

1 Defining "Candy-Like" Nonprescription Drug Products  
2 Hybrid Public Workshop

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5 Hosted by Dr. Brandon McClary  
6 Monday, October 30, 2023  
7 8:30 a.m.

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10 FDA Great Room, Building 131  
11 10903 New Hampshire Avenue  
12 Silver Spring, MD 20993

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19 Reported by: Richard Livengood  
20 JOB NO.: 6085671

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## A P P E A R A N C E S

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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

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

2           Gilbert Burckart, Associate Director of Pediatrics,

3           Office of Clinical Pharmacology, Pediatrics, FDA

4           Cynthia Connolly, Professor of Nursing, University of

5           Pennsylvania, School of Nursing

6           Jennifer Lind, Epidemiologist and Captain, U.S. Public

7           Health Service Commissioned Corps.

8           Maribeth Sivilus, Lead Epidemiologist, CDC Medication

9           and Safety Program in the Division of Healthcare

10          Quality Promotion

11          Christopher Hoyte, Medical Director, Rocky Mountain

12          Poison and Drug Safety

13          Suzanne Doyon, Director, Connecticut Poison Control

14          Center, UConn Health

15          Kristine Parbuoni, Associate Professor, University of

16          Maryland, School of Pharmacy

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## P R O C E E D I N G S

1 DR. MCCLARY: Good morning, everyone.  
2 All right. I am Dr. Brandon McClary,  
3 Interdisciplinary Sciences with the Office of  
4 Nonprescription Drugs here at FDA. So I just want to  
5 welcome everyone, and thank you for joining this  
6 public workshop on defining candy-like nonprescription  
7 drug products.  
8

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

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

1 about their amazing work.

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

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

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

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

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

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

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

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



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

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

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

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

1 technology provides increasing options for how we can  
2 formulate drugs.

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

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

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

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

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

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

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

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

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

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

21                   And finally, I'd like to thank everyone

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

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

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

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

1 chewable gels, marketed as gummies.

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

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

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

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

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

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

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

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

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

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

21           Chewable gels are also known as



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

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

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

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

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

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

9 Here's an example of two labels from  
10 different gummy products. And you can see that the  
11 content of ingredient is completely different. For  
12 example, one product has vitamin A with daily value of  
13 133 percent, and another product can have vitamin A  
14 only 32 percent daily value -- for example, one  
15 product has 100 percent daily value and another  
16 product 166 percent daily value.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 comprehensive statistical analysis of almost 1,000  
2 weights measurements.

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

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

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

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

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

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

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



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

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

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

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

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

21 Our next speaker is Mr. David Tisi,

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

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

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

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

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

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

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

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

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

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

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

21           And then the final element of flavor is

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

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

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

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

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

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

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

1 like or dislike.

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

21 Chemical complexation. This is -- this

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21            So not only intensity is important, but

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

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

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

21 So we have most pediatric drugs have a



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

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

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

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

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

1 less intensity in aromatic.

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

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

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

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

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

21                   We love chocolate so much you can take

1 out the flavor and it becomes an enjoyable product.

2 If you've ever had white chocolate, you have taken

3 that cocoa flavor out of that -- out of that product,

4 and it becomes a palatable formulation. You're eating

5 plant lard. But we love that -- we love that texture

6 change so much, that that's what we perceive.

7 Obviously, major differences in

8 branding. Major differences in the packaging and the

9 color intensity. Extremely vibrant colors. Again,

10 you're just not seeing most of these areas in the

11 field of OTCs you are in every commercial candy

12 product.

13 Color has a big -- color has an effect

14 on the perceived flavor intensity. So as you increase

15 the color, that flavor intensity goes up, a does

16 overall acceptability. So most confectionary

17 companies are very interested in pumping up the color

18 because of those -- because of those responses.

19 And of course these -- these questions

20 that I brought up are not going to be limited to the

21 more simple route of oral liquids, like in most OTCs.

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

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

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

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

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

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

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

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

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

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

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

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

1 3D printing technology in this area. Specifically, I  
2 would like to talk about three aspect. The first one  
3 is the personalized dosing, the second one is the drug  
4 delivery, the third one is the manufacturing. How we  
5 can utilize the 3D printing technology to -- to  
6 achieve all these three aspect.

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

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



1 market right now, approved by FDA.

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

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

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

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

21           Let's first take a look of the

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

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

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

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

4 The characteristics of this product is  
5 it can instantly disintegrate. It's very fast.

6 Utilizing the 3D printing technology, really what we  
7 can do or what we can achieve, is try to build a  
8 structure. Both internal and external structure.

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

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

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

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

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

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

21           So we took about 206 GRAS material and

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

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

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

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

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

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

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

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

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

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

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

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

1 release as the time is going to increase.

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

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

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

21           They proposed a geometric shape which



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

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

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

21           And we can have multiple component in

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 are achieving is a digital product development and  
2 digital manufacturing.

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

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

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

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

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

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

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

1 pretty sure the technology can be easily trickle into  
2 the OTC or monograph drug. So with that, I would like  
3 to thank my team. Now it's about 140 people.  
4 One-third of them is engineer. And also would like to  
5 thank -- organization and on right-hand side you see  
6 the company received TCT healthcare award. TCT is a  
7 3D printing community. The annual award, it's  
8 considered Oscar in 3D printing. So we are very proud  
9 we received that award.

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

12 DR. MCCLARY: Thanks again, Dr. Li.

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

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



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

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

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

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

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

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

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

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

21 Chewable gels maintain their molded

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

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

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

17 DR. CHRISTODOULOU: Thank you.

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

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

4 DR. CHRISTODOULOU: Thank you very  
5 much.

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

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

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

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

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

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

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

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

21 And as my colleague described, it's

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

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

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

1 nothing more.

2 DR. CHRISTODOULOU: Thank you.

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

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

13 DR. CHRISTODOULOU: Psychological  
14 factors, yeah.

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

21 Although, you know, the topic probably

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

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

10 DR. CHRISTODOULOU: Thank you.

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

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

15 DR. SWAPAN DE: Yeah, may I ask you  
16 some question? I think this is very interesting, this  
17 3D technology. Because the drug is forming layer by  
18 layer; right? So is that excipient -- excipient  
19 solution and active solutions. Do the excipient  
20 solution, is they are definition separate or each  
21 excipient is -- is going in there?



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

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

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

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

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

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

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

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

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

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

9 DR. SWAPAN DE: Yes.

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

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

21 DR. DAVYDOVA: Yeah, just again, I

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

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

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

21                   From actually possibility of the

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

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

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

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

16           DR. CHRISTODOULOU: Thank you.

17           Mr. Worthington?

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

1 looking for a solution.

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

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

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

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

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

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

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

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

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

1 might be better served defining what a candy is not.

2 DR. CHRISTODOULOU: Thank you.

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

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

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

15 DR. LI: Definitely, definitely. From  
16 technology-wise, I don't think that's an issue. The  
17 3D printing technology is a big advantage. It's not  
18 mold related. It's -- if you can imagine it, you can  
19 draw it, you will be able to make it. So any shape,  
20 as long as you define or you can draw it, you can even  
21 take a picture and then convert it, digitalize, and



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

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

6 Swapan De, do you have any comments?

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

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

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

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

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

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

10 MR. WORTHINGTON: Can I --

11 DR. CHRISTODOULOU: Yes.

12 MR. WORTHINGTON: Can I add an item on?

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

15 MR. WORTHINGTON: Yes.

16 DR. CHRISTODOULOU: Please go ahead.

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

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

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

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

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

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

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

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

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

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

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

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

16 DR. CHRISTODOULOU: For certain drugs.

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

19 DR. CHRISTODOULOU: Thank you.

20 Yes, please.

21 MR. WORTHINGTON: Yeah, manufacturing

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

10 DR. CHRISTODOULOU: Shelf-life.

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

15 DR. CHRISTODOULOU: That's very  
16 interesting.

17 Any comments from you, Dr. Li?

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

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

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

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

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

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

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

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

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



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

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

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

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

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

1 ingredient.

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

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

17 So -- but usually when we analyze, we  
18 analyze assay procedure which is usually, for example,  
19 150 percent for vitamin A or 160 percent.

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

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

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

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

21           DR. CHRISTODOULOU: Thank you.

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

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

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

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

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

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

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

6 DR. LI: It's on the packaging.

7 DR. CHRISTODOULOU: It's on the  
8 package.

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

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

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

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

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

3 DR. LI: So just same thing, yeah.

4 DR. CHRISTODOULOU: From the packaging,  
5 yeah.

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

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

16 DR. DAVYDOVA: Could I add?

17 DR. CHRISTODOULOU: Sure.

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

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

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

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

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

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

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

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

3 (Off the record.)

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

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

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

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



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

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

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

21 So we're going to talk about some of

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

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

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

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

21 Now liquids, though, sometime the

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

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

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

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

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

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

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

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

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

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

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

1 a concern of mine as a pharmacist.

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

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

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

21 So I would like to focus -- and my

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

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

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

21           And then I know our colleague from the

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13           The geriatric population, it's a little  
14 bit less simplistic. So the age proposed by the ICH  
15 [ph] is early old, 65/74-year-old; middle old,  
16 75/84-year-old; and late old, over 85. However, this  
17 often does not reflect the biological age, and there  
18 is a further physiological approach that uses the  
19 classification of fit, of frail, old adult.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

1 granules, pellets, and mini tablets.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 So just a few notes. 50 percent of



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

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

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

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

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

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

5 We have to really take a lot of things  
6 into consideration while we're treating -- when we  
7 want to treat a patient. How old is the patient? Are  
8 they neurotypical or do they have cognitive concerns  
9 that we have to be aware of? A four-year-old patient  
10 is much different than a ten-year-old patient or a  
11 16-year-old patient. How are we going to treat them?

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

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

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

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

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

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

1 be a big concern.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

1 use as much to get the effect that we need.

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

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

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

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

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

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

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

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

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

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

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

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

21 And how quickly did they consume a

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

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

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

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

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

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

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

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

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

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

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

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

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



1 closely to the microphone. Thank you.

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

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

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

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

1 about toxic drugs, think about acetaminophen. You  
2 know?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. CHIN: No.

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

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

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

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

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

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

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

13 DR. CHIN: Correct.

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

21 However, it requires a device, and that

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

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

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

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

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

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

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

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

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

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

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

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

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

9 DR. CHI: Sucralose.

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

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

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

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

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

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

21 And again, it depends on how much of



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

5 DR. BURCKART: Okay, thank you.

6 DR. TULEU: If I may?

7 DR. BURCKART: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

1 to take solid dosage forms.

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

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

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

21 So yeah, we've got those resources that

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

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

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

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

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

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

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

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

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

1 audience or panelist want to mention beyond  
2 pediatrics?

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

6 DR. BURCKART: Okay.

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

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

12 DR. TULEU: It's a big market.

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

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

20 DR. TULEU: Yeah, there is.

21 DR. BURCKART: Okay.

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

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

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

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

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



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

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

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

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

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

21           So this is the trick, when it's only

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

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

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

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

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

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

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

17 Yeah, there's a comment in the back?

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

1 given one time, and the final conclusion, it works.

2 That's it. It works.

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

5 UNIDENTIFIED SPEAKER 1: Yes, because  
6 it works.

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

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

19 DR. BURCKART: All right, thank you.

20 (Off the record.)

21 DR. MCCLARY: All right, everyone. It

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

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

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

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

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

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

1 past.

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

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

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

1 take Prednisolone that was coming out of their mouth.

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

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

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

1 of medication they want to take.

