that. You can see some examples of common look a likes in the image here on the right, which we use as part of our Up and Away education campaign that focuses on safe medication use and storage.

And distinguishing the medications from the candy can be very difficult, even for adults. And so this graphic is a reminder to parents and other caregivers with young children, that if they can't tell the difference the children probably also can't tell the difference. So it's important to keep all medication in a place that young children cannot reach or seek.

And the next slide. So after finding this increase in ED visits for unsupervised Melatonin exposures, we have updated our safe storage messaging.

So the Up and Away campaign specifically includes gummies. And so this message now reads, "Keep medicines, vitamins, and other supplements, including gummies, in a safe place that young kids can't see or reach.

And the next slide. We plan to continue monitoring trends in these ED visits. Healthy People 2030 is an initiative of the U.S. Department of Health and Human Services, and it's a national ten-year plan for addressing the most critical public health priorities.

The next slide. One of the Healthy People 2030 objectives is to reduce emergency department visits for medication overdoses in young children. And so the baseline measurement for Healthy People 2030 is 25.6 estimated ED visits per 10,000 children under five years old in 2016 and 2017.

And on the next slide, the target rate to be achieved within a decade is 16.6 ED visits per 10,000 children under five years of age. And so that amounts to an additional 35 percent reduction by

2026/2027.

Some of the data that we presented earlier suggests that we're making progress in achieving the targets. But it will be important to continue to monitor trends and ED visits and medication exposures so that we can target the prevention efforts based on the latest available data.

And that is all I have for you today, so thank you very much.

DR. MCCLARY: Thank you, both, again for that presentation.

So our next speaker is Dr. Christopher Hoyte, medical director of the Rocky Mountain Poison Center and the fellowship director of the Medical Toxicology Fellowship Program at the Rocky Mountain Poison and Drug Center.

Dr. Hoyte is also a professor of emergency medicine, medical toxicology, and pharmacology at the University of Colorado School of Medicine. And today he'll be giving some information regarding poison control guidelines, and the title of

his presentation is, "When Drugs Look Like Candy, What Role Do Poison Centers Play?"

DR. HOYTE: Thanks very much, Brandon. I have to say, actually Brandon, we talked about coming on and doing this lecture series and I will tell you that I was this close, Brandon, to wearing my Halloween costume or I asked if I could wear one. My nine-year-old daughter really wanted me to come on and do that, but I'm glad I didn't because nobody else has theirs on and I didn't want to embarrass myself. So glad I didn't do that.

Thanks for the invitation to come talk about poison centers, as Brandon just mentioned. And one of the things is, you know, we all recognize the role that over-the-counter medications play in our society. Very important.

However, one of the things that really kind of disturbs me, and Dr. Doyon [ph] sitting in the front row can attest, we sort of do the same thing professionally, is that it seems like there's this sort of thought that, oh, because kids are really

small and young there's no way they would take enough of a medication for them to get sick, which is just patently not true.

And this is sort of the case of this. So there's a two-year-old boy that came into an emergency department in one of the hospital at which my poison center covers. Came in really sleepy, and at first there was no sort of, like, why is this kid so sleepy. Parents didn't fess up at first what happened.

But the kids was -- you see the vital signs here. These are all very normal vital signs for a two-year-old boy. But the mother then sort of later on fessed up that she found the boy sort of really sleeping near a bottle that was open where there was a certain gummy formulation of a medication that was found on the ground.

Child was sleepy, really minimally responsive. Everything else sort of neurologically was intact. But the issue with this particular case was that the care providers that we were dealing with,

with this case did not feel as though a kid that's under the age of five could take enough of a drug that would make them this sleepy.

So they did what's called NAT or non-accidental trauma workup on the kid, because they thought that this must be a trauma because there's no way that it could be a drug. Kid's too small to take enough medications to get sick.

And so they subjected this child to CAT scans, they subjected this child to a lumbar puncture thinking, well, maybe this is meningitis. They subjected this child to all these things, when really the culprit was sitting right in front of them and we just need to change the attitude that kids that are under five years old who take drugs can definitely get ill.

And lots of times there are bad outcomes. Like Dr. Lind said the Methadone case. You know, opioids are notorious for that. How important it is to lock those up. But kids under five can get sick.

So what are we going to talk about? I'm going to introduce you to poison centers and the role that we can help play in doing surveillance to keep kids and everybody else really safe from these over-the-counter medications. Obviously, again, they're very important in society. But we want to keep people safe.

We're going to talk about some poison center data and go through that. Talk about trends and some trends that we see. And age is more than just a number. I think Dr. Lind maybe just sort of went through talking about why would a young kid want to get into these medications. Why would a kid that's maybe a little bit older want to do it? Why do young adults do it? And so we're going to talk about that.

And then we're going to talk about how sort of poison centers come to creating guidelines and how we can be helpful in doing surveillance, and also with the care that we deliver for poison patients.

So poison centers. We practice toxicology, and we are public health institutions. We

are -- really, our mandates are to prevent and mitigate poisoning injury. We do that through a lot of different ways. Clinical care, education, research. Many ways. But sort of preventing and mitigating poisoning injuries are at the core of what we do.

The first poison center was established in 1953 and was really focused on household ingestions in little kids. That's sort of the genesis for a lot of where poison centers started from.

1958, American's poison centers was actually called the American Association for Poison Control Centers before, recently changed the name. It's now America's Poison Centers. It was founded in the 50s.

And then there was a rapid increase in the number of PCs, all the way over 400 by the time the 1970s came along. And then the 80s and 90s, we recognized we didn't need that many centers, so we consolidated a lot of them so that we could become more efficient and provide 24/7 service.

So in 2002, we now have 1-800-222-1222, which is the number that you can call from anywhere in the United States and you will get the corresponding poison center to where you're -- well, actually, it's really to the ZIP code that you're calling from. We're changing that. But you'll get the corresponding poison center that you should. And currently, we have 55 poison centers in the U.S.

Embarrassingly, but this was really high technology at the time, this is how our agents who were taking these calls, this is how they answered these calls. So if you had someone who, you know, called, this is an Acetaminophen card, you called about Acetaminophen, they could go grab a card and it had information about Acetaminophen on it. So this is how we used to answer calls from the public, with our agents answering the phone.

We branded Mr. Yuk. I think it's very apt and is a good -- it's a good sort of representation of beware, and who you can call if you get in trouble. And then we changed it, got a little

bit more modernized, so the AAPCC logo came about. And now we have this logo, which is America's Poison Centers. So that's sort of how the branding has gone throughout the years.

And now we've become much more technological savvy. So instead of using those cards, you can actually go to a product database. There's always being new products added to this database, where our agents will answer calls and they can look them up quickly on their digital database to give you the mot accurate information on whatever you're calling about.

Here's a representation of the 55 poison centers. All the states are covered. Some of the states, as you can see, have multiple poison centers in the same states, really based on your population of your state. And then you can also see that some states cover multiple states for efficiency sake.

So for example, this is Colorado, where I'm from. We cover multiple other states, like

Montana we cover, we cover the State of Nevada, we cover Hawaii. So we'll cover some other states, really for efficiency sake. But the reason why it's important we have all these poison centers -- I get that question a lot. Like, what are there so many poison centers? Why don't you just have one national poison center? Well, there are regional variations in what we actually see as poison centers, and some poison centers see environmental toxins that other ones do not see, which is why it's important that we have different poison centers so that people can get the best care that they can when they call us.

So poison center is a 24/7 service, 365. It's staffed by specialists in poisoning information, called SPIES. I have a lot of jokes about that, but I won't give them here now because I don't have enough time to follow them through.

We are governed by best practice call center infrastructure with KPIs, or key performance indicators. So we follow best practice call center guidelines. But at our core, what we do is we provide

medical management for poisonings and exposures.

Here you can see a list of, you know, some caller types. We get all sorts of caller types, but this is a pretty common list of the people who call us.

Here's our staffing. So, you know, we have these SPIES, our agents that answer the phone. Usually they're nurses or they're PharmDs who are doing that. My center has 29 SPIES currently. 77 percent of them are certified, which is the CSPI, which is an exam you take after you've been doing this for a while, in order to be, quote, certified.

77 percent. We have some new SPIES that started recently with us. It takes a while for you to -- you have to sit for a period of time, and then there's an examination that you have to take. Some poison centers have PIPs, which are poison information providers, that take lower acuity calls. They're really paraprofessionals. And so most of the clinical stuff goes through our SPIES.

And then there's backup support. So we

have -- at all poison centers there's backup support. There's medical toxicologists who are physicians who do some backup. My program has a fellowship program, so we have doctors who are training to become medical toxicologists that also do some of the backup, and they're all board-certified medical toxicologists.