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

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

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



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

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

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

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

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

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

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

21           There are also, at the same time, there

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

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

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

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

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

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

9           Other companies would follow, but  
10 nobody could compete with Plough. By 1955, they owned  
11 81 percent of the market. It's so -- it's bringing  
12 such big business to his company, that he's being --  
13 that, you know, he's being promoted as a big business  
14 built for little customers.

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

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

1 children increased dramatically.

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

7           But by 1951, this group accounted for  
8 80 percent of the deaths from Aspirin. In the seven  
9 years alone between 1947 and 1954, the American  
10 Academy of Pediatrics estimated the incidents of  
11 Aspirin poisoning in young children had increased by  
12 500 percent.

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

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

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

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

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

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

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

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

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

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

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

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

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



1 fever in children.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 percent, according to the Public Health Service.

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

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

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

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

21 And really, a deep dive into the data

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

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

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

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

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

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

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

21                    And then finally, you know, this is a

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 experts.

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

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

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

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

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

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

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

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

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

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

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

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

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

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



1 prior to the child accessing them.

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

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

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

21           And so the top two images that you'll

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

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

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

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

1 age.

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

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

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

21 So through PROTECT, partners have

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

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

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

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

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

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

12 In addition to the tools and resources  
13 and materials available online at [upandaway.org](http://upandaway.org), we  
14 also have rallies throughout the year to extend the  
15 reach of our messages about safe medication use and  
16 storage in a variety of media channels. We have print  
17 and online articles, social media, advertisement,  
18 radio, and video. We also encourage our PROTECT  
19 partners to help us reach broader audiences by  
20 participating in the rallies.

21 And then this is an example of some of

1 our core Up and Away messaging which has historically  
2 been centered around very simple, data-driven actions  
3 that parents and caregivers can take to prevent  
4 medication overdoses in children. I won't read  
5 through all of them, but you know, it really shows  
6 that, you know, telling parents again, keep your child  
7 safe, keep medications up and away and out of sight.  
8 And so some of this advertising looks very similar to  
9 what Dr. Connolly was showing in her presentation.

10 And so the question is with all of the  
11 interventions mentioned, have we seen any improvements  
12 in emergency department visits among young children.  
13 And so I'll now turn it over to my colleague,  
14 Maribeth, who's on the phone, to discuss some of the  
15 recent trends.

16 MS. SIVILUS: Thank you, Dr. Lind, and  
17 good afternoon, everyone. I'm going to start by  
18 sharing some recent data from the NEISS-CADES  
19 surveillance system that Dr. Lind introduced earlier.

20 So in recent years, we have seen  
21 overall declines in national estimates of emergency

1 department or ED visits for unsupervised medication  
2 exposures by children aged five or younger. So from  
3 approximately 76,000 ED visits in 2010 to about 36,000  
4 visits in 2020.

5 The next slide. When we looked at  
6 trends in ED visits for unsupervised medication  
7 exposures by medication class, we found estimated  
8 visits for many classes from the period of 2009 to  
9 2012 to 2017 to 2020. And the table shows trends and  
10 estimates of ED visits for pediatric medication  
11 exposures. The solid dosage form medication.

12 And so the green arrows on the right  
13 indicate classes for which there was significant  
14 decline, and the red arrow indicates a class for which  
15 there was a significant increase during this period.  
16 And that corresponds to herbal products and  
17 alternative remedies.

18 And so when we look more closely at the  
19 medications within this class on the next slide, we  
20 found that the increase was driven by a substantial  
21 increase in ED visits for Melatonin exposures. An

1 increase of about 400 percent from 2009 to 2020.

2           The next slide. And so we looked more  
3 closely at these ED visits for unsupervised Melatonin  
4 exposures by young children, and we compared them to  
5 visits for unsupervised exposure that involved other  
6 medication.

7           And then on the next slide, you see we  
8 found that the ED visits for unsupervised Melatonin  
9 exposures involved slightly older children than the  
10 visits for exposures to other medication.

11           So over half, or 53.5 percent of visits  
12 for Melatonin exposure involved children ages three to  
13 five years, whereas only 25.9 percent of the visits  
14 involving other medications involved that age group.

15           So nearly three-quarters of the visits  
16 involving exposures to other medications were made by  
17 children age two or younger. And so that includes the  
18 developmental stages when children are gradually  
19 increasing their mobility, they're learning about  
20 their environment by putting things into their mouth.  
21 But as children get older, we know that they become



1 more selective or at least, you know, relatively so  
2 about what they put into their mouth. And they may  
3 seek things that interest them.

4           And so in our surveillance activity, we  
5 see narratives indicating that children in this age  
6 group or the somewhat older toddlers, they sometimes  
7 climb to reach medication. Sometimes they even move a  
8 chair or stool to help them access the medication. I  
9 think we saw some graphics of that earlier from Dr.  
10 Connolly's presentation.

11           And sometimes we see narratives, too,  
12 in which multiple children are involved. And so maybe  
13 a slightly older toddler opens the -- you know, gets  
14 into the medication and shares it with their sibling.

15           We also found that about 46 percent of  
16 the visits involved female children, both for the  
17 Melatonin exposures and the exposures that involved  
18 other medication. So there really was not any  
19 difference there.

20           And an estimated 94 percent of ED  
21 visits for unsupervised Melatonin exposures, the child

1 did not require subsequent hospitalization. But for  
2 visits involving exposure to other medications,  
3 approximately 81 percent did not require  
4 hospitalization. And so the visits for the  
5 unsupervised Melatonin exposures appear to be less  
6 series.

7 For ED visits involving exposures to  
8 Melatonin and also for those involving exposures to  
9 other medications, about 87 percent involved only  
10 access to a single medication. And so that means that  
11 for 87 percent of the visits of Melatonin exposures,  
12 the child only accessed Melatonin and no other  
13 medication or supplement.

14 We're currently working on an analysis  
15 for identifying circumstances from the case narratives  
16 that might help with targeting interventions. So for  
17 instance, although we know that most of the Melatonin  
18 exposures involved solid dosage forms of the product,  
19 we're working to characterize the specific dosage form  
20 that was accessed.

21 So for instance, what prevented the

1 exposures in soft gummies? That's something that  
2 we're -- that we're currently working on.

3           Okay, next slide. We know that many  
4 medications might look like candy. So again, this is  
5 a timely reminder with Halloween being tomorrow. I  
6 know that my kids are very excited about that. You  
7 can see some examples of common look a likes in the  
8 image here on the right, which we use as part of our  
9 Up and Away education campaign that focuses on safe  
10 medication use and storage.

11           And distinguishing the medications from  
12 the candy can be very difficult, even for adults. And  
13 so this graphic is a reminder to parents and other  
14 caregivers with young children, that if they can't  
15 tell the difference the children probably also can't  
16 tell the difference. So it's important to keep all  
17 medication in a place that young children cannot reach  
18 or seek.

19           And the next slide. So after finding  
20 this increase in ED visits for unsupervised Melatonin  
21 exposures, we have updated our safe storage messaging.

1 So the Up and Away campaign specifically includes  
2 gummies. And so this message now reads, "Keep  
3 medicines, vitamins, and other supplements, including  
4 gummies, in a safe place that young kids can't see or  
5 reach.

6 And the next slide. We plan to  
7 continue monitoring trends in these ED visits.  
8 Healthy People 2030 is an initiative of the U.S.  
9 Department of Health and Human Services, and it's a  
10 national ten-year plan for addressing the most  
11 critical public health priorities.

12 The next slide. One of the Healthy  
13 People 2030 objectives is to reduce emergency  
14 department visits for medication overdoses in young  
15 children. And so the baseline measurement for Healthy  
16 People 2030 is 25.6 estimated ED visits per 10,000  
17 children under five years old in 2016 and 2017.

18 And on the next slide, the target rate  
19 to be achieved within a decade is 16.6 ED visits per  
20 10,000 children under five years of age. And so that  
21 amounts to an additional 35 percent reduction by

1 2026/2027.

2           Some of the data that we presented  
3 earlier suggests that we're making progress in  
4 achieving the targets. But it will be important to  
5 continue to monitor trends and ED visits and  
6 medication exposures so that we can target the  
7 prevention efforts based on the latest available data.

8           And that is all I have for you today,  
9 so thank you very much.

10           DR. MCCLARY: Thank you, both, again  
11 for that presentation.

12           So our next speaker is Dr. Christopher  
13 Hoyte, medical director of the Rocky Mountain Poison  
14 Center and the fellowship director of the Medical  
15 Toxicology Fellowship Program at the Rocky Mountain  
16 Poison and Drug Center.

17           Dr. Hoyte is also a professor of  
18 emergency medicine, medical toxicology, and  
19 pharmacology at the University of Colorado School of  
20 Medicine. And today he'll be giving some information  
21 regarding poison control guidelines, and the title of

1 his presentation is, "When Drugs Look Like Candy, What  
2 Role Do Poison Centers Play?"

3 DR. HOYTE: Thanks very much, Brandon.  
4 I have to say, actually Brandon, we talked about  
5 coming on and doing this lecture series and I will  
6 tell you that I was this close, Brandon, to wearing my  
7 Halloween costume or I asked if I could wear one. My  
8 nine-year-old daughter really wanted me to come on and  
9 do that, but I'm glad I didn't because nobody else has  
10 theirs on and I didn't want to embarrass myself. So  
11 glad I didn't do that.

12 Thanks for the invitation to come talk  
13 about poison centers, as Brandon just mentioned. And  
14 one of the things is, you know, we all recognize the  
15 role that over-the-counter medications play in our  
16 society. Very important.

17 However, one of the things that really  
18 kind of disturbs me, and Dr. Doyon [ph] sitting in the  
19 front row can attest, we sort of do the same thing  
20 professionally, is that it seems like there's this  
21 sort of thought that, oh, because kids are really

1 small and young there's no way they would take enough  
2 of a medication for them to get sick, which is just  
3 patently not true.

4           And this is sort of the case of this.  
5 So there's a two-year-old boy that came into an  
6 emergency department in one of the hospital at which  
7 my poison center covers. Came in really sleepy, and  
8 at first there was no sort of, like, why is this kid  
9 so sleepy. Parents didn't fess up at first what  
10 happened.

11           But the kids was -- you see the vital  
12 signs here. These are all very normal vital signs for  
13 a two-year-old boy. But the mother then sort of later  
14 on fessed up that she found the boy sort of really  
15 sleeping near a bottle that was open where there was a  
16 certain gummy formulation of a medication that was  
17 found on the ground.

18           Child was sleepy, really minimally  
19 responsive. Everything else sort of neurologically  
20 was intact. But the issue with this particular case  
21 was that the care providers that we were dealing with,

1 with this case did not feel as though a kid that's  
2 under the age of five could take enough of a drug that  
3 would make them this sleepy.

4 So they did what's called NAT or  
5 non-accidental trauma workup on the kid, because they  
6 thought that this must be a trauma because there's no  
7 way that it could be a drug. Kid's too small to take  
8 enough medications to get sick.

9 And so they subjected this child to CAT  
10 scans, they subjected this child to a lumbar puncture  
11 thinking, well, maybe this is meningitis. They  
12 subjected this child to all these things, when really  
13 the culprit was sitting right in front of them and we  
14 just need to change the attitude that kids that are  
15 under five years old who take drugs can definitely get  
16 ill.

17 And lots of times there are bad  
18 outcomes. Like Dr. Lind said the Methadone case. You  
19 know, opioids are notorious for that. How important  
20 it is to lock those up. But kids under five can get  
21 sick.



1                   So what are we going to talk about?  
2                   I'm going to introduce you to poison centers and the  
3                   role that we can help play in doing surveillance to  
4                   keep kids and everybody else really safe from these  
5                   over-the-counter medications. Obviously, again,  
6                   they're very important in society. But we want to  
7                   keep people safe.

8                   We're going to talk about some poison  
9                   center data and go through that. Talk about trends  
10                  and some trends that we see. And age is more than  
11                  just a number. I think Dr. Lind maybe just sort of  
12                  went through talking about why would a young kid want  
13                  to get into these medications. Why would a kid that's  
14                  maybe a little bit older want to do it? Why do young  
15                  adults do it? And so we're going to talk about that.

16                  And then we're going to talk about how  
17                  sort of poison centers come to creating guidelines and  
18                  how we can be helpful in doing surveillance, and also  
19                  with the care that we deliver for poison patients.

20                  So poison centers. We practice  
21                  toxicology, and we are public health institutions. We

1 are -- really, our mandates are to prevent and  
2 mitigate poisoning injury. We do that through a lot  
3 of different ways. Clinical care, education,  
4 research. Many ways. But sort of preventing and  
5 mitigating poisoning injuries are at the core of what  
6 we do.

7           The first poison center was established  
8 in 1953 and was really focused on household ingestions  
9 in little kids. That's sort of the genesis for a lot  
10 of where poison centers started from.

11           1958, American's poison centers was  
12 actually called the American Association for Poison  
13 Control Centers before, recently changed the name.  
14 It's now America's Poison Centers. It was founded in  
15 the 50s.

16           And then there was a rapid increase in  
17 the number of PCs, all the way over 400 by the time  
18 the 1970s came along. And then the 80s and 90s, we  
19 recognized we didn't need that many centers, so we  
20 consolidated a lot of them so that we could become  
21 more efficient and provide 24/7 service.

1           So in 2002, we now have 1-800-222-1222,  
2           which is the number that you can call from anywhere in  
3           the United States and you will get the corresponding  
4           poison center to where you're -- well, actually, it's  
5           really to the ZIP code that you're calling from.  
6           We're changing that. But you'll get the corresponding  
7           poison center that you should. And currently, we have  
8           55 poison centers in the U.S.

9                       Embarrassingly, but this was really  
10          high technology at the time, this is how our agents  
11          who were taking these calls, this is how they answered  
12          these calls. So if you had someone who, you know,  
13          called, this is an Acetaminophen card, you called  
14          about Acetaminophen, they could go grab a card and it  
15          had information about Acetaminophen on it. So this is  
16          how we used to answer calls from the public, with our  
17          agents answering the phone.

18                      We branded Mr. Yuk. I think it's very  
19          apt and is a good -- it's a good sort of  
20          representation of beware, and who you can call if you  
21          get in trouble. And then we changed it, got a little

1 bit more modernized, so the AAPCC logo came about.  
2 And now we have this logo, which is America's Poison  
3 Centers. So that's sort of how the branding has gone  
4 throughout the years.

5 And now we've become much more  
6 technological savvy. So instead of using those cards,  
7 you can actually go to a product database. There's  
8 always being new products added to this database,  
9 where our agents will answer calls and they can look  
10 them up quickly on their digital database to give you  
11 the most accurate information on whatever you're  
12 calling about.

13 Here's a representation of the 55  
14 poison centers. All the states are covered. Some of  
15 the states, as you can see, have multiple poison  
16 centers in the same states, really based on your  
17 population of your state. And then you can also see  
18 that some states cover multiple states for efficiency  
19 sake.

20 So for example, this is Colorado, where  
21 I'm from. We cover multiple other states, like

1 Montana we cover, we cover the State of Nevada, we  
2 cover Hawaii. So we'll cover some other states,  
3 really for efficiency sake. But the reason why it's  
4 important we have all these poison centers -- I get  
5 that question a lot. Like, what are there so many  
6 poison centers? Why don't you just have one national  
7 poison center? Well, there are regional variations in  
8 what we actually see as poison centers, and some  
9 poison centers see environmental toxins that other  
10 ones do not see, which is why it's important that we  
11 have different poison centers so that people can get  
12 the best care that they can when they call us.

13 So poison center is a 24/7 service,  
14 365. It's staffed by specialists in poisoning  
15 information, called SPIES. I have a lot of jokes  
16 about that, but I won't give them here now because I  
17 don't have enough time to follow them through.

18 We are governed by best practice call  
19 center infrastructure with KPIs, or key performance  
20 indicators. So we follow best practice call center  
21 guidelines. But at our core, what we do is we provide

1 medical management for poisonings and exposures.

2 Here you can see a list of, you know,  
3 some caller types. We get all sorts of caller types,  
4 but this is a pretty common list of the people who  
5 call us.

6 Here's our staffing. So, you know, we  
7 have these SPIES, our agents that answer the phone.  
8 Usually they're nurses or they're PharmDs who are  
9 doing that. My center has 29 SPIES currently. 77  
10 percent of them are certified, which is the CSPI,  
11 which is an exam you take after you've been doing this  
12 for a while, in order to be, quote, certified.

13 77 percent. We have some new SPIES  
14 that started recently with us. It takes a while for  
15 you to -- you have to sit for a period of time, and  
16 then there's an examination that you have to take.  
17 Some poison centers have PIPs, which are poison  
18 information providers, that take lower acuity calls.  
19 They're really paraprofessionals. And so most of the  
20 clinical stuff goes through our SPIES.

21 And then there's backup support. So we

1 have -- at all poison centers there's backup support.  
2 There's medical toxicologists who are physicians who  
3 do some backup. My program has a fellowship program,  
4 so we have doctors who are training to become medical  
5 toxicologists that also do some of the backup, and  
6 they're all board-certified medical toxicologists.

7           Then we have clinical toxicologists.  
8 My partner, who helps operate Rocky Mountain Poison  
9 Center, Shireen Banerji, she's a PharmD. She is the  
10 managing director of our center, and she's a clinical  
11 toxicologist. And then we have a medical director,  
12 which is me.

13           So interesting, let's get into the  
14 data. So what we collect: Age; gender, obvious;  
15 substances, all that are involved; how much  
16 approximately it is. You can imagine historically  
17 it's hard to get really accurate information, but  
18 we're just -- we are beholden to what is being  
19 reported to us.

20           The root of exposure is important. The  
21 reason, obviously for today's discussion is really

1 important, is, you know, what's the intentionality?  
2 Did you do this on purpose, or did you not do it on  
3 purpose? And if you didn't do it on purpose, what  
4 happened? Therapeutic errors. There's just general,  
5 you know, a child was exploratory, got into it. If  
6 you're intentionally doing it, misuse is different  
7 from abuse.

8 Misuse is different from abuse. Misuse  
9 is you did not use that particular drug or whatever  
10 that substance is for its intended use.

11 And a story I've got. So there's a  
12 person who had arthritis of the knee, was not getting  
13 her pain controlled, so what she did was she took an  
14 over-the-counter medication that's usually used for  
15 upset stomach, and she took it because of the amount  
16 of calcium in it because she thought it would help her  
17 bones. And then she was also spraying her knee with  
18 WD-40 to help her with her pain. Both of those are  
19 not intended use, so we would count that as a misuse  
20 of a product.

21 Clinical information. When our



1 patients go to the hospital, we follow them and we a  
2 lot of times will do consultation with the care  
3 providers in the hospital. We record all that  
4 clinical information, including lab work, diagnostic  
5 imaging, and others.

6 The site. Was it at home? Did they go  
7 into a hospital? You know, where -- if they did go to  
8 a hospital, did they get admitted to an ICU? Did they  
9 go to the ED? Was it just a clinic? We record that  
10 information as well. And that's part of the  
11 disposition.

12 Medical outcome is what happened. So  
13 did they have a major, moderate, minor outcome? Was  
14 there no effects? Was there death? So we record  
15 that. We follow our cases to outcome and then what  
16 therapies or interventions were involved.

17 So this is a picture -- this is from  
18 the National Poison Data System. And I should say the  
19 National Poison Data System is America's Poison  
20 Centers big repository of data that every poison  
21 center, when you're entering these cases into it,

1 every eight minutes all 55 poison centers load their  
2 cases into the National Poison Data System.

3 And as you can see, this one goes out  
4 to the data that we have through 2022, yeah, it's  
5 2022. And here, that year there were over two million  
6 reports to poison centers that year. And as you can  
7 see, it's like 6,000 encounters or so per day in the  
8 database.

9 I just show this because we used to  
10 take all these drug identification questions. So,  
11 hey, my child got into this pill that fell on the  
12 ground; can you identify this drug for me? I don't  
13 know what it is. So that has gone down because we  
14 have the internet, and so Google is very good at  
15 giving pictures for people of what these drugs look  
16 like, and so those calls have gone down.

17 But what has gone up is these are  
18 healthcare facility calls. So our calls from  
19 healthcare facilities, especially hospitals, for  
20 patients that have come in after ingesting or being  
21 exposed to some substance or medication have gone up.

1           And where it's difficult but great for  
2 us is that these cases are more complicated and more  
3 complex. They take a little bit more time. And the  
4 patients, in general, are sicker.

5           This is a depiction of lease squares  
6 logistic progression, looking at the seriousness of  
7 the cases that poison centers have seen. And as you  
8 can see, the baseline is 2,000. And so these  
9 percentages are the increase from 2,000. And you can  
10 see, obviously that line there, that regression, you  
11 can see that the cases over time have gotten more and  
12 more serious that are called to poison centers. So --  
13 and then the number of cases with the less serious  
14 cases is going down.

15           There -- I will say -- just, I'll  
16 quickly go through this. This is a depiction of  
17 something that we were tracking for a while. A  
18 substance of interest, of high interest. The edibles  
19 portion of this is something that Dr. Doyon and I were  
20 talking about this, and we can probably as poison  
21 centers do a little bit better job of tracking some of

1 these cases, but we can track them.

2 And if you look at edibles in this  
3 particular high-interest product has gone up  
4 significantly. And so I think edibles, no matter what  
5 the form -- what the drug, whatever the medication is,  
6 are going to be of high interest in the future.

7 So why do we care about any of this?  
8 So a little kid, you can see a little kid looking  
9 over. Most of these are exploratory. That's why  
10 little kids get into these. And so if you look at our  
11 data it's mostly like, hey, there was a drug sitting  
12 around, I wanted to put it in my mouth and see what  
13 happened. That's usually the case.

14 Little, little -- Dr. Lind showed some  
15 data, and I'm going to show you some that looks very  
16 similar to hers, that the younger you are, so the kids  
17 under one, they don't get into that many drugs  
18 probably because of mobility is one of the big things.  
19 But as you get a little older, you're more mobile, you  
20 have to be even more careful because then kids really  
21 can move over, get to drugs, and they really want to

1 put them in their mouth.

2 You get a little older. You think, oh,  
3 these are really cool and I want to check these out.  
4 Oh, I want to put it in my mouth. It can't be that  
5 bad because they look like candy, so they really can't  
6 hurt me. Which is, you know, definitely not the case.

7 And then as you get older, younger  
8 adults, also I think it was mentioned earlier that  
9 it's deemed also by adults that if you have a gummy or  
10 a food-like product, it is deemed that those are not  
11 as dangerous as the actual pills, and that's  
12 definitely the case as well. And so young adults  
13 sometimes will experiment with those as well.

14 And then as we get older as well, there  
15 is sometimes where we get confused by the way the  
16 drugs look, medications look, and so that's what is,  
17 you know, behind some of the cases that we get on our  
18 older citizens, where they got confused by the way a  
19 drug looked and maybe took too much of their own or  
20 they took their spouses that was in the house that  
21 they shouldn't or whatever.