Then we have clinical toxicologists. My partner, who helps operate Rocky Mountain Poison Center, Shireen Banerji, she's a PharmD. She is the managing director of our center, and she's a clinical toxicologist. And then we have a medical director, which is me.

So interesting, let's get into the data. So what we collect: Age; gender, obvious; substances, all that are involved; how much approximately it is. You can imagine historically it's hard to get really accurate information, but we're just -- we are beholden to what is being reported to us.

The root of exposure is important. The reason, obviously for today's discussion is really

important, is, you know, what's the intentionality? Did you do this on purpose, or did you not do it on purpose? And if you didn't do it on purpose, what happened? Therapeutic errors. There's just general, you know, a child was exploratory, got into it. If you're intentionally doing it, misuse is different from abuse.

Misuse is different from abuse. Misuse is you did not use that particular drug or whatever that substance is for its intended use.

And a story I've got. So there's a person who had arthritis of the knee, was not getting her pain controlled, so what she did was she took an over-the-counter medication that's usually used for upset stomach, and she took it because of the amount of calcium in it because she thought it would help her bones. And then she was also spraying her knee with WD-40 to help her with her pain. Both of those are not intended use, so we would count that as a misuse of a product.

Clinical information. When our

patients go to the hospital, we follow them and we a lot of times will do consultation with the care providers in the hospital. We record all that clinical information, including lab work, diagnostic imaging, and others.

The site. Was it at home? Did they go into a hospital? You know, where -- if they did go to a hospital, did they get admitted to an ICU? Did they go to the ED? Was it just a clinic? We record that information as well. And that's part of the disposition.

Medical outcome is what happened. So did they have a major, moderate, minor outcome? Was there no effects? Was there death? So we record that. We follow our cases to outcome and then what therapies or interventions were involved.

So this is a picture -- this is from the National Poison Data System. And I should say the National Poison Data System is America's Poison Centers big repository of data that every poison center, when you're entering these cases into it,

every eight minutes all 55 poison centers load their cases into the National Poison Data System.

And as you can see, this one goes out to the data that we have through 2022, yeah, it's 2022. And here, that year there were over two million reports to poison centers that year. And as you can see, it's like 6,000 encounters or so per day in the database.

I just show this because we used to take all these drug identification questions. So, hey, my child got into this pill that fell on the ground; can you identify this drug for me? I don't know what it is. So that has gone down because we have the internet, and so Google is very good at giving pictures for people of what these drugs look like, and so those calls have gone down.

But what has gone up is these are healthcare facility calls. So our calls from healthcare facilities, especially hospitals, for patients that have come in after ingesting or being exposed to some substance or medication have gone up.

And where it's difficult but great for us is that these cases are more complicated and more complex. They take a little bit more time. And the patients, in general, are sicker.

This is a depiction of lease squares logistic progression, looking at the seriousness of the cases that poison centers have seen. And as you can see, the baseline is 2,000. And so these percentages are the increase from 2,000. And you can see, obviously that line there, that regression, you can see that the cases over time have gotten more and more serious that are called to poison centers. So -- and then the number of cases with the less serious cases is going down.

There -- I will say -- just, I'll quickly go through this. This is a depiction of something that we were tracking for a while. A substance of interest, of high interest. The edibles portion of this is something that Dr. Doyon and I were talking about this, and we can probably as poison centers do a little bit better job of tracking some of

these cases, but we can track them.

And if you look at edibles in this particular high-interest product has gone up significantly. And so I think edibles, no matter what the form -- what the drug, whatever the medication is, are going to be of high interest in the future.

So why do we care about any of this? So a little kid, you can see a little kid looking over. Most of these are exploratory. That's why little kids get into these. And so if you look at our data it's mostly like, hey, there was a drug sitting around, I wanted to put it in my mouth and see what happened. That's usually the case.

Little, little -- Dr. Lind showed some data, and I'm going to show you some that looks very similar to hers, that the younger you are, so the kids under one, they don't get into that many drugs probably because of mobility is one of the big things. But as you get a little older, you're more mobile, you have to be even more careful because then kids really can move over, get to drugs, and they really want to

put them in their mouth.

You get a little older. You think, oh, these are really cool and I want to check these out. Oh, I want to put it in my mouth. It can't be that bad because they look like candy, so they really can't hurt me. Which is, you know, definitely not the case.

And then as you get older, younger adults, also I think it was mentioned earlier that it's deemed also by adults that if you have a gummy or a food-like product, it is deemed that those are not as dangerous as the actual pills, and that's definitely the case as well. And so young adults sometimes will experiment with those as well.

And then as we get older as well, there is sometimes where we get confused by the way the drugs look, medications look, and so that's what is, you know, behind some of the cases that we get on our older citizens, where they got confused by the way a drug looked and maybe took too much of their own or they took their spouses that was in the house that they shouldn't or whatever.

So getting into some of the data, if you look, so the big -- this is always very shocking to people, but if you look, under five, so zero to five years, a little over 40 percent of all the reports to the poison centers was in that small age range. So of a little over two million cases, a little bit over 40 percent of the reports came in on that small age range.

And then you can see down there, this obviously doesn't equal 100 percent because I just left this large group out between 30 and 70 because it's very similar to what these looks like, but the big message here is that young kids get into medications and those reports come to poison centers.

And then this is what I was talking about. Dr. Lind's slide looks very similar to ours. If you break out the ages and reports to poison centers, it's that, hey, I'm starting to be mobile and I really want to check out whatever that medication is, so I'm going to go check it out and put it in my mouth and see what happens. And so you can see of

that zero to five age range, the one and two-year-olds have the most reports to poison centers.

And then so what about the reason -- I mentioned intentionality. So these unintentional exposures, as you can see, are by far and away the biggest group here. You know, up near 70 percent of cases are due to unintentional exposures. Again, this is like, hey, I -- you know, a kid getting into a medication that they just wanted to be exploratory with, or a therapeutic error or something like that is unintentional.

Intentional is obviously self-harm attempt, unfortunately, which is common. Abuse of drugs, misuse of drugs. Those are really the intentional group. And then you have adverse reactions on there.

And here I just wanted to depict. So if you look at the unintentional group, you see the blue bar there represents the under five group. By far and away the most -- the biggest group represented there is that zero to five pediatric group, followed

second by that six to 12.

So if you look at zero to 12, makes up the vast majority of those unintentional overdoses and exposures to poison centers.

And I'll finish up here. So these are medical outcomes, just to round this out. Most of the time nothing bad happens to that zero to five group. But you -- and you can see it falls off from none to minor to moderate, major, and death. There's very few deaths in that zero to five. I think there were 21 deaths in the zero to five group in 2022 reported to our poison centers.

Obviously, that's an underreport because there's going to be more deaths that are just not called to us. But what you can see is, you know, as you get a little older that decrease shrinks. So you see the six to 12 group, little bit more -- a little bit more severe outcomes here, because I think as you get older your intentionality changes, which is why some of those severe outcomes are more represented here as people are getting older.

And this is just a representation of the percentages of these, sort of to stop talking about the same point, which I most of the cases, especially in the zero to five group, are -- there's really no significant affect. But we do have those cases where there are, and those are really -- they're preventable.

So there's things that we can do, which is why I'm glad we're talking about this. There are things that we can do to prevent some of these things from happening, especially in that young age category.

So the last I will say is we wanted to talk about some guidelines. So if you look, this is, on the left, the Acetaminophen guideline that was recently done that was a project that was a collaboration among all of our poison centers and our sister societies as well. And we -- we came together to put this together.

And this is really more consensus guideline, like talking to people from various poison centers to -- and other of our colleagues to put

together this consensus guideline. So that's a consensus guideline.

This one on the right, atypical antipsychotics, this is just a representation of one that we did recently, where it was an internal guideline using our own poison center data and statistical analysis in order to come up with what people should do, should not do. And these are some -- you know, for example, some send in -- when do we send people in? Based on what dose will we send them to the hospital? That's represented here as well. This is more of an internal guideline.

I put this. This is a -- this is a product of high interest that we recently have got a lot of calls about. It's, hey, what do you guys do with this particular product? How do you know when to send someone to the hospital?

So what we did is went through all of our charts on this particular product and we pulled all the cases for children that were exposed to this particular product to look to see what happened to

them, based on the data that we collect. And we were able to do the statistical analysis and come up with a recommended dose, where even in the absence of symptoms at the time we would recommend that a child go to seek healthcare because there's a chance that that child is going to have a clinical exacerbation in a negative way.