1           So getting into some of the data, if  
2 you look, so the big -- this is always very shocking  
3 to people, but if you look, under five, so zero to  
4 five years, a little over 40 percent of all the  
5 reports to the poison centers was in that small age  
6 range. So of a little over two million cases, a  
7 little bit over 40 percent of the reports came in on  
8 that small age range.

9           And then you can see down there, this  
10 obviously doesn't equal 100 percent because I just  
11 left this large group out between 30 and 70 because  
12 it's very similar to what these looks like, but the  
13 big message here is that young kids get into  
14 medications and those reports come to poison centers.

15           And then this is what I was talking  
16 about. Dr. Lind's slide looks very similar to ours.  
17 If you break out the ages and reports to poison  
18 centers, it's that, hey, I'm starting to be mobile and  
19 I really want to check out whatever that medication  
20 is, so I'm going to go check it out and put it in my  
21 mouth and see what happens. And so you can see of

1 that zero to five age range, the one and two-year-olds  
2 have the most reports to poison centers.

3 And then so what about the reason -- I  
4 mentioned intentionality. So these unintentional  
5 exposures, as you can see, are by far and away the  
6 biggest group here. You know, up near 70 percent of  
7 cases are due to unintentional exposures. Again, this  
8 is like, hey, I -- you know, a kid getting into a  
9 medication that they just wanted to be exploratory  
10 with, or a therapeutic error or something like that is  
11 unintentional.

12 Intentional is obviously self-harm  
13 attempt, unfortunately, which is common. Abuse of  
14 drugs, misuse of drugs. Those are really the  
15 intentional group. And then you have adverse  
16 reactions on there.

17 And here I just wanted to depict. So  
18 if you look at the unintentional group, you see the  
19 blue bar there represents the under five group. By  
20 far and away the most -- the biggest group represented  
21 there is that zero to five pediatric group, followed

1 second by that six to 12.

2 So if you look at zero to 12, makes up  
3 the vast majority of those unintentional overdoses and  
4 exposures to poison centers.

5 And I'll finish up here. So these are  
6 medical outcomes, just to round this out. Most of the  
7 time nothing bad happens to that zero to five group.  
8 But you -- and you can see it falls off from none to  
9 minor to moderate, major, and death. There's very few  
10 deaths in that zero to five. I think there were 21  
11 deaths in the zero to five group in 2022 reported to  
12 our poison centers.

13 Obviously, that's an underreport  
14 because there's going to be more deaths that are just  
15 not called to us. But what you can see is, you know,  
16 as you get a little older that decrease shrinks. So  
17 you see the six to 12 group, little bit more -- a  
18 little bit more severe outcomes here, because I think  
19 as you get older your intentionality changes, which is  
20 why some of those severe outcomes are more represented  
21 here as people are getting older.



1           And this is just a representation of  
2 the percentages of these, sort of to stop talking  
3 about the same point, which I most of the cases,  
4 especially in the zero to five group, are -- there's  
5 really no significant affect. But we do have those  
6 cases where there are, and those are really -- they're  
7 preventable.

8           So there's things that we can do, which  
9 is why I'm glad we're talking about this. There are  
10 things that we can do to prevent some of these things  
11 from happening, especially in that young age category.

12           So the last I will say is we wanted to  
13 talk about some guidelines. So if you look, this is,  
14 on the left, the Acetaminophen guideline that was  
15 recently done that was a project that was a  
16 collaboration among all of our poison centers and our  
17 sister societies as well. And we -- we came together  
18 to put this together.

19           And this is really more consensus  
20 guideline, like talking to people from various poison  
21 centers to -- and other of our colleagues to put

1 together this consensus guideline. So that's a  
2 consensus guideline.

3 This one on the right, atypical  
4 antipsychotics, this is just a representation of one  
5 that we did recently, where it was an internal  
6 guideline using our own poison center data and  
7 statistical analysis in order to come up with what  
8 people should do, should not do. And these are  
9 some -- you know, for example, some send in -- when do  
10 we send people in? Based on what dose will we send  
11 them to the hospital? That's represented here as  
12 well. This is more of an internal guideline.

13 I put this. This is a -- this is a  
14 product of high interest that we recently have got a  
15 lot of calls about. It's, hey, what do you guys do  
16 with this particular product? How do you know when to  
17 send someone to the hospital?

18 So what we did is went through all of  
19 our charts on this particular product and we pulled  
20 all the cases for children that were exposed to this  
21 particular product to look to see what happened to

1 them, based on the data that we collect. And we were  
2 able to do the statistical analysis and come up with a  
3 recommended dose, where even in the absence of  
4 symptoms at the time we would recommend that a child  
5 go to seek healthcare because there's a chance that  
6 that child is going to have a clinical exacerbation in  
7 a negative way.

8           And so, again, this is using poison  
9 center data. This is using our -- our expertise, our  
10 experience, our data, and our statistical analysis in  
11 order to be able to put these sorts of things out to  
12 help our -- our colleagues and help parents as well.

13           So we talked about some poison center  
14 functions, data, trends, and how guidelines are  
15 approached. I think we're going to do questions at  
16 the end, so I'll leave it right there.

17           DR. MCCLARY: Thank you, Dr. Hoyte.

18           So our final speaker for this session  
19 is Dr. Suzanne Doyon. Dr. Doyon is the director of  
20 the Connection Poison Control Center and associated  
21 professor in the Department of Emergency Medicine,

1 both at UConn Health.

2 The title of Dr. Doyon's talk is,  
3 "Pediatric Ingestions of Gummy-Formulated  
4 Medications."

5 DR. DOYON: Thank you. And I believe  
6 I'm the last speaker today before the panel, so thank  
7 you for sticking it out.

8 So I've been here all day, and I wanted  
9 to summarize at least some of the stuff I heard from  
10 this morning. I heard about the use of the word  
11 "chewable gels." I love that new term. I learned  
12 about overage, and I even heard something mentioned  
13 along the lines of 400 percent.

14 Heard stuff about taste and plant lard.  
15 Something I've never heard about before. I heard  
16 about 3D printing. I heard about -- or I saw blister  
17 packs with QR codes in it. And I thought to myself,  
18 I'm not sure the American consumer is ready for a QR  
19 code, but there it is. I heard about unusual  
20 combinations of medications achieved by 3D printing.

21 From the panel, I heard that we set out

1 to create a palatable product, not candy. We should  
2 remind ourselves of that. On the second part of the  
3 morning, that children are able to swallow pills from  
4 two speakers. I also heard that in a controlled  
5 setting, a controlled medication made into a gummy can  
6 be safely administered.

7 And from the afternoon, I heard that,  
8 you know, we have to think about the unintended  
9 consequences of the decisions that we make. It's on  
10 that topic, I think, that poison centers are invited  
11 to the conversation.

12 So these are my objectives. We're  
13 going to go over just a few scenarios, and then poison  
14 center data from my poison center. Nice data, because  
15 I just want to make a parallel right there. We heard  
16 about nice data already. Going to talk a little bit  
17 about literature as it pertains to how we package  
18 medications. And then final point on imprints and  
19 embossing.

20 So when I was confronted -- not  
21 confronted, but asked to speak here, I actually went

1 to my staff. The people who actually answer the  
2 calls, to the tune, from my poison center, of hundreds  
3 of calls per year. What are the scenarios you're  
4 hearing about when a gummy preparation is involved?  
5 And strictly a gummy preparation.

6 And by far, the most common scenario,  
7 by far, by far, by far, from, again, the entirety of  
8 my staff is that children are breaking through the  
9 child-resistant containers. They're jumping -- not  
10 jumping. They're climbing, they're getting into  
11 cupboards, but they're breaking through those  
12 child-resistant containers.

13 So we must keep that in mind. That  
14 even though something is in a child-resistant  
15 container doesn't really, really mean the child cannot  
16 get into it.

17 I've also heard that, this was the  
18 second most common scenario, the parent opens up the  
19 child-resistant container, takes one or two of the  
20 gummies, sets them out for siblings, but the little  
21 toddler who is not meant to receive the gummies comes

1 in and just laps them all up. And if there are  
2 multiple siblings getting multiple chewables, it can  
3 easily go into eight or ten chewables right then and  
4 there. So that's a common scenario.

5 I've heard a couple of other scenarios.  
6 A babysitter or babysitters not knowing which are the  
7 gummies are medications and which of the gummies are  
8 actually gummies, giving the patient or the child, you  
9 know, what they thought was a candy gummy when in fact  
10 it was a dietary supplement or something like that.  
11 And then the parents coming home and kind of realizing  
12 the issue and calling.

13 So those would have been the more  
14 common scenarios that we heard. But by far, by far,  
15 by far is children breaking through the  
16 child-resistant packaging. And in the words of one of  
17 my poison specialists, the reward is candy. They're  
18 kids. What can we do?

19 We've heard about these other  
20 scenarios. And again, I know there are a lot of  
21 manufacturers listening to this. I know there are a

1 lot of manufacturers in the room. I want you to  
2 listen to the next scenario very carefully.

3 A four-year-old, and I saw by the  
4 slides that four-year-olds are not a primary age.  
5 It's usually the one-and-a-half-year-old, the  
6 two-year-old, but the four-year-old were playing with  
7 gummies. They were shaped like little grapes. She  
8 was feeding them to her stuffed animals. Because  
9 that's what four-year-olds do, is they play with their  
10 stuffed animals. And then one for the animal, one for  
11 me, one for the animal, one for me, so on and so  
12 forth.

13 And then the other scenario, something  
14 else, again, for CDC perhaps to pay attention to. An  
15 eight-year-old got into Melatonin gummies. He was  
16 having -- the mom was asleep. He was having trouble  
17 falling asleep. So he went to mom's sleep candy,  
18 because that's what mom called it, her candy for  
19 sleep. So if it's good enough for Mom, should be good  
20 enough for me.

21 An eight-year-old. All right? There's



1 a bit of thought process here. It's not really that  
2 unsupervised ingestion that we think about. And he  
3 took a whole bunch of them and so on and so forth. So  
4 these scenarios are important to remind ourselves of  
5 as we, again, think about these issues.

6 Okay. So I want to show poison center  
7 data, and this is from my poison center. And I had to  
8 a lot of kind of digging to get this data. But  
9 basically, for every call that comes in, our poison  
10 specialists type in notes. And in the notes, there  
11 will be the word "gummy" if the product in question  
12 was a gummy.

13 And the reason I had to go through  
14 those notes and use a natural language processing is  
15 because before I heard about chewable gels, our  
16 Melatonin products, just to use Melatonin as an  
17 example, would come maybe as a liquid, maybe as a  
18 solid. Those would be the two sort of categories.  
19 Which of the two do you choose? That kind of stuff.

20 So to really get down to the gummy, I  
21 had to use some pretty extensive natural language

1 processing. Get some data people involved. I had to  
2 read through 2,700 records to basically give you this  
3 slide. I went back ten years.

4           So you see that there's a rapid uptick  
5 in the year 2019/2020 or so in our gummy ingestions.  
6 Now the State of Connecticut is about 3.4 million  
7 people. It's about one percent of the entire  
8 population of the United States. It has a  
9 proportionality of Hispanic or Latinx people and black  
10 people and -- that it's very, very similar to the  
11 distribution in the United States.

12           So often when we pick up a signal at  
13 the Connecticut Poison Center, we just multiply it by  
14 100, roughly, and it gives us an idea of what's going  
15 on nationally. So again, just use that a little bit  
16 as you're looking at this.

17           But you see that my staff are -- my  
18 poison specialists are answering 400 or so such calls  
19 per day. That more than one per day in the State of  
20 Connecticut. Again, multiply that and you get into a  
21 lot.

1           And we heard this morning that these  
2           are calls about gummies. Any gummy, really. And we  
3           heard this morning that there is predicted over the  
4           next ten years or so, a five to six-fold increase in  
5           gummy activity, gummy market. So multiply this by 100  
6           and multiply this by six and this is where we are in  
7           2030. We're really talking not quite millions of  
8           exposures, but a lot of exposures. So just realize  
9           that this is getting to be a problem, and the signals  
10          are there.

11           But what happened during those years?  
12          What happened in 2019? What happened in 2020? So  
13          this is again where I had to do a lot of digging. And  
14          these are -- read them from left to right, and then  
15          the first line and then a second line and so on and so  
16          forth. It's those same ten years and I looked at  
17          every single product and I reclassified it into a  
18          vitamin or a multivitamin. That would be the blue.  
19          And then the Melatonin, which would be the dark  
20          orange. And then we have others.

21           So in terms of vitamins, it doesn't

1 matter if it's a children's vitamin, if it's a  
2 prenatal vitamin, it's a multivitamin for adults, a  
3 hair and nail vitamin. I had all kinds of different  
4 vitamins there. Ascorbic acid only. Vitamin D.  
5 Vitamin -- they all got classified into vitamins in my  
6 book, and that became vitamins. And then Melatonin  
7 was pretty much Melatonin.

8           So the others in there, there are some  
9 laxatives out there that are in gummy form. There are  
10 some probiotics, I believe, that are in gummy form.  
11 Couple of other things.

12           Funny enough, none of them -- and maybe  
13 some of you are veterinarian pharmacists, but none of  
14 these were veterinarian preparations. There are  
15 chewable-ish preparations, you know, for dogs and cats  
16 and so on and so forth. None of them were. I was a  
17 little bit surprised about that. And maybe I just  
18 didn't read the cases. Again, 2,700. There were a  
19 lot. But anyway, just letting you know about that.  
20 You see elderberry making a bit of an entry there as  
21 well in 2019.

1           But I think if you look at this, you  
2 see the blue, the amount of blue reduces, but remember  
3 you have a proportionality issue here. The total  
4 number goes up. So, you know, you have to kind of do  
5 those gymnastics in your mind.

6           And what I mean by that is for example,  
7 in the year 2021, we answered around 170 such calls  
8 that involved vitamins -- excuse me, 152 that involved  
9 vitamins. And it was 227 that involved vitamins in  
10 2013. So, you know, yes, we're answering less calls  
11 about vitamins but how big is that.

12           And in 2022, it's 175 for vitamins. So  
13 again, how much did our vitamins, our actual number of  
14 vitamins go up or down. Not that much.

15           But what really, really strikes you is  
16 that orange, that dark orange piece of pie. And it  
17 goes up and up and up, and you see it really starting  
18 to take off in 2019 in a significant way. 2020,  
19 significant way. It takes over vitamins, really, in  
20 2021, and it's reduced a little bit in 2022. So it  
21 seems like Melatonin gummies is really the explanation

1 for that uptick in those years.

2 This was somewhat picked up by CDC. So  
3 the CDC put up an MMWR on Melatonin ingestions in  
4 children, and they noticed or published an increase  
5 in, again, Melatonin exposures in children. And they  
6 explained it by the fact that COVID had something to  
7 do with it. People just purchased more Melatonin  
8 during COVID.

9 I would argue that that might be part  
10 of the reason, but I think really if you look, their  
11 increase is 20 -- most notable in 2019/2020, which is  
12 when our gummies in Connecticut seem to really have  
13 taken off. I think that's what -- part of the  
14 explanation as well. There's a lot of gummy Melatonin  
15 out there, and that's what we're seeing.

16 NEISS data that was already explained  
17 to you a little bit. NEISS data is -- there are 5,000  
18 or so emergency departments in the United States.  
19 NEISS data has sampled, you know, a representative  
20 sample of 100 of them, collect data from these 100  
21 emergency departments. Those data are publicly

1 available. There were coded data in there and  
2 narrative data as well.

3 And those data were collected by a  
4 Texas poison center and presented at a meeting three  
5 weeks ago in Montreal. So I happened to kind of  
6 stumble on them. We had a great talk and we followed  
7 it up with some phone calls and some Zooms, so I was  
8 able to really get to what they were saying.

9 But this was a poster presentation. So  
10 because it was a poster presentation you won't be able  
11 to find it on Palm Med [ph] because it's a poster  
12 presentation. So I really kind of dug with them to  
13 try to get to what it is that they were doing.

14 But they did something very, very  
15 similar to what I was trying to show you with the  
16 Connecticut data. So those narratives are a little,  
17 you know, kind of handwritten or dictated, you know,  
18 stories. And they use natural language processing to  
19 look for the word "gummy," just like I did in my  
20 database, but this is a different database.

21 They went back 22 years; I went back 10

1 years. And their threshold is children under four.  
2 My threshold was children under six. Typically,  
3 poison center data is presented as children under six  
4 or children up to five years of age. Think of it  
5 whichever way you want. And I did it for much fewer  
6 years and I had, you know, 2,700 cases to go through.  
7 They did it for a total of 10 years and they had 193  
8 cases to go through. So their job was a lot easier  
9 than mine.

10 Okay, so this was a chart that they  
11 presented. So we again see a big uptick in the word  
12 "gummies" in these emergency department visit in  
13 children under four years of age. And you see my data  
14 showing an uptick in 2019, and their data showing  
15 again in boxes, but still pretty much showing the same  
16 thing.

17 And they separated their data as well.  
18 They had a proportion of Melatonin that was 50.3  
19 percent and multivitamins 24 percent. Just to show it  
20 with mine. This was 2021 for them, so I'm presenting  
21 2021. So I had vitamins at 39 percent; they had



1 vitamins at 24 percent. I had Melatonin at 44  
2 percent; they had Melatonin at 50 percent. Remember  
3 there's a bit of a difference here. Poison center  
4 data sometimes reflect what goes on in the household.  
5 Not everybody that we get called about gets referred  
6 to the emergency department. So it's a slightly,  
7 slightly different scenario.

8           And not surprisingly, because most  
9 multivitamins even when taken in excessive amounts,  
10 can be safely managed in the home. We tend to have a  
11 little bit more of sort of those and -- and they end  
12 up, because they're an emergency department, a higher  
13 proportion of Melatonin. Melatonin not quite as well  
14 tolerated in the home, so they get referred into the  
15 emergency department.

16           So bottom line, two databases that look  
17 at the same issue from different angles. Pointing  
18 really, really in the same direction. That we seem to  
19 have a problem with gummies in children. And  
20 "multivits" are part of the problem, but it sounds  
21 like Melatonin is part of the problem as well.

1           And I just want to reiterate. I don't  
2 know if you spent -- after doing all this, I went to  
3 my local retail pharmacy just to see, like, how are  
4 these Melatonin packaged? I want to see what this  
5 looks like and so on and so forth. So I spent a  
6 little bit of time at my retail pharmacy.

7           And if it's a Melatonin five milligram  
8 tablet, a tablet, not a gummy, a tablet, no child-  
9 resistant packaging. At least the products I saw. If  
10 it's a Melatonin gummy, child-resistant packaging. I  
11 just thought that was very, very interesting.

12           But the vast, vast majority of the  
13 gummies I had read about that I found on the shelf,  
14 get them over the counter, they're right there, were  
15 in child-resistant packaging. I didn't find a single  
16 one that was not in a child-resistant packaging. And  
17 you know what that means. I mean, it's just like a  
18 push and turn and all that kind of good stuff.

19           Okay. So I want to take a little bit  
20 of a deep dive or take you on a little bit of a  
21 journey to look at the medical literature and where my

1 next recommendation or my next point comes from.

2 It's Halloween. I put some Halloween  
3 candy there, but there's a reason for that. Big  
4 advocate of unit dose packaging. Individual wrapping.  
5 I think -- I think it's something we need to spend  
6 some time thinking about.

7 So the first time we kind of thought  
8 about this in poison center circles was with -- this  
9 was published in 2005. It doesn't translate well  
10 here, but this is a publication from 2005 from Milton  
11 Tenenbein, one of the titans in poison center circles.

12 Some of you might be old enough to  
13 remember how iron used to be prescribed and how iron  
14 kind of made -- the different iron salts and so on and  
15 so forth. But just to give you a recap, in the 1990s  
16 and before, iron ingestions in children were  
17 problematic. Associated with deaths every year in the  
18 United States.

19 And when you did a little bit of  
20 digging, you figured out pretty quickly that it was  
21 usually the ferrous sulfate preparation that was the

1 problem. The typical ferrous sulfate preparation is  
2 325 milligrams with 65 milligrams of elemental iron  
3 per unit dose. A typical ten-kilogram child needs  
4 only seven or eight tablets to get into the toxic  
5 range. A few more than that to get really in the  
6 lethal range. There's ferrous gluconate out there,  
7 there's ferrous fumarate. There are now  
8 polysaccharides. A whole host of different iron  
9 preparations.

10 But by and large, the ferrous fumarate  
11 and ferrous gluconate salts are usually actually found  
12 in the over-the-counter market, but they're usually  
13 not nearly as problematic as ferrous sulfate. We knew  
14 that in the 1990s.

15 And we approached a number of agencies,  
16 including the FDA, to do something, do something, do  
17 something. And some of you that are old enough to  
18 remember will remember that in 1997, something changed  
19 dramatically about the dispensing of ferrous sulfate  
20 products in the entire United States.

21 Of course it wasn't child-resistant

1 packaging. Had been, because of the 1970s, Child  
2 Prevention Act, you know, it had to be in  
3 child-resistant packaging. Oh, but change was on top  
4 of child-resistant packaging. These ferrous sulfate  
5 preparations, again, ferrous sulfate 325 with 65  
6 milligrams of elemental iron per unit dose, had to  
7 also be in a blister pack.

8           So for you that are pharmacists, you  
9 understand what that means. Blister pack in a  
10 child -- the bottles were huge because you had to fit  
11 the blister packs in there.

12           I invite you to go get this  
13 publication, because it still to this day sends chills  
14 down my spine. And I'm afraid I didn't copy the table  
15 for you, although I have it written there -- printed  
16 there for you. It looks at the number of deaths prior  
17 to 1997 and after 1997. Therefore, 1998, zero. 1999,  
18 one. 2000, zero. The 1999 death, I believe, was to a  
19 pre-1990-date product.

20           It's just chilling to see deaths,  
21 deaths, deaths, and then zero, zero, zero. An

1 absolute marvel of, you know, kind of public health.

2 So we learned from that that  
3 child-resistant packaging has its limitations. But  
4 adding unit dose packaging seemed to really strengthen  
5 that public health measure.

6 So this was looked at by other people.  
7 This is a publication from actually Rocky Mountain  
8 Poison Center, their RADARS project. For those of you  
9 who don't know, Buprenorphine wasn't available as a  
10 sublingual lozenge initially, but then the  
11 manufacturer made it into a sublingual film. We have  
12 bioavailability issues with Buprenorphine, so it has  
13 to be administered sort of intrabuccally or under the  
14 tongue.

15 And the film looked a little bit like  
16 the Listerine -- you know, if you've seen them. But  
17 in so doing that, they -- so it's kind of difficult to  
18 put films, I guess, in a bottle and they would be --  
19 when exposed to moisture, they would kind of crumple  
20 up or whatever. There were issues with it.

21 So they packaged every sublingual film

1 in an envelope. A foil envelope. It actually had a  
2 barcode on it. But as you were dispensed your  
3 Buprenorphine, it's actually Buprenorphine Naloxone.  
4 This is a Naloxone product. But anyways, so you  
5 opened up the bottle, child-resistant bottle, and then  
6 in it you would have a number of those little  
7 envelopes. And then you would use those envelopes and  
8 so on and so forth.