And so, again, this is using poison center data. This is using our -- our expertise, our experience, our data, and our statistical analysis in order to be able to put these sorts of things out to help our -- our colleagues and help parents as well.

So we talked about some poison center functions, data, trends, and how guidelines are approached. I think we're going to do questions at the end, so I'll leave it right there.

DR. MCCLARY: Thank you, Dr. Hoyte.

So our final speaker for this session is Dr. Suzanne Doyon. Dr. Doyon is the director of the Connection Poison Control Center and associated professor in the Department of Emergency Medicine,

both at UConn Health.

The title of Dr. Doyon's talk is, "Pediatric Ingestions of Gummy-Formulated Medications."

DR. DOYON: Thank you. And I believe I'm the last speaker today before the panel, so thank you for sticking it out.

So I've been here all day, and I wanted to summarize at least some of the stuff I heard from this morning. I heard about the use of the word "chewable gels." I love that new term. I learned about overage, and I even heard something mentioned along the lines of 400 percent.

Heard stuff about taste and plant lard. Something I've never heard about before. I heard about 3D printing. I heard about -- or I saw blister packs with QR codes in it. And I thought to myself, I'm not sure the American consumer is ready for a QR code, but there it is. I heard about unusual combinations of medications achieved by 3D printing.

From the panel, I heard that we set out

to create a palatable product, not candy. We should remind ourselves of that. On the second part of the morning, that children are able to swallow pills from two speakers. I also heard that in a controlled setting, a controlled medication made into a gummy can be safety administered.

And from the afternoon, I heard that, you know, we have to think about the unintended consequences of the decisions that we make. It's on that topic, I think, that poison centers are invited to the conversation.

So these are my objectives. We're going to go over just a few scenarios, and then poison center data from my poison center. Nice data, because I just want to make a parallel right there. We heard about nice data already. Going to talk a little bit about literature as it pertains to how we package medications. And then final point on imprints and embossing.

So when I was confronted -- not confronted, but asked to speak here, I actually went

to my staff. The people who actually answer the calls, to the tune, from my poison center, of hundreds of calls per year. What are the scenarios you're hearing about when a gummy preparation is involved? And strictly a gummy preparation.

And by far, the most common scenario, by far, by far, by far, from, again, the entirety of my staff is that children are breaking through the child-resistant containers. They're jumping -- not jumping. They're climbing, they're getting into cupboards, but they're breaking through those child-resistant containers.

So we must keep that in mind. That even though something is in a child-resistant container doesn't really, really mean the child cannot get into it.

I've also heard that, this was the second most common scenario, the parent opens up the child-resistant container, takes one or two of the gummies, sets them out for siblings, but the little toddler who is not meant to receive the gummies comes

in and just laps them all up. And if there are multiple siblings getting multiple chewables, it can easily go into eight or ten chewables right then and there. So that's a common scenario.

I've heard a couple of other scenarios. A babysitter or babysitters not knowing which are the gummies are medications and which of the gummies are actually gummies, giving the patient or the child, you know, what they thought was a candy gummy when in fact it was a dietary supplement or something like that. And then the parents coming home and kind of realizing the issue and calling.

So those would have been the more common scenarios that we heard. But by far, by far, by far is children breaking through the child-resistant packaging. And in the words of one of my poison specialists, the reward is candy. They're kids. What can we do?

We've heard about these other scenarios. And again, I know there are a lot of manufacturers listening to this. I know there are a

lot of manufacturers in the room. I want you to listen to the next scenario very carefully.

A four-year-old, and I saw by the slides that four-year-olds are not a primary age. It's usually the one-and-a-half-year-old, the two-year-old, but the four-year-old were playing with gummies. They were shaped like little grapes. She was feeding them to her stuffed animals. Because that's what four-year-olds do, is they play with their stuffed animals. And then one for the animal, one for me, one for the animal, one for me, so on and so forth.

And then the other scenario, something else, again, for CDC perhaps to pay attention to. An eight-year-old got into Melatonin gummies. He was having -- the mom was asleep. He was having trouble falling asleep. So he went to mom's sleep candy, because that's what mom called it, her candy for sleep. So if it's good enough for Mom, should be good enough for me.

An eight-year-old. All right? There's

a bit of thought process here. It's not really that unsupervised ingestion that we think about. And he took a whole bunch of them and so on and so forth. So these scenarios are important to remind ourselves of as we, again, think about these issues.

Okay. So I want to show poison center data, and this is from my poison center. And I had to a lot of kind of digging to get this data. But basically, for every call that comes in, our poison specialists type in notes. And in the notes, there will be the word "gummy" if the product in question was a gummy.

And the reason I had to go through those notes and use a natural language processing is because before I heard about chewable gels, our Melatonin products, just to use Melatonin as an example, would come maybe as a liquid, maybe as a solid. Those would be the two sort of categories. Which of the two do you choose? That kind of stuff.

So to really get down to the gummy, I had to use some pretty extensive natural language

processing. Get some data people involved. I had to read through 2,700 records to basically give you this slide. I went back ten years.

So you see that there's a rapid uptick in the year 2019/2020 or so in our gummy ingestions. Now the State of Connecticut is about 3.4 million people. It's about one percent of the entire population of the United States. It has a proportionality of Hispanic or Latinx people and black people and -- that it's very, very similar to the distribution in the United States.

So often when we pick up a signal at the Connecticut Poison Center, we just multiply it by 100, roughly, and it gives us an idea of what's going on nationally. So again, just use that a little bit as you're looking at this.

But you see that my staff are -- my poison specialists are answering 400 or so such calls per day. That more than one per day in the State of Connecticut. Again, multiply that and you get into a lot.

And we heard this morning that these are calls about gummies. Any gummy, really. And we heard this morning that there is predicted over the next ten years or so, a five to six-fold increase in gummy activity, gummy market. So multiply this by 100 and multiply this by six and this is where we are in 2030. We're really talking not quite millions of exposures, but a lot of exposures. So just realize that this is getting to be a problem, and the signals are there.

But what happened during those years? What happened in 2019? What happened in 2020? So this is again where I had to do a lot of digging. And these are -- read them from left to right, and then the first line and then a second line and so on and so forth. It's those same ten years and I looked at every single product and I reclassified it into a vitamin or a multivitamin. That would be the blue. And then the Melatonin, which would be the dark orange. And then we have others.

So in terms of vitamins, it doesn't

matter if it's a children's vitamin, if it's a prenatal vitamin, it's a multivitamin for adults, a hair and nail vitamin. I had all kinds of different vitamins there. Ascorbic acid only. Vitamin D. Vitamin -- they all got classified into vitamins in my book, and that became vitamins. And then Melatonin was pretty much Melatonin.

So the others in there, there are some laxatives out there that are in gummy form. There are some probiotics, I believe, that are in gummy form. Couple of other things.

Funny enough, none of them -- and maybe some of you are veterinarian pharmacists, but none of these were veterinarian preparations. There are chewable-ish preparations, you know, for dogs and cats and so on and so forth. None of them were. I was a little bit surprised about that. And maybe I just didn't read the cases. Again, 2,700. There were a lot. But anyway, just letting you know about that. You see elderberry making a bit of an entry there as well in 2019.

But I think if you look at this, you see the blue, the amount of blue reduces, but remember you have a proportionality issue here. The total number goes up. So, you know, you have to kind of do those gymnastics in your mind.

And what I mean by that is for example, in the year 2021, we answered around 170 such calls that involved vitamins -- excuse me, 152 that involved vitamins. And it was 227 that involved vitamins in 2013. So, you know, yes, we're answering less calls about vitamins but how big is that.

And in 2022, it's 175 for vitamins. So again, how much did our vitamins, our actual number of vitamins go up or down. Not that much.

But what really, really strikes you is that orange, that dark orange piece of pie. And it goes up and up and up, and you see it really starting to take off in 2019 in a significant way. 2020, significant way. It takes over vitamins, really, in 2021, and it's reduced a little bit in 2022. So it seems like Melatonin gummies is really the explanation

for that uptick in those years.

This was somewhat picked up by CDC. So the CDC put up an MMWR on Melatonin ingestions in children, and they noticed or published an increase in, again, Melatonin exposures in children. And they explained it by the fact that COVID had something to do with it. People just purchased more Melatonin during COVID.

I would argue that that might be part of the reason, but I think really if you look, their increase is 20 -- most notable in 2019/2020, which is when our gummies in Connecticut seem to really have taken off. I think that's what -- part of the explanation as well. There's a lot of gummy Melatonin out there, and that's what we're seeing.

NEISS data that was already explained to you a little bit. NEISS data is -- there are 5,000 or so emergency departments in the United States. NEISS data has sampled, you know, a representative sample of 100 of them, collect data from these 100 emergency departments. Those data are publicly

available. There were coded data in there and narrative data as well.