9 But it's unit dose packaging just like  
10 the iron was unit dose packaging, in a child-resistant  
11 packaging. And they, too, were capable of showing  
12 that when you zero in on that product and look at  
13 poison center data, you can clearly, clearly show that  
14 the number of unintentional pediatric ingestions  
15 plummeted after the introduction of this product. So  
16 yet another engineering that resulted in sort of  
17 public health good.

18 And lastly, this is from the UK. I  
19 just want to mention this. In the UK, they have a  
20 problem with Acetaminophen over there. Paracetamol is  
21 what they call it over there. They have a lot more

1 overdoses than we have here in the United States per  
2 patient population.

3           They decided to address this by  
4 limiting a number of things, but one of the things  
5 they did was to make their Paracetamol blister packs.  
6 And it didn't so much influence pediatric dosing. Or  
7 it may have. If it did, they didn't publish it. But  
8 what it really, really helped was decrease the number  
9 of teenagers' suicidal ingestions that were severe and  
10 resulting in death, because they had to do the blister  
11 pack thing and that takes a lot of time, this that and  
12 the other.

13           So just another example of how unit  
14 dose packaging seems to do some public good. So I've  
15 shown you three aspects of the medical literature that  
16 really, really support sort of unit dose packaging.

17           And lastly, my last point would be on  
18 embossing and imprints. I have no idea how you can  
19 emboss or imprint anything on a gel, but embossing and  
20 imprinting is important. It may not be important to  
21 you in the room, but it's definitely important to us



1 in poison center circles.

2           You have no idea how many times a child  
3 gets into the tablet, and the only thing that we have  
4 to indicate what the child got into is the other  
5 tablet the child did not ingest, and it's got an  
6 imprint on it. And that's all we have to for -- or go  
7 with.

8           And so being able to quickly identify  
9 the ingredients in a pharmaceutical product, based on  
10 the tablet imprint, is essential to the functioning of  
11 poison center. I'm an emergency physician. It's  
12 essential to my functioning as a physician.

13           We get calls also from law enforcement.  
14 They arrest people, they have pills in their pockets,  
15 and we're trying to figure out what's going on with  
16 all of this. Again, tablet imprints, very, very  
17 helpful. So I don't want this discussion to not touch  
18 upon the importance of either embossing or a tablet  
19 imprint.

20           So lastly, I hope I've convinced you of  
21 the public health implications of what it is that

1 we're discussing today. If you were to ask me my  
2 personal opinion, my personal opinion is let's not go  
3 down the chewables. Let's not go down the gel route.  
4 Let's not have all these over-the-counter products in  
5 gel forms. We've shown children will get into them,  
6 and it's going to be a serious problem.

7 But if the train or that horse has left  
8 the barn or the train is now on the train tracks,  
9 whatever, then strong, strong, strong guardrails.  
10 Very strong guardrails. And I would urge everybody in  
11 the room to think about unit dose packaging beyond  
12 just child-resistant packaging, as well as all the  
13 measures that I talked about. So thank you.

14 DR. MCCLARY: Thank you once again, Dr.  
15 Doyon.

16 So we're running a little over time,  
17 but our third panel will run from 3 to 3:50, but given  
18 our time, I'm still going to suggest a short break. A  
19 five-minute stretch break just until 3:05, and then  
20 we'll go ahead and get started with our panel session.

21 (Off the record.)

1 DR. MCCLARY: All right, so it is now  
2 3:05, so we will now get started with our third and  
3 final panel session. Again, all of our speakers for  
4 this session previously, they are joining us again for  
5 the panel. So as a reminder, we have Dr. Cyndi  
6 Connolly, Dr. Jennifer Lind, Dr. Christopher Hoyte,  
7 and Dr. Suzanne Doyon. And in addition to our  
8 panelists, in person we have Ms. Maribeth Sivilus, who  
9 is also joining us virtually.

10 And this panel discussion will go until  
11 3:50. And now it's my pleasure to introduce Dr.  
12 Kristine Parbuoni, who will be moderating this  
13 session. So Dr. Parbuoni is an associate professor at  
14 the University of Maryland School of Pharmacy in the  
15 Department of Practice, Sciences, and Health Outcomes  
16 Research.

17 Dr. Parbuoni is a pediatric clinical  
18 pharmacy specialist and also serves as the director of  
19 post-graduate training at the University of Maryland  
20 School of Pharmacy, so welcome.

21 DR. PARBUONI: Thank you, everyone.

1 I'm excited to be here, and thank you all for sticking  
2 around. I realize it's the last session of the day.  
3 Hopefully you all learned as much as I have from all  
4 of our great speakers.

5 And I would like to share I also work  
6 at the pediatric ICU at University of Maryland  
7 Children's Hospital and I've taken a lot of patients  
8 in who have come in with poisonings and made my own  
9 calls to the poison centers, and actually spent some  
10 time in a poison center when I was a resident  
11 learning. So I appreciate all of you guys' input.

12 I want to first start off with asking  
13 each of you the question of the day. What would you  
14 define a candy-like drug product to be, from your  
15 professional perspective, and what characteristics  
16 maybe contribute to that definition for you?

17 And maybe if we can start with Dr.  
18 Connolly?

19 DR. CONNOLLY: Sure. You can hear me;  
20 correct? All right. So I'll answer that two ways.  
21 As a historian and trying to put myself back into what

1 those Aspirin makers or actually the developers of the  
2 broad spectrum antibiotics in the late 1940s/early  
3 1950s were in a major arms race to do the same thing.  
4 And this is all the FDA archives. You can see them  
5 writing back and forth, "We need to have a pediatric  
6 formulation."

7 I think they were consciously trying to  
8 get, again, color, flavor. Basically anything that  
9 they could appeal -- that could get children to take.  
10 And as much, like, that they could sort of say it  
11 tastes like your favorite candy, in an era where I  
12 think there certainly was not the knowledge about over  
13 ingestion and poison that we have now. And so it was  
14 a strategy to get kids to take medicine.

15 I guess I would say as a pediatric  
16 nurse, it's using growth and development knowledge and  
17 theory to deliberately manipulate taste, flavor,  
18 texture in order to make it appeal to children of a  
19 certain age. A two-year-old versus a three-year-old  
20 versus a four-year-old. And so I hope that answers.

21 DR. PARBUONI: Yeah, I love that.

1 Thank you so much.

2 Dr. Lind?

3 DR. LIND: Yes, sure. So at CDC, we  
4 actually don't have a formal definition. But I did  
5 chat with my colleagues about it, and some of the  
6 characteristics that we talked about that we think  
7 might make a drug product be more candy-like would be  
8 a lot of the things that have already been mentioned.

9 Appealing flavoring or taste, shape,  
10 color, consistency, smell, sugary coatings, or  
11 appealing packaging. Things that look like toys or  
12 candies that kids would know, would all kind of go  
13 into that, what we would classify as a gummy or a  
14 candy-like product.

15 DR. HOYTE: I don't have too much to  
16 add to what's been said already. I would just, you  
17 know, say that also when you look at those studies  
18 that look at, you know, some of these candy products,  
19 candy-like products, and whether or not people can  
20 tell them apart from the actual candy versus the  
21 medication, I would say really anything that we would

1 look at and reasonably we would say any reasonable  
2 person would look at it and have a sort of difficult  
3 time telling the difference between the two.

4 Because a little kid that's two, you  
5 know, we're talking about it from an adult standpoint,  
6 but a little kid that's two is not going to be able to  
7 tell those apart. And they're not really going to try  
8 to discern whether or not like, hey, is this candy or  
9 is this actually a medication?

10 So to me, the word "reasonable" comes  
11 in. What I mean by reasonable is thinking about a  
12 two-year-old. Would a two-year-old be able to tell  
13 those things apart, is sort of where I would also  
14 add -- put that definition.

15 DR. DOYON: I think the day started  
16 with I know it when I see it. I don't think anybody  
17 has a great definition for what a candy-like  
18 medication is.

19 I agree with what has been said before.  
20 I think it has a shape, the taste, the look, the feel,  
21 the texture of some existing candy. There you go.

1 But what about future candies? So it's a very, very  
2 difficult question to answer.

3 DR. PARBUONI: Dr. Doyon, I think one  
4 of my questions for you, I know you focused on  
5 gummy-like products, but I don't know if you saw in  
6 your investigations, were there other types of things  
7 that were candy-like maybe that weren't gummy focused  
8 or?

9 DR. DOYON: There are plenty of gums  
10 out there and different kinds of chewables. Again,  
11 are chewables candy? Augmented chewable. But there  
12 are plenty of gums. So I honestly didn't go into the  
13 gum products. That would be another deep dive.  
14 Probably another 2,000 cases. I just don't have the  
15 time.

16 But gum, I think, should be somewhat  
17 classified under candy. And I think most people  
18 consider gum to be candy. So again, very, very  
19 difficult to define candy.

20 DR. PARBUONI: Our next question asks,  
21 are there particular therapeutic classes of drugs that



1 pose greater risk if supplied in a candy-like  
2 formulation? Go ahead, yes, Dr. Doyon.

3 DR. DOYON: Oh boy, opioids big time.  
4 But you must remember there are a lot of people taking  
5 at home chemo-therapeutic agents. There's some stuff  
6 out that are really, really difficult.

7 We have a list at poison centers of one  
8 tablet can kill. So those definitely would make the  
9 list. Our calcium channel blockers, Bupropion in the  
10 strengths that it's available in. So there are many,  
11 many. As poison centers, we'll be able to give you a  
12 list.

13 In the realm of nonprescription  
14 products, again, we're talking over-the-counter stuff.  
15 Ibuprofen, Naproxen, Acetaminophen. I wouldn't say  
16 they're harmless, you know, the dose makes the poison.  
17 We have toxic doses for all these things. But, you  
18 know, one, two, or three candy, chewables, whatever we  
19 want to call them, gels, probably not so problematic.

20 But the controlled substances would be  
21 problematic. A lot of our cardiovascular medications

1 would be problematic. A lot of our psychiatric  
2 medications would be problematic. And a lot of our  
3 anti-epileptics to some degree would be problematic.  
4 So that's a lot of medications.

5 DR. LIND: If I could just add to that,  
6 because Dr. Doyon covered a lot of the things that we  
7 came up with, but one of the things we also said was,  
8 like, potential for abuse on the prescription side.  
9 But then on the OTC side, maybe potential for  
10 self-harm as well.

11 So products are -- you know, maybe  
12 teens or a little bit older adolescents might be more  
13 likely to utilize or use for self-harm. At least  
14 something to consider.

15 DR. HOYTE: I'll just add one of the  
16 medications, not to pick on any medication, but  
17 definitely not just the zero to five range, but as  
18 kids get older they want to -- you know, social media,  
19 hey, you can go and get high on certain medications.

20 So Diphenhydramine would basically be  
21 the poster child for that. That swallowing pills is

1 more difficult than chewing a gummy, and so you have  
2 to work a little bit harder to get the dose of  
3 Diphenhydramine you would need to get, quote, high  
4 and/or to see the toxic effects, the effects that we  
5 worry about.

6 Now that being said, we have plenty of  
7 people who get smart, they make vats of water, they  
8 put the pills in them, they make slurries out of them  
9 so they can drink those down. So people get smart  
10 with it. But a drug like Diphenhydramine, I would  
11 be -- also put on that list as well.

12 DR. CONNOLLY: And I guess I would  
13 conclude with sort of saying, again, historically I  
14 think people thought that -- you know, in the 1950s  
15 when prescription drugs were new, parents were --  
16 there's historical evidence that parents understood  
17 that those drugs might have some danger to them. That  
18 they didn't think, necessarily, with drugs that they  
19 were getting direct advertised in magazines, like  
20 Parents, that -- you know, the direct-to-consumer  
21 advertising for all drugs.

1           And I think anecdotally, as a nurse in  
2 the twenty first century, there are still a lot of  
3 people who don't really have a sense of the history of  
4 over-the-counter drugs and think that someone has  
5 tested them to make sure that they are absolutely safe  
6 for the -- you know, for all consumers.

7           And that -- so I do think that I don't  
8 know if it's as much a drug class as I would sort of  
9 say over-the-counter drugs partly because the  
10 ubiquity, partly because I think there is in some  
11 people, historically and today, a false sense of  
12 safety from them.

13           DR. PARBUONI: And I'll say I  
14 appreciated your Aspirin historical perspective. We  
15 had just put out some data from the last 20 years of  
16 Aspirins ingestions, because as a pediatric pharmacist  
17 I feel like it had been engrained in me, you know, no  
18 Aspirin for kids, no Aspirin for kids, except for the  
19 small group of people.

20           But there's still Aspirin ingestions  
21 and exposures and there's still 2,000 a year reported

1 to poison centers, you know, and I definitely didn't  
2 expect to see that data that it's still out there as a  
3 potential harm for our kids, even though it's over-  
4 the-counter and we've gotten rid of the, you know,  
5 child flavor. They're still taking it.

6           Considering current strategies for  
7 reducing the risk of accidental exposure of drug  
8 products, what role does labeling and packaging play?  
9 And I think Dr. Doyon spent a little bit of time on  
10 that, but any other thoughts on how that can help us  
11 limit the abuse of these candy-like dosage forms for  
12 other products?

13           DR. LIND: So I can chime in a little  
14 bit. One of the things that we didn't mention in  
15 terms of the packaging, also sometimes the  
16 over-the-counter product, they tend to be transparent  
17 bottles as well. So, you know, you have these bottles  
18 with gummies and things and they're all these assorted  
19 colors. To a young child, a two-year-old, they can't  
20 tell the difference. So maybe considering having the  
21 packaging be opaque so it's less appealing for kids to

1 try and, you know, break that barrier.

2           Also having, you know, pills in unit  
3 dose packaging. We've mentioned that as a good way to  
4 limit some of the access. But then also within the  
5 bottle, maybe individually wrapping. I know some of  
6 the chews are individually wrapped within the  
7 packaging, so even if the child breaks the  
8 child-resistant barrier, then there's still that kind  
9 of having to open up each individual one which might  
10 limit some of the access.

11           DR. PARBUONI: Go ahead.

12           DR. DOYON: So something I forgot to  
13 mention. So as you have unit dose packaging, so of  
14 course it creates an extra barrier for the child to  
15 get into the product, which means it's going to take  
16 more time to get into the product. The more time it  
17 takes, the longer the parent has to discover,  
18 intervene, stop, and so on and so forth. So I think  
19 about it that way as well.

20           And something else to remember. We get  
21 called -- the poison center gets called and child got

1 into the bottle of gummies. And you're like, well,  
2 how many did they get into? Again, the dose makes the  
3 poison. Oh, I don't know, you know, the bottle -- if  
4 you have individual unit dose packaging, well, how  
5 many empty wrappers are there? Or how many broken  
6 blisters are there? I don't know, whatever it is.  
7 Five.

8 Okay, that's something I can work with  
9 and I can do some dose calculations and I can decide  
10 whether this is going to be a problem for your child  
11 or not as opposed to, "I don't know; the bottle is  
12 open. I don't know how many were in there. I don't  
13 know how many my child got into." We're like, okay,  
14 well then we send the child to the emergency  
15 department because worst-case scenario.

16 So keep that in mind. Unit dose  
17 packaging adds to the discovery time but also gives us  
18 a clue as to how many the child got into. All great  
19 critical kind of points.

20 DR. HOYTE: And I'm just going to put a  
21 plug in. So we are -- and by we, poison centers are

1 pretty sensitive to this because -- not because we're  
2 trying to be a pain but, you know, this is a public  
3 health institution. We've all heard the parable about  
4 the people walking along the river, people falling in  
5 the river, we jump in the river to pull them out of  
6 the river, then right when you get out there's another  
7 person in the river, you have to jump in the river  
8 again and pull somebody out, and then finally we get  
9 smart, we go upstream and find out why people are  
10 falling in the river.

11           So the issue is, is that people think,  
12 "Oh, why can't people just be smart and parents be  
13 smart and just put their medications up?" Because if  
14 you put your medications up, these two-year-olds  
15 should not be able to get into it. We've seen over  
16 time that's not the case. People accidentally leave  
17 their medications out.

18           People go to their grandparent's house.  
19 The grandparent is not accustomed to having a child  
20 there, they leave the medication out. And as Dr.  
21 Doyon said, some of those medications are some of the



1 most dangerous ones.

2                   And so the point of my -- what I'm  
3 getting -- I'll get off my soapbox, but my point is  
4 saying we cannot rely on everyone to all the time have  
5 medications put in the right place. And so these  
6 other strategies that people are talking about will, I  
7 agree with Dr. Doyon, will limit the access of little  
8 kids to these. And if we can do that, then I think  
9 that that's a victory for everybody.

10                   DR. CONNOLLY: I'll just conclude by  
11 saying yes, I think it's for -- safety packaging is  
12 one prong, all right, in a multifaceted educational  
13 campaign. Packaging and others.

14                   And I guess I would sort of, in terms  
15 of safety packaging, Dr. Doyon made me think of the  
16 importance of slowing down the child from getting into  
17 that packaging. I don't know that it is possible to  
18 build a -- you know, a package that a three-year-old,  
19 a determined three-year-old really can't get into with  
20 an unlimited time.

21                   And if you ever just have unlimited

1 free time and you want to have some fun, go back and  
2 look -- and I could certainly tell you where they are.  
3 The time motion studies that led to the early safety  
4 caps. The pediatricians and the engineers are  
5 incredibly frustrated. A famous poison control --  
6 anti-poison doctor, a toxicologist from University of  
7 Utah, presents to Congress in, I think, 1969, and  
8 he -- because Congress is saying why is it taking you  
9 so long to develop this cap.

10           And he says we have one that we were  
11 sure. Right? Nobody could get into this -- this  
12 bottle. But this was still the year of glass  
13 packaging. And so they gave it to a room full of  
14 three-year-olds and one little three-year-old takes it  
15 and cracks the glass on the edge of the table, which  
16 of course no adult had thought to do. The glass  
17 shatters, it goes everywhere, and the kids are into  
18 what was sugar tablets.

19           And so they -- it was -- again, a bunch  
20 of adults are -- it's always going to be very  
21 difficult to think like a three-year-old for us.

1           And they also -- and there is no visual  
2 on this that I can find, is that the safety cap  
3 committees, the partnerships between industry and  
4 academics, bring prototypes for the congressmen to  
5 play around with. And they all are very frustrated  
6 because they can't get into them. And again, I wish  
7 someone had thought to take a picture. It would have  
8 been great for my book, for this presentation, and  
9 just sort of for history.

10           DR. PARBUONI: Thank you. Maribeth, I  
11 didn't mean to exclude you from the conversation if  
12 you had anything to add to that?

13           DR. SIVILUS: No, not at this time. I  
14 guess just another anecdote, I guess related to the  
15 one that Dr. Connolly was just mentioning.

16           A while ago we really were digging into  
17 the history of all of this as well, and one of the  
18 things we came across was that one of the initial  
19 designs of the child safety packs, you know, they had  
20 tested and I think it was -- it limited. And then  
21 what they realized was that children were not

1 necessarily easy -- it wasn't very easy for them to  
2 open with their hands, but then some kids started to  
3 use their mouth and they were able to pry it open that  
4 way.

5           And so I think currently when they do  
6 the testing for using the Poison Prevention Packaging  
7 Act, the testing method, at some point in the testing  
8 I think the facilitators, you know, tell the children  
9 involved in the testing that they can use their mouths  
10 if they want to.

11           Because they might not necessarily do  
12 it if they -- you know, if they see observers watching  
13 them. But then given a prompt, well, feel free to use  
14 your mouth if you want to, then, you know, they might  
15 be more inclined to do so.

16           DR. PARBUONI: Children will find a  
17 way.

18           DR. SIVILUS: They will find a way.

19           DR. PARBUONI: Related to that, I know  
20 several of you have mentioned blister packaging being  
21 a potential way to slow down and to help with reducing

1 overdoses.

2                   On the flip side of that there is some  
3 concern about that not being maybe environmentally  
4 friendly or increasing waste, I guess. Any  
5 recommendations on how to balance the environmental  
6 factor versus the safety aspect?

7                   UNIDENTIFIED SPEAKER 2: I have not  
8 thought that far yet.

9                   DR. LIND: I have not either, but I  
10 mean, just in thinking, technology can do a lot and I  
11 know there are a lot of products that are  
12 biodegradable now, even like some straws and things  
13 like that. So I'm sure smart people could come up  
14 with a way.

15                   DR. PARBUONI: Thank you. Our next  
16 question is can you share any insights into candy-like  
17 characteristics that may lead adults to misuse or  
18 abuse some of these drug products?

19                   DR. HOYTE: So I can say for some --  
20 and this is pure anecdote. I have not done analysis  
21 on this. But the stories that I've heard from young

1 adults first is that they -- this is more therapeutic  
2 misuse. Is that they believe that the gummy -- well,  
3 sorry. Different formulations. They're safer, so you  
4 can take more of them and it's okay to take more of  
5 them because they're -- because of the way they're  
6 formulated.

7 That they don't think it's like taking  
8 a pill. And so they think that the dose they're  
9 getting is not going to make them sick. So they think  
10 they can take more of them. I've heard that multiple  
11 times from -- especially from young adults.

12 DR. PARBUONI: It's made for kids. It  
13 must be safe for everyone.

14 Do we have any insights from pediatric  
15 medication overdose prevention efforts that might  
16 extend to the geriatric population? Are there  
17 differences in medication management challenges with  
18 pediatric versus adults?

19 DR. HOYTE: I'm going to say it the  
20 opposite way. So one of my colleagues actually did a  
21 study looking at pill minders for our geriatric

1 population. And we had been -- and to be said, the  
2 confounding here is that these are calls to the poison  
3 centers, based on the inappropriate and the inaccurate  
4 use of their pill minders for their medications. It  
5 is not uncommon for our geriatric population to  
6 accidentally take wrong medications out of a pill  
7 minder.

8           So I've heard some -- you know, we've  
9 talked about -- some people have actually talked  
10 about, well, maybe we should use pill minders for  
11 pediatric patients also, because normally their  
12 parents will be giving them the medication. So it'd  
13 be in a pill minder; it'd be hard for them to get into  
14 it.

15           People are looking at that now. I  
16 don't know if that's going to be any better or not.  
17 I'll leave that to people with more expertise here who  
18 deal with that. But I know that people are looking at  
19 that, going back from taking it from the geriatric  
20 population down to the pediatric population for using  
21 pill minders.

1 DR. DOYON: You would think pill  
2 organizers would take care of problems, but my gosh.  
3 They take their evening dose instead of morning dose.  
4 They forgot they've taken -- it's Tuesday and they go  
5 to the Tuesday and the Tuesday is empty. So it's like  
6 they have no idea, oh no. Husband and wife. He takes  
7 hers; she takes his. Two different pill organizers.  
8 Oh my gosh, the scenarios are multifold.

9 But bottom line is pill organizer is  
10 not the solution, and I have a particular issue with  
11 filling a pill minder with candy-like medications. I  
12 think that's just a recipe for disaster.