And those data were collected by a Texas poison center and presented at a meeting three weeks ago in Montreal. So I happened to kind of stumble on them. We had a great talk and we followed it up with some phone calls and some Zooms, so I was able to really get to what they were saying.

But this was a poster presentation. So because it was a poster presentation you won't be able to find it on Palm Med [ph] because it's a poster presentation. So I really kind of dug with them to try to get to what it is that they were doing.

But they did something very, very similar to what I was trying to show you with the Connecticut data. So those narratives are a little, you know, kind of handwritten or dictated, you know, stories. And they use natural language processing to look for the word "gummy," just like I did in my database, but this is a different database.

They went back 22 years; I went back 10

years. And their threshold is children under four. My threshold was children under six. Typically, poison center data is presented as children under six or children up to five years of age. Think of it whichever way you want. And I did it for much fewer years and I had, you know, 2,700 cases to go through. They did it for a total of 10 years and they had 193 cases to go through. So their job was a lot easier than mine.

Okay, so this was a chart that they presented. So we again see a big uptick in the word "gummies" in these emergency department visit in children under four years of age. And you see my data showing an uptick in 2019, and their data showing again in boxes, but still pretty much showing the same thing.

And they separated their data as well. They had a proportion of Melatonin that was 50.3 percent and multivitamins 24 percent. Just to show it with mine. This was 2021 for them, so I'm presenting 2021. So I had vitamins at 39 percent; they had

vitamins at 24 percent. I had Melatonin at 44 percent; they had Melatonin at 50 percent. Remember there's a bit of a difference here. Poison center data sometimes reflect what goes on in the household. Not everybody that we get called about gets referred to the emergency department. So it's a slightly, slightly different scenario.

And not surprisingly, because most multivitamins even when taken in excessive amounts, can be safely managed in the home. We tend to have a little bit more of sort of those and -- and they end up, because they're an emergency department, a higher proportion of Melatonin. Melatonin not quite as well tolerated in the home, so they get referred into the emergency department.

So bottom line, two databases that look at the same issue from different angles. Pointing really, really in the same direction. That we seem to have a problem with gummies in children. And "multivits" are part of the problem, but it sounds like Melatonin is part of the problem as well.

And I just want to reiterate. I don't know if you spent -- after doing all this, I went to my local retail pharmacy just to see, like, how are these Melatonin packaged? I want to see what this looks like and so on and so forth. So I spent a little bit of time at my retail pharmacy.

And if it's a Melatonin five milligram tablet, a tablet, not a gummy, a tablet, no child-resistant packaging. At least the products I saw. If it's a Melatonin gummy, child-resistant packaging. I just thought that was very, very interesting.

But the vast, vast majority of the gummies I had read about that I found on the shelf, get them over the counter, they're right there, were in child-resistant packaging. I didn't find a single one that was not in a child-resistant packaging. And you know what that means. I mean, it's just like a push and turn and all that kind of good stuff.

Okay. So I want to take a little bit of a deep dive or take you on a little bit of a journey to look at the medical literature and where my

next recommendation or my next point comes from.

It's Halloween. I put some Halloween candy there, but there's a reason for that. Big advocate of unit dose packaging. Individual wrapping. I think -- I think it's something we need to spend some time thinking about.

So the first time we kind of thought about this in poison center circles was with -- this was published in 2005. It doesn't translate well here, but this is a publication from 2005 from Milton Tenenbein, one of the titans in poison center circles.

Some of you might be old enough to remember how iron used to be prescribed and how iron kind of made -- the different iron salts and so on and so forth. But just to give you a recap, in the 1990s and before, iron ingestions in children were problematic. Associated with deaths every year in the United States.

And when you did a little bit of digging, you figured out pretty quickly that it was usually the ferrous sulfate preparation that was the

problem. The typical ferrous sulfate preparation is 325 milligrams with 65 milligrams of elemental iron per unit dose. A typical ten-kilogram child needs only seven or eight tablets to get into the toxic range. A few more than that to get really in the lethal range. There's ferrous gluconate out there, there's ferrous fumarate. There are now polysaccharides. A whole host of different iron preparations.

But by and large, the ferrous fumarate and ferrous gluconate salts are usually actually found in the over-the-counter market, but they're usually not nearly as problematic as ferrous sulfate. We knew that in the 1990s.

And we approached a number of agencies, including the FDA, to do something, do something, do something. And some of you that are old enough to remember will remember that in 1997, something changed dramatically about the dispensing of ferrous sulfate products in the entire United States.

Of course it wasn't child-resistant

packaging. Had been, because of the 1970s, Child Prevention Act, you know, it had to be in child-resistant packaging. Oh, but change was on top of child-resistant packaging. These ferrous sulfate preparations, again, ferrous sulfate 325 with 65 milligrams of elemental iron per unit dose, had to also be in a blister pack.

So for you that are pharmacists, you understand what that means. Blister pack in a child -- the bottles were huge because you had to fit the blister packs in there.

I invite you to go get this publication, because it still to this day sends chills down my spine. And I'm afraid I didn't copy the table for you, although I have it written there -- printed there for you. It looks at the number of deaths prior to 1997 and after 1997. Therefore, 1998, zero. 1999, one. 2000, zero. The 1999 death, I believe, was to a pre-1990-date product.

It's just chilling to see deaths, deaths, deaths, and then zero, zero, zero. An

absolute marvel of, you know, kind of public health.

So we learned from that that child-resistant packaging has its limitations. But adding unit dose packaging seemed to really strengthen that public health measure.

So this was looked at by other people. This is a publication from actually Rocky Mountain Poison Center, their RADARS project. For those of you who don't know, Buprenorphine wasn't available as a sublingual lozenge initially, but then the manufacturer made it into a sublingual film. We have bioavailability issues with Buprenorphine, so it has to be administered sort of intrabuccaly or under the tongue.

And the film looked a little bit like the Listerine -- you know, if you've seen them. But in so doing that, they -- so it's kind of difficult to put films, I guess, in a bottle and they would be -- when exposed to moisture, they would kind of crimple up or whatever. There were issues with it.

So they packaged every sublingual film

in an envelope. A foil envelope. It actually had a barcode on it. But as you were dispensed your Buprenorphine, it's actually Buprenorphine Naloxone. This is a Naloxone product. But anyways, so you opened up the bottle, child-resistant bottle, and then in it you would have a number of those little envelopes. And then you would use those envelopes and so on and so forth.

But it's unit dose packaging just like the iron was unit dose packaging, in a child-resistant packaging. And they, too, were capable of showing that when you zero in on that product and look at poison center data, you can clearly, clearly show that the number of unintentional pediatric ingestions plummeted after the introduction of this product. So yet another engineering that resulted in sort of public health good.

And lastly, this is from the UK. I just want to mention this. In the UK, they have a problem with Acetaminophen over there. Paracetamol is what they call it over there. They have a lot more

overdoses than we have here in the United States per patient population.

They decided to address this by limiting a number of things, but one of the things they did was to make their Paracetamol blister packs. And it didn't so much influence pediatric dosing. Or it may have. If it did, they didn't publish it. But what it really, really helped was decrease the number of teenagers' suicidal ingestions that were severe and resulting in death, because they had to do the blister pack thing and that takes a lot of time, this that and the other.

So just another example of how unit dose packaging seems to do some public good. So I've shown you three aspects of the medical literature that really, really support sort of unit dose packaging.

And lastly, my last point would be on embossing and imprints. I have no idea how you can emboss or imprint anything on a gel, but embossing and imprinting is important. It may not be important to you in the room, but it's definitely important to us

in poison center circles.

You have no idea how many times a child gets into the tablet, and the only thing that we have to indicate what the child got into is the other tablet the child did not ingest, and it's got an imprint on it. And that's all we have to for -- or go with.

And so being able to quickly identify the ingredients in a pharmaceutical product, based on the tablet imprint, is essential to the functioning of poison center. I'm an emergency physician. It's essential to my functioning as a physician.

We get calls also from law enforcement. They arrest people, they have pills in their pockets, and we're trying to figure out what's going on with all of this. Again, tablet imprints, very, very helpful. So I don't want this discussion to not touch upon the importance of either embossing or a tablet imprint.

So lastly, I hope I've convinced you of the public health implications of what it is that

we're discussing today. If you were to ask me my personal opinion, my personal opinion is let's not go down the chewables. Let's not go down the gel route. Let's not have all these over-the-counter products in gel forms. We've shown children will get into them, and it's going to be a serious problem.

But if the train or that horse has left the barn or the train is now on the train tracks, whatever, then strong, strong, strong guardrails. Very strong guardrails. And I would urge everybody in the room to think about unit dose packaging beyond just child-resistant packaging, as well as all the measures that I talked about. So thank you.

DR. MCCLARY: Thank you once again, Dr. Doyon.

So we're running a little over time, but our third panel will run from 3 to 3:50, but given our time, I'm still going to suggest a short break. A five-minute stretch break just until 3:05, and then we'll go ahead and get started with our panel session.

(Off the record.)

DR. MCCLARY: All right, so it is now 3:05, so we will now get started with our third and final panel session. Again, all of our speakers for this session previously, they are joining us again for the panel. So as a reminder, we have Dr. Cyndi Connolly, Dr. Jennifer Lind, Dr. Christopher Hoyte, and Dr. Suzanne Doyon. And in addition to our panelists, in person we have Ms. Maribeth Sivilus, who is also joining us virtually.

And this panel discussion will go until 3:50. And now it's my pleasure to introduce Dr. Kristine Parbuoni, who will be moderating this session. So Dr. Parbuoni is an associate professor at the University of Maryland School of Pharmacy in the Department of Practice, Sciences, and Health Outcomes Research.

Dr. Parbuoni is a pediatric clinical pharmacy specialist and also serves as the director of post-graduate training at the University of Maryland School of Pharmacy, so welcome.

DR. PARBUONI: Thank you, everyone.

I'm excited to be here, and thank you all for sticking around. I realize it's the last session of the day. Hopefully you all learned as much as I have from all of our great speakers.

And I would like to share I also work at the pediatric ICU at University of Maryland Children's Hospital and I've taken a lot of patients in who have come in with poisonings and made my own calls to the poison centers, and actually spent some time in a poison center when I was a resident learning. So I appreciate all of you guys' input.

I want to first start off with asking each of you the question of the day. What would you define a candy-like drug product to be, from your professional perspective, and what characteristics maybe contribute to that definition for you?

And maybe if we can start with Dr. Connolly?

DR. CONNOLLY: Sure. You can hear me; correct? All right. So I'll answer that two ways. As a historian and trying to put myself back into what

those Aspirin makers or actually the developers of the broad spectrum antibiotics in the late 1940s/early 1950s were in a major arms race to do the same thing. And this is all the FDA archives. You can see them writing back and forth, "We need to have a pediatric formulation."

I think they were consciously trying to get, again, color, flavor. Basically anything that they could appeal -- that could get children to take. And as much, like, that they could sort of say it tastes like your favorite candy, in an era where I think there certainly was not the knowledge about over ingestion and poison that we have now. And so it was a strategy to get kids to take medicine.

I guess I would say as a pediatric nurse, it's using growth and development knowledge and theory to deliberately manipulate taste, flavor, texture in order to make it appeal to children of a certain age. A two-year-old versus a three-year-old versus a four-year-old. And so I hope that answers.

DR. PARBUONI: Yeah, I love that.

Thank you so much.

Dr. Lind?

DR. LIND: Yes, sure. So at CDC, we actually don't have a formal definition. But I did chat with my colleagues about it, and some of the characteristics that we talked about that we think might make a drug product be more candy-like would be a lot of the things that have already been mentioned.

Appealing flavoring or taste, shape, color, consistency, smell, sugary coatings, or appealing packaging. Things that look like toys or candies that kids would know, would all kind of go into that, what we would classify as a gummy or a candy-like product.

DR. HOYTE: I don't have too much to add to what's been said already. I would just, you know, say that also when you look at those studies that look at, you know, some of these candy products, candy-like products, and whether or not people can tell them apart from the actual candy versus the medication, I would say really anything that we would

look at and reasonably we would say any reasonable person would look at it and have a sort of difficult time telling the difference between the two.

Because a little kid that's two, you know, we're talking about it from an adult standpoint, but a little kid that's two is not going to be able to tell those apart. And they're not really going to try to discern whether or not like, hey, is this candy or is this actually a medication?

So to me, the word "reasonable" comes in. What I mean by reasonable is thinking about a two-year-old. Would a two-year-old be able to tell those things apart, is sort of where I would also add -- put that definition.

DR. DOYON: I think the day started with I know it when I see it. I don't think anybody has a great definition for what a candy-like medication is.

I agree with what has been said before. I think it has a shape, the taste, the look, the feel, the texture of some existing candy. There you go.

But what about future candies? So it's a very, very difficult question to answer.

DR. PARBUONI: Dr. Doyon, I think one of my questions for you, I know you focused on gummy-like products, but I don't know if you saw in your investigations, were there other types of things that were candy-like maybe that weren't gummy focused or?

DR. DOYON: There are plenty of gums out there and different kinds of chewables. Again, are chewables candy? Augmented chewable. But there are plenty of gums. So I honestly didn't go into the gum products. That would be another deep dive. Probably another 2,000 cases. I just don't have the time.

But gum, I think, should be somewhat classified under candy. And I think most people consider gum to be candy. So again, very, very difficult to define candy.

DR. PARBUONI: Our next question asks, are there particular therapeutic classes of drugs that

pose greater risk if supplied in a candy-like formulation? Go ahead, yes, Dr. Doyon.

DR. DOYON: Oh boy, opioids big time. But you must remember there are a lot of people taking at home chemo-therapeutic agents. There's some stuff out that are really, really difficult.

We have a list at poison centers of one tablet can kill. So those definitely would make the list. Our calcium channel blockers, Bupropion in the strengths that it's available in. So there are many, many. As poison centers, we'll be able to give you a list.

In the realm of nonprescription products, again, we're talking over-the-counter stuff. Ibuprofen, Naproxen, Acetaminophen. I wouldn't say they're harmless, you know, the dose makes the poison. We have toxic doses for all these things. But, you know, one, two, or three candy, chewables, whatever we want to call them, gels, probably not so problematic.

But the controlled substances would be problematic. A lot of our cardiovascular medications

would be problematic. A lot of our psychiatric medications would be problematic. And a lot of our anti-epileptics to some degree would be problematic. So that's a lot of medications.

DR. LIND: If I could just add to that, because Dr. Doyon covered a lot of the things that we came up with, but one of the things we also said was, like, potential for abuse on the prescription side. But then on the OTC side, maybe potential for self-harm as well.

So products are -- you know, maybe teens or a little bit older adolescents might be more likely to utilize or use for self-harm. At least something to consider.

DR. HOYTE: I'll just add one of the medications, not to pick on any medication, but definitely not just the zero to five range, but as kids get older they want to -- you know, social media, hey, you can go and get high on certain medications.

So Diphenhydramine would basically be the poster child for that. That swallowing pills is

more difficult than chewing a gummy, and so you have to work a little bit harder to get the dose of Diphenhydramine you would need to get, quote, high and/or to see the toxic effects, the effects that we worry about.

Now that being said, we have plenty of people who get smart, they make vats of water, they put the pills in them, they make slurries out of them so they can drink those down. So people get smart with it. But a drug like Diphenhydramine, I would be -- also put on that list as well.

DR. CONNOLLY: And I guess I would conclude with sort of saying, again, historically I think people thought that -- you know, in the 1950s when prescription drugs were new, parents were -- there's historical evidence that parents understood that those drugs might have some danger to them. That they didn't think, necessarily, with drugs that they were getting direct advertised in magazines, like Parents, that -- you know, the direct-to-consumer advertising for all drugs.

And I think anecdotally, as a nurse in the twenty first century, there are still a lot of people who don't really have a sense of the history of over-the-counter drugs and think that someone has tested them to make sure that they are absolutely safe for the -- you know, for all consumers.

And that -- so I do think that I don't know if it's as much a drug class as I would sort of say over-the-counter drugs partly because the ubiquity, partly because I think there is in some people, historically and today, a false sense of safety from them.

DR. PARBUONI: And I'll say I appreciated your Aspirin historical perspective. We had just put out some data from the last 20 years of Aspirins ingestions, because as a pediatric pharmacist I feel like it had been engrained in me, you know, no Aspirin for kids, no Aspirin for kids, except for the small group of people.

But there's still Aspirin ingestions and exposures and there's still 2,000 a year reported

to poison centers, you know, and I definitely didn't expect to see that data that it's still out there as a potential harm for our kids, even though it's over-the-counter and we've gotten rid of the, you know, child flavor. They're still taking it.

Considering current strategies for reducing the risk of accidental exposure of drug products, what role does labeling and packaging play? And I think Dr. Doyon spent a little bit of time on that, but any other thoughts on how that can help us limit the abuse of these candy-like dosage forms for other products?

DR. LIND: So I can chime in a little bit. One of the things that we didn't mention in terms of the packaging, also sometimes the over-the-counter product, they tend to be transparent bottles as well. So, you know, you have these bottles with gummies and things and they're all these assorted colors. To a young child, a two-year-old, they can't tell the difference. So maybe considering having the packaging be opaque so it's less appealing for kids to

try and, you know, break that barrier.

Also having, you know, pills in unit dose packaging. We've mentioned that as a good way to limit some of the access. But then also within the bottle, maybe individually wrapping. I know some of the chews are individually wrapped within the packaging, so even if the child breaks the child-resistant barrier, then there's still that kind of having to open up each individual one which might limit some of the access.

DR. PARBUONI: Go ahead.

DR. DOYON: So something I forgot to mention. So as you have unit dose packaging, so of course it creates an extra barrier for the child to get into the product, which means it's going to take more time to get into the product. The more time it takes, the longer the parent has to discover, intervene, stop, and so on and so forth. So I think about it that way as well.

And something else to remember. We get called -- the poison center gets called and child got

into the bottle of gummies. And you're like, well, how many did they get into? Again, the dose makes the poison. Oh, I don't know, you know, the bottle -- if you have individual unit dose packaging, well, how many empty wrappers are there? Or how many broken blisters are there? I don't know, whatever it is. Five.

Okay, that's something I can work with and I can do some dose calculations and I can decide whether this is going to be a problem for your child or not as opposed to, "I don't know; the bottle is open. I don't know how many were in there. I don't know how many my child got into." We're like, okay, well then we send the child to the emergency department because worst-case scenario.

So keep that in mind. Unit dose packaging adds to the discovery time but also gives us a clue as to how many the child got into. All great critical kind of points.

DR. HOYTE: And I'm just going to put a plug in. So we are -- and by we, poison centers are

pretty sensitive to this because -- not because we're trying to be a pain but, you know, this is a public health institution. We've all heard the parable about the people walking along the river, people falling in the river, we jump in the river to pull them out of the river, then right when you get out there's another person in the river, you have to jump in the river again and pull somebody out, and then finally we get smart, we go upstream and find out why people are falling in the river.

So the issue is, is that people think, "Oh, why can't people just be smart and parents be smart and just put their medications up?" Because if you put your medications up, these two-year-olds should not be able to get into it. We've seen over time that's not the case. People accidentally leave their medications out.

People go to their grandparent's house. The grandparent is not accustomed to having a child there, they leave the medication out. And as Dr. Doyon said, some of those medications are some of the

most dangerous ones.

And so the point of my -- what I'm getting -- I'll get off my soapbox, but my point is saying we cannot rely on everyone to all the time have medications put in the right place. And so these other strategies that people are talking about will, I agree with Dr. Doyon, will limit the access of little kids to these. And if we can do that, then I think that that's a victory for everybody.

DR. CONNOLLY: I'll just conclude by saying yes, I think it's for -- safety packaging is one prong, all right, in a multifaceted educational campaign. Packaging and others.

And I guess I would sort of, in terms of safety packaging, Dr. Doyon made me think of the importance of slowing down the child from getting into that packaging. I don't know that it is possible to build a -- you know, a package that a three-year-old, a determined three-year-old really can't get into with an unlimited time.

And if you ever just have unlimited

free time and you want to have some fun, go back and look -- and I could certainly tell you where they are. The time motion studies that led to the early safety caps. The pediatricians and the engineers are incredibly frustrated. A famous poison control -- anti-poison doctor, a toxicologist from University of Utah, presents to Congress in, I think, 1969, and he -- because Congress is saying why is it taking you so long to develop this cap.

And he says we have one that we were sure. Right? Nobody could get into this -- this bottle. But this was still the year of glass packaging. And so they gave it to a room full of three-year-olds and one little three-year-old takes it and cracks the glass on the edge of the table, which of course no adult had thought to do. The glass shatters, it goes everywhere, and the kids are into what was sugar tablets.

And so they -- it was -- again, a bunch of adults are -- it's always going to be very difficult to think like a three-year-old for us.

And they also -- and there is no visual on this that I can find, is that the safety cap committees, the partnerships between industry and academics, bring prototypes for the congressmen to play around with. And they all are very frustrated because they can't get into them. And again, I wish someone had thought to take a picture. It would have been great for my book, for this presentation, and just sort of for history.

DR. PARBUONI: Thank you. Maribeth, I didn't mean to exclude you from the conversation if you had anything to add to that?

DR. SIVILUS: No, not at this time. I guess just another anecdote, I guess related to the one that Dr. Connolly was just mentioning.

A while ago we really were digging into the history of all of this as well, and one of the things we came across was that one of the initial designs of the child safety packs, you know, they had tested and I think it was -- it limited. And then what they realized was that children were not

necessarily easy -- it wasn't very easy for them to open with their hands, but then some kids started to use their mouth and they were able to pry it open that way.

And so I think currently when they do the testing for using the Poison Prevention Packaging Act, the testing method, at some point in the testing I think the facilitators, you know, tell the children involved in the testing that they can use their mouths if they want to.

Because they might not necessarily do it if they -- you know, if they see observers watching them. But then given a prompt, well, feel free to use your mouth if you want to, then, you know, they might be more inclined to do so.

DR. PARBUONI: Children will find a way.

DR. SIVILUS: They will find a way.

DR. PARBUONI: Related to that, I know several of you have mentioned blister packaging being a potential way to slow down and to help with reducing

overdoses.

On the flip side of that there is some concern about that not being maybe environmentally friendly or increasing waste, I guess. Any recommendations on how to balance the environmental factor versus the safety aspect?

UNIDENTIFIED SPEAKER 2: I have not thought that far yet.

DR. LIND: I have not either, but I mean, just in thinking, technology can do a lot and I know there are a lot of products that are biodegradable now, even like some straws and things like that. So I'm sure smart people could come up with a way.

DR. PARBUONI: Thank you. Our next question is can you share any insights into candy-like characteristics that may lead adults to misuse or abuse some of these drug products?

DR. HOYTE: So I can say for some -- and this is pure anecdote. I have not done analysis on this. But the stories that I've heard from young

adults first is that they -- this is more therapeutic misuse. Is that they believe that the gummy -- well, sorry. Different formulations. They're safer, so you can take more of them and it's okay to take more of them because they're -- because of the way they're formulated.

That they don't think it's like taking a pill. And so they think that the dose they're getting is not going to make them sick. So they think they can take more of them. I've heard that multiple times from -- especially from young adults.

DR. PARBUONI: It's made for kids. It must be safe for everyone.

Do we have any insights from pediatric medication overdose prevention efforts that might extend to the geriatric population? Are there differences in medication management challenges with pediatric versus adults?

DR. HOYTE: I'm going to say it the opposite way. So one of my colleagues actually did a study looking at pill minders for our geriatric

population. And we had been -- and to be said, the confounding here is that these are calls to the poison centers, based on the inappropriate and the inaccurate use of their pill minders for their medications. It is not uncommon for our geriatric population to accidentally take wrong medications out of a pill minder.

So I've heard some -- you know, we've talked about -- some people have actually talked about, well, maybe we should use pill minders for pediatric patients also, because normally their parents will be giving them the medication. So it'd be in a pill minder; it'd be hard for them to get into it.

People are looking at that now. I don't know if that's going to be any better or not. I'll leave that to people with more expertise here who deal with that. But I know that people are looking at that, going back from taking it from the geriatric population down to the pediatric population for using pill minders.

DR. DOYON: You would think pill organizers would take care of problems, but my gosh. They take their evening dose instead of morning dose. They forgot they've taken -- it's Tuesday and they go to the Tuesday and the Tuesday is empty. So it's like they have no idea, oh no. Husband and wife. He takes hers; she takes his. Two different pill organizers. Oh my gosh, the scenarios are multifold.

But bottom line is pill organizer is not the solution, and I have a particular issue with filling a pill minder with candy-like medications. I think that's just a recipe for disaster.

DR. CONNOLLY: I think a real challenge, of course, is that we expect, in the United States, we have so few social supports, we expect until people are very old and really quite cognitively impaired, that they're going to have to manage their medications completely on their own.

And I would sort of say, as one of those people who uses a pill minder, again I think it was you, Dr. Doyon, mentioned, I do find it very

useful when there is some kind of notation, a number or something inscribed on the pill. Because when I'm trying to figure out whether I've dropped my Losartan or my Statin and they're small white pills, I just sort of throw them both away unless I can somehow identify them by the other pills in the bottle.

So I guess I do think that that has potential for help for across the board, but certainly for older people who tend to take more medications than younger people.

DR. PARBUONI: Our next question from the audience, I believe, is how do parents perceive gummies for their children? Are parents more likely to overdose their own children using gummies or candy-like drugs just because of the dosage form that they are? Any insight from reports?

DR. CONNOLLY: I think parents really want to do well by their children. The overwhelming majority of parents want to do the right thing for their children, so they would never set out to overdose their children. That would not -- you know,

I'm just going to be very frank about this.

However, I did see some patients over the weekend, because I was working shifts, and I did have a six or seven-year-old that was starting on an antibiotic, and the first demand or ask from the parents is, "Is this antibiotic available as a chewable?"

So I do think that parents are seeking the chewables. And again, when you're age five or six, are you on liquids, can you take pills? You know, that's kind of that nebulous area there. Usually teenagers pills are okay, younger children liquids are okay. But at that age group, whatever.

And so parents are starting to ask for chewable preparations. This antibiotic was not available in chewables, so there you go.

DR. HOYTE: I just, again, anecdotally, I think that with the question that you asked, there's definitely something to that. I think, you know, the standard pill form, you know, that everyone has had and using certain medication that have been in pill

form, I think the parents -- I don't think that all parents would do this, but I think that some parents would have the idea, erroneously, that they could take more of a gummy-like medication or that it's somehow safer than a pill or whatever that is.

I think that anecdotally I have heard that from people. But I don't know, over a population, how that would look. But just in select cases, I've definitely heard that sort of sentiment.

DR. SIVILUS: This is Maribeth Sivilus online. I just wanted to add that another characteristic of the product that I thought that might lead parents or caregivers to just assume that -- some of these products that we know in gummy form that are currently available.

That, you know, I can see in my house, you know, I have two kids under six, and they take a multivitamin, it is a gummy form, and the dose for that is four gummies each.

And so, you know, having a dose that's so many individual units also might lead one to think

that, well, these things are harmless because, look, I have to take four every single time I take some. And, you know, my kids are very attuned to all of this as well. So if I'm running low on them, you know, I'll give them three. Or if I don't have anymore they'll say, "Wait a minute, you missed one. I'm supposed to get another one."

And then another issue that we've run into with some of our analysis with the Melatonin work is, you know, we're looking into additional details from these case narratives. The text information. We have some information about how many units, you know, the children got into, what was the strength of the unit.

And then for Melatonin it becomes quite an issue because we found that they -- you know, we found the dosage is small, the individual unit is as little as .3 milligrams, all the way up to 60 milligrams for just one unit. And so, you know, trying to figure out, you know, what they got into, how many, and what could the dose have been, the total

amount ingested has been very difficult.

DR. PARBUONI: Melatonin is tricky. Various reasons going into pediatric patients.

Are there any cultural or demographic factors that influence the risk of accidental exposures to candy-like medicines? Anything that you've been able to see from some of your data analysis?

DR. HOYTE: I haven't looked, but now you gave me a good idea.

DR. PARBUONI: There you go.

DR. LIND: Same here. I didn't look at the social determinants of -- so I cannot answer that.

DR. CONNOLLY: I would just add that in the safety cap work in the 60s, they're not collecting a lot of data about families, but they do want to know marital status of the mother, and they are looking for race and income of the family. I don't know how they thought they'd use that information. They're not looking for anything else, but those are particularly important.

It made me think of sort of things that would have been biases that were sort of -- that were not even beginning to be acknowledged in the practice of -- of medicine or nursing or healthcare.

DR. PARBUONI: Hopefully the manufacturers that are maybe on the call are listening to making sure that these are -- if we're packaging them more safely that they are still financially available to all people and not priced at a point that is going to disadvantage some others.

One of the questions from online is could some of the poison center calls on gummy-related concerns be calls related to choking versus overdosing?

DR. LIND: So we have a great way of coding for this. These are ingestions, oral ingestions. If they were aspirated or inhaled, the root of administration would have been different. So these are ingestions. They were oral ingestions.

DR. PARBUONI: Thank you for clarifying.

DR. LIND: And I should say there were no aspirations, no inhalations in the whole group.

DR. PARBUONI: I think that's all the questions I see from online. Do we have questions from the audience for the panel we have?

Yes, sir, in the back. I think we have a microphone coming to you.

UNIDENTIFIED SPEAKER 3: A lot of the conversations today went from category to category. We had drugs, supplements, and even cannabis. Do you think the category is important if we're going to be determining what's appropriate in each category? Or is it just across the board we should handle it all the same?

Does that make sense? Like, because, you know, it would be pretty easy to conclude cannabis shouldn't be in candy form. Right? But some of it, like fiber maybe, something with a high dose, hard to consume, things like that. Or does that sort of stop us from being able to solve the problem ultimately of accidental ingestion?

DR. HOYTE: It's a good question. I think it gets back to -- I think it gets down to what the goal is. And if we're trying to make sure that there are no accidental ingestions of kids, then I think, you know, it would have to be an across the board thing.

But I don't think, you know, if you look at -- if you look at all the substances these kids get into, not all of them are causing significant -- you know, significant injury to kids.

And so I think probably, this is my personal opinion, probably should be a little targeted. Look at our data, analyze it, you know, with all stakeholders and look at the data and analyze it and sort of make it a more targeted thing rather than going after every single substance on the market.

But that's what I would do, is target the ones that we think are going to be more dangerous, but I think probably there'd be some disagreement with that.

DR. DOYON: The second paper I quoted,

the one regarding the Buprenorphine, the Naloxone sublingual film, had a number of authors. And if you read their discussion and their conclusion, so of course they're talking about Buprenorphine and Naloxone. Buprenorphine is a prescription product. It's also a controlled product. So of course they're in that realm.

But they do make a good -- and I think they spent a lot of time thinking about this, but they do make a good point that they're advocating for single dose packaging for certain products that have been determined to be particularly problematic in children.

So I'll echo the comments of my colleague. Perhaps a targeted approach would be preferable. And again, there are people who have thought about this, thought about it for months, so I'm going to kind of take their thoughts and just communicate that to you. But I'd have to agree with that. Thank you.

DR. PARBUONI: Another question I've

seen from online is based on research data that you've seen, how likely do parents measure their liquid medications properly? How has it affected the number of overdoses or adverse reactions seen, especially in children, whether they're using teaspoons or MLs? This kind of speaks to me as a pediatric pharmacist, but I'll let you all share from your data.

DR. LIND: So I can jump in there. So in the presentation, I hope, you know, from the three-pronged approach we did talk a little bit about the medication errors. And while the vast majority were unintentional ingestions, there were a percentage that were medication errors, but only about five percent.

But, I mean, the good thing about this, it is generally preventable, you know, in terms of the med error. So a lot of times if it is in standard metric units that we have found and studies have shown that that decreases the risk of medication errors for parents.

There was -- or there has been in the

past a perception that maybe parents may not understand milliliters. And that, you know, there's this perception, oh, we need to put teaspoons or spoon-based units as well on there. But studies of health literacy have shown that parents actually do understand milliliters. And then by having the single metric unit only dosing or units on dosing devices that there are less, you know, errors with that as opposed to when you have both units or multiple units on a dosing device, that does increase the chance of, like, overdosing or underdosing depending on, you know, what the parent expects it to be.

And so yes, you know, that is definitely an issue. It is a much smaller percentage of what we're seeing in terms of ED visits. However, you know, we have found ways to prevent it.

And I don't know, I mean, Maribeth, do you have anything additional that you want to share in terms of data?

DR. SIVILUS: So in terms of the data, when we look a little bit more closely in what those

errors were, I mean, most of them were dosing errors. You know, we see some errors that are, you know -- administration or maybe, you know, the -- was given by mistake. But most of them are dosing errors.

And then also most of them involve, you know -- most of them involved liquid medications. And we don't always have the level of detail to see what the underlying or the root cause was, but some of the ones that Dr. Lind just mentioned were, you know, mixing different units of measure. Maybe using household spoons to administer medication also can be problematic because, you know, they're not standardized in any way. You know, there's -- and such.

DR. CONNOLLY: I just want to relate just a scenario from this weekend. Again, I worked this weekend. Prescribing an antibiotic to a family -- to the child. And I was talking to the family. It's going to be one teaspoon twice a day, whatever.

And so this was a two-year-old. A

COVID baby. Right? And the parents were probably in their late 20s. And she goes, "I don't understand what a teaspoon is. Can you explain this to me in MLs?" And I was just so happy. Just so happy.

I think our young parents are moving towards the metric system. I think Acetaminophen is now dispensed with a syringe. They're getting used to it. And again, these young parents are really, really -- they all want to do the right thing for their child.

So I was just -- and I was like, "Do you have a syringe at home? You're used to syringes." Well yeah, talk to us in syringes, kind of syringe language. I was more than happy to do that. And again, I'm sharing the story with you so this tells you how happy I was with the story.

DR. MEYERS: So I just want to add to that. So Rachel Meyers, pediatric pharmacist, again, so I love that. I think one thing FDA could do to help us with that is stop labeling the medications for 5 ML. All the antibiotics, like Amoxicillin, 400

milligram per 5 ML.

That is from the era of when we dosed in teaspoons, and that era is gone. And that is one of my biggest wishes. It needs to be just per ML. Nobody cares how much per 5 ML anymore. It's not relevant information.

DR. PARBUONI: Too much math. And this would apply to over-the-counter products also. Not just the antibiotics. But the Tylenols, the Ibuprofens, all that stuff over the counter.

Yes, in the back?

UNIDENTIFIED SPEAKER 4: So we've had some interesting suggestions about packaging and things like that. And, you know, just reminded me something from the past and I was wondering. Does it make sense in the context of supplements and, you know, nonprescription medications in general, to have some kind of a symbol that makes it very easy to communicate?

You know, like back in the day there was a radioactive symbol that would be put on a lot of

things. It was a very clear indication that, you know, this is something that's dangerous. And, you know, to just highlight the fact that, yes, you're using it as a supplement, you're using it as something, you know, which is over the counter, but there are consequences.

DR. HOYTE: I will say, without naming the substance, but being from the State of Colorado, and I'm not talking about mushrooms, that being from the State of Colorado, exactly what you're saying on a particular product where people have now gone off and made things that look like candy or energy drinks or all sorts of things, by law now we got passed that you have to put a particular symbol that denotes that kind of substance it is so that when people go to take it they know exactly that, hey, just FYI, there is this particular substance here, just in case you didn't know that.

And so I think, you know, we don't want to do too many symbols, I think, because then there's a confusion to that, but to your --

UNIDENTIFIED SPEAKER 4: No, just one universal symbol that basically says this can be a drug and could be toxic, you know, something.

DR. HOYTE: Right. Yeah, no, I think you're making a good point. It's another potential deterrent upstream to, you know, reduce the risk of somebody getting something that they didn't really want to or not knowing the risk of what they were taking or whatever it is. So it seems to have worked in Colorado at this point.

DR. DOYON: I think that suggestion is going to have to be refined a little bit because the dose is the poison. Water, in enough quantity, will kill someone. Do we need labels on water? I'm being facetious here, obviously, but I think it's a little bit more complex than just sticking a logo and doing something like that, so.

DR. PARBUONI: I think I found one question I might have skipped over earlier. Focusing on the OTC drug product market, what are the most common drugs involved in poisonings? And I think we

focused maybe on gummy earlier, but I guess OTC drugs overall, the most common in poisonings.

DR. DOYON: So -- some of the Ibuprofen product, Naproxen products, but mostly Ibuprofen, and then Acetaminophen. We've seen quite a decrease in cough and cold preparations. If you look at data from the year 2000 to 2007, 2008, you have quite a few pediatric exposures to cough and cold preparations. The multi-symptom cough and cold preparations. But they've gone down tremendously, and we have plenty of data to show that.

The reason they went down so much is because of the voluntary withdrawal, based on an FDA recommendation, but the voluntary withdrawal of these cough and cold preparations for children under the age of four.

You're going to have trouble right now going to a retail pharmacy and finding a cough and cold product for your one-year-old or two-year-old or whatever. They are no longer available, so they're not bought by parents. They're not found in the

household. Children don't get into them, and therefore we have less calls and less ED visits.

So cough and cold preparations used to be quite high up on the list, but no longer. So it's back to our over-the-counter nonsteroidals or Acetaminophen products, and then maybe our antihistamines. And yes, Diphenhydramine was mentioned, but there's a lot of Loratadine and, you know, the second-generation antihistamine, so to speak. A lot of that being used in children as well. They have a lot of children formulations of these. So again, children get into those.

DR. PARBUONI: Any other questions from the audience? That's all I have. Thank you, all, very much for your time, and thank you for the panel. I'll leave it up to Brandon to close us out.

DR. MCCLARY: All right. Thanks again, Dr. Parbuoni, for moderating this session.

So again, I want to thank our panelists. Amazing discussion. And now we'll close out the workshop with final remarks from Dr. Terri

Michele, and director of the Office of Nonprescription Drugs here at FDA.

DR. MICHELE: All right. Well, I think I have to start with just wow. This has been such a terrific workshop. Just really excellent presentations. I've been so impressed. And I think the audience will agree.

I would like to once again thank all of our speakers, panelists, moderators, for all of the terrific information that we heard, the opinions. Just so much good stuff.

I think all of you who were here in the room saw me taking copious notes, and certainly we'll all be taking this back and there will be lots of discussion on all of these topics here at FDA.

So just reflecting back on what we heard, we heard from three very different panels. The first one was focused on manufacturing. The second one was focused on issues related to adherence. And the third was really focused on risks.

So for panel 1, we appreciated the USP

definition of a chewable gel dosage form for dietary supplements. And about some of the manufacturing and stability issues that can come up with these dosage forms. We also heard about some of the tricks of the trade that formulators use to mask the bitter tastes of drugs and the feel of drugs. I mean, certainly all kinds of things about taste that I never even knew, and yet it all makes intuitive sense when you hear about it.

And finally, we heard about some of the creative options that are becoming available, some of the newer technologies with 3D printing, all kinds of things we can do with individualized dosage forms that can be particularly useful for particular patients and particular challenges in formulation.

So this panel was very helpful in comparing some of the characteristics of candy with the characteristics of a typical drug product. And we heard that candies generally have sweeter taste palates, they have stronger aromatic flavors, novel textures, novel forms, brighter colors, creative

packaging. All kinds of things.

And I hadn't really thought about it, but that color really does make a difference in how you think about the flavor of something. So something to keep in mind.

Then in panel 2, we heard a little bit on the flipside. You know, some of the unique and rare circumstances where candy-like dosage forms are helpful to achieve a therapeutic intent. Certainly the example from our dental colleague was very useful. And some of the benefits of other creative dosage forms, like mini tabs and orally disintegrating tablets, as well as the benefits of maybe encouraging kids to be able to swallow tablets, because that's, of course, the best taste masking is if it never really gets much in your mouth.

An important takeaway that I took from all of these examples that we heard was that they were all used in very controlled circumstances. Under the direct supervision of a healthcare provider. And that's really just not the case in the OTC market.

So when we start to think about where do these fit in, we're hearing some great examples from the prescription world and a direct supervision, but maybe less in the OTC space.

Then in panel 3, we sort of focused on the risks. And we heard from some of our colleagues with poison control experience. We started off with a fantastic historical example of some of the unintended consequences that can happen when a dosage form tastes too good. I mean, I certainly grew up with the concept of a St. Joseph's Aspirin. And I remember it was such a rare treat to get to take one.

So something that we need to kind of keep in the back of our mind as we are exploring what's going on with these new and more candy-like dosage formulations.

The other thing that I think came through loud and clear from this panel is that children will get into anything, and children will especially get into anything that tastes like or looks like candy. They'll find a way. Kids are incredibly

creative. I'm always amazed at the things that they do that we never would have thought of.

We heard about some of the things that we can do, some of the tool in our toolbox as regulators, as manufacturers, a formulators, to try to protect against some of these things, related to, you know, child-resistant packaging. What an incredible benefit that has been for public health. Some of the newer flow restrictors and the unit dose packaging and how they has made a difference in certain circumstances.

But I think the perception also makes a huge difference in the market. You know, we heard that OTCs as a whole, and we've known this for a lot of years, are perceived by the general public to be less harmful or less risky than a prescription drug product.

And then that gets multiplied with some of these more candy-like dosage forms like gummies. So we have to think about that perception factor and how do we factor that in when we're thinking about

these formulations.

So again, thank you to our panelists, to our speakers. We'll be taking all this feedback back. I can hear the conversations already going on. There's going to be lots of them. And I wish all of you a very pleasant day. Safe travels. And thanks again for joining us for this very important workshop.

(Whereupon, the workshop concluded at 3:54 p.m.)

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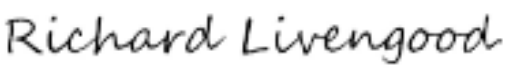

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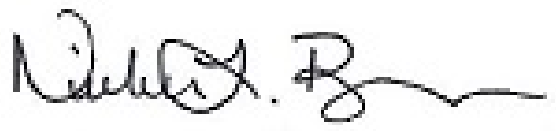

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