13 DR. CONNOLLY: I think a real  
14 challenge, of course, is that we expect, in the United  
15 States, we have so few social supports, we expect  
16 until people are very old and really quite cognitively  
17 impaired, that they're going to have to manage their  
18 medications completely on their own.

19 And I would sort of say, as one of  
20 those people who uses a pill minder, again I think it  
21 was you, Dr. Doyon, mentioned, I do find it very



1 useful when there is some kind of notation, a number  
2 or something inscribed on the pill. Because when I'm  
3 trying to figure out whether I've dropped my Losartan  
4 or my Statin and they're small white pills, I just  
5 sort of throw them both away unless I can somehow  
6 identify them by the other pills in the bottle.

7 So I guess I do think that that has  
8 potential for help for across the board, but certainly  
9 for older people who tend to take more medications  
10 than younger people.

11 DR. PARBUONI: Our next question from  
12 the audience, I believe, is how do parents perceive  
13 gummies for their children? Are parents more likely  
14 to overdose their own children using gummies or  
15 candy-like drugs just because of the dosage form that  
16 they are? Any insight from reports?

17 DR. CONNOLLY: I think parents really  
18 want to do well by their children. The overwhelming  
19 majority of parents want to do the right thing for  
20 their children, so they would never set out to  
21 overdose their children. That would not -- you know,

1 I'm just going to be very frank about this.

2           However, I did see some patients over  
3 the weekend, because I was working shifts, and I did  
4 have a six or seven-year-old that was starting on an  
5 antibiotic, and the first demand or ask from the  
6 parents is, "Is this antibiotic available as a  
7 chewable?"

8           So I do think that parents are seeking  
9 the chewables. And again, when you're age five or  
10 six, are you on liquids, can you take pills? You  
11 know, that's kind of that nebulous area there.  
12 Usually teenagers pills are okay, younger children  
13 liquids are okay. But at that age group, whatever.

14           And so parents are starting to ask for  
15 chewable preparations. This antibiotic was not  
16 available in chewables, so there you go.

17           DR. HOYTE: I just, again, anecdotally,  
18 I think that with the question that you asked, there's  
19 definitely something to that. I think, you know, the  
20 standard pill form, you know, that everyone has had  
21 and using certain medication that have been in pill

1 form, I think the parents -- I don't think that all  
2 parents would do this, but I think that some parents  
3 would have the idea, erroneously, that they could take  
4 more of a gummy-like medication or that it's somehow  
5 safer than a pill or whatever that is.

6 I think that anecdotally I have heard  
7 that from people. But I don't know, over a  
8 population, how that would look. But just in select  
9 cases, I've definitely heard that sort of sentiment.

10 DR. SIVILUS: This is Maribeth Sivilus  
11 online. I just wanted to add that another  
12 characteristic of the product that I thought that  
13 might lead parents or caregivers to just assume  
14 that -- some of these products that we know in gummy  
15 form that are currently available.

16 That, you know, I can see in my house,  
17 you know, I have two kids under six, and they take a  
18 multivitamin, it is a gummy form, and the dose for  
19 that is four gummies each.

20 And so, you know, having a dose that's  
21 so many individual units also might lead one to think

1 that, well, these things are harmless because, look, I  
2 have to take four every single time I take some. And,  
3 you know, my kids are very attuned to all of this as  
4 well. So if I'm running low on them, you know, I'll  
5 give them three. Or if I don't have anymore they'll  
6 say, "Wait a minute, you missed one. I'm supposed to  
7 get another one."

8                   And then another issue that we've run  
9 into with some of our analysis with the Melatonin work  
10 is, you know, we're looking into additional details  
11 from these case narratives. The text information. We  
12 have some information about how many units, you know,  
13 the children got into, what was the strength of the  
14 unit.

15                   And then for Melatonin it becomes quite  
16 an issue because we found that they -- you know, we  
17 found the dosage is small, the individual unit is as  
18 little as .3 milligrams, all the way up to 60  
19 milligrams for just one unit. And so, you know,  
20 trying to figure out, you know, what they got into,  
21 how many, and what could the dose have been, the total

1 amount ingested has been very difficult.

2 DR. PARBUONI: Melatonin is tricky.  
3 Various reasons going into pediatric patients.

4 Are there any cultural or demographic  
5 factors that influence the risk of accidental  
6 exposures to candy-like medicines? Anything that  
7 you've been able to see from some of your data  
8 analysis?

9 DR. HOYTE: I haven't looked, but now  
10 you gave me a good idea.

11 DR. PARBUONI: There you go.

12 DR. LIND: Same here. I didn't look at  
13 the social determinants of -- so I cannot answer that.

14 DR. CONNOLLY: I would just add that in  
15 the safety cap work in the 60s, they're not collecting  
16 a lot of data about families, but they do want to know  
17 marital status of the mother, and they are looking for  
18 race and income of the family. I don't know how they  
19 thought they'd use that information. They're not  
20 looking for anything else, but those are particularly  
21 important.

1           It made me think of sort of things that  
2 would have been biases that were sort of -- that were  
3 not even beginning to be acknowledged in the practice  
4 of -- of medicine or nursing or healthcare.

5           DR. PARBUONI: Hopefully the  
6 manufacturers that are maybe on the call are listening  
7 to making sure that these are -- if we're packaging  
8 them more safely that they are still financially  
9 available to all people and not priced at a point that  
10 is going to disadvantage some others.

11           One of the questions from online is  
12 could some of the poison center calls on gummy-related  
13 concerns be calls related to choking versus  
14 overdosing?

15           DR. LIND: So we have a great way of  
16 coding for this. These are ingestions, oral  
17 ingestions. If they were aspirated or inhaled, the  
18 root of administration would have been different. So  
19 these are ingestions. They were oral ingestions.

20           DR. PARBUONI: Thank you for  
21 clarifying.

1 DR. LIND: And I should say there were  
2 no aspirations, no inhalations in the whole group.

3 DR. PARBUONI: I think that's all the  
4 questions I see from online. Do we have questions  
5 from the audience for the panel we have?

6 Yes, sir, in the back. I think we have  
7 a microphone coming to you.

8 UNIDENTIFIED SPEAKER 3: A lot of the  
9 conversations today went from category to category.  
10 We had drugs, supplements, and even cannabis. Do you  
11 think the category is important if we're going to be  
12 determining what's appropriate in each category? Or  
13 is it just across the board we should handle it all  
14 the same?

15 Does that make sense? Like, because,  
16 you know, it would be pretty easy to conclude cannabis  
17 shouldn't be in candy form. Right? But some of it,  
18 like fiber maybe, something with a high dose, hard to  
19 consume, things like that. Or does that sort of stop  
20 us from being able to solve the problem ultimately of  
21 accidental ingestion?

1 DR. HOYTE: It's a good question. I  
2 think it gets back to -- I think it gets down to what  
3 the goal is. And if we're trying to make sure that  
4 there are no accidental ingestions of kids, then I  
5 think, you know, it would have to be an across the  
6 board thing.

7 But I don't think, you know, if you  
8 look at -- if you look at all the substances these  
9 kids get into, not all of them are causing  
10 significant -- you know, significant injury to kids.

11 And so I think probably, this is my  
12 personal opinion, probably should be a little  
13 targeted. Look at our data, analyze it, you know,  
14 with all stakeholders and look at the data and analyze  
15 it and sort of make it a more targeted thing rather  
16 than going after every single substance on the market.

17 But that's what I would do, is target  
18 the ones that we think are going to be more dangerous,  
19 but I think probably there'd be some disagreement with  
20 that.

21 DR. DOYON: The second paper I quoted,



1 the one regarding the Buprenorphine, the Naloxone  
2 sublingual film, had a number of authors. And if you  
3 read their discussion and their conclusion, so of  
4 course they're talking about Buprenorphine and  
5 Naloxone. Buprenorphine is a prescription product.  
6 It's also a controlled product. So of course they're  
7 in that realm.

8 But they do make a good -- and I think  
9 they spent a lot of time thinking about this, but they  
10 do make a good point that they're advocating for  
11 single dose packaging for certain products that have  
12 been determined to be particularly problematic in  
13 children.

14 So I'll echo the comments of my  
15 colleague. Perhaps a targeted approach would be  
16 preferable. And again, there are people who have  
17 thought about this, thought about it for months, so  
18 I'm going to kind of take their thoughts and just  
19 communicate that to you. But I'd have to agree with  
20 that. Thank you.

21 DR. PARBUONI: Another question I've

1 seen from online is based on research data that you've  
2 seen, how likely do parents measure their liquid  
3 medications properly? How has it affected the number  
4 of overdoses or adverse reactions seen, especially in  
5 children, whether they're using teaspoons or MLs?  
6 This kind of speaks to me as a pediatric pharmacist,  
7 but I'll let you all share from your data.

8 DR. LIND: So I can jump in there. So  
9 in the presentation, I hope, you know, from the  
10 three-pronged approach we did talk a little bit about  
11 the medication errors. And while the vast majority  
12 were unintentional ingestions, there were a percentage  
13 that were medication errors, but only about five  
14 percent.

15 But, I mean, the good thing about this,  
16 it is generally preventable, you know, in terms of the  
17 med error. So a lot of times if it is in standard  
18 metric units that we have found and studies have shown  
19 that that decreases the risk of medication errors for  
20 parents.

21 There was -- or there has been in the

1 past a perception that maybe parents may not  
2 understand milliliters. And that, you know, there's  
3 this perception, oh, we need to put teaspoons or  
4 spoon-based units as well on there. But studies of  
5 health literacy have shown that parents actually do  
6 understand milliliters. And then by having the single  
7 metric unit only dosing or units on dosing devices  
8 that there are less, you know, errors with that as  
9 opposed to when you have both units or multiple units  
10 on a dosing device, that does increase the chance of,  
11 like, overdosing or underdosing depending on, you  
12 know, what the parent expects it to be.

13 And so yes, you know, that is  
14 definitely an issue. It is a much smaller percentage  
15 of what we're seeing in terms of ED visits. However,  
16 you know, we have found ways to prevent it.

17 And I don't know, I mean, Maribeth, do  
18 you have anything additional that you want to share in  
19 terms of data?

20 DR. SIVILUS: So in terms of the data,  
21 when we look a little bit more closely in what those

1 errors were, I mean, most of them were dosing errors.  
2 You know, we see some errors that are, you know --  
3 administration or maybe, you know, the -- was given by  
4 mistake. But most of them are dosing errors.

5 And then also most of them involve, you  
6 know -- most of them involved liquid medications. And  
7 we don't always have the level of detail to see what  
8 the underlying or the root cause was, but some of the  
9 ones that Dr. Lind just mentioned were, you know,  
10 mixing different units of measure. Maybe using  
11 household spoons to administer medication also can be  
12 problematic because, you know, they're not  
13 standardized in any way. You know, there's -- and  
14 such.

15 DR. CONNOLLY: I just want to relate  
16 just a scenario from this weekend. Again, I worked  
17 this weekend. Prescribing an antibiotic to a  
18 family -- to the child. And I was talking to the  
19 family. It's going to be one teaspoon twice a day,  
20 whatever.

21 And so this was a two-year-old. A

1 COVID baby. Right? And the parents were probably in  
2 their late 20s. And she goes, "I don't understand  
3 what a teaspoon is. Can you explain this to me in  
4 MLs?" And I was just so happy. Just so happy.

5 I think our young parents are moving  
6 towards the metric system. I think Acetaminophen is  
7 now dispensed with a syringe. They're getting used to  
8 it. And again, these young parents are really,  
9 really -- they all want to do the right thing for  
10 their child.

11 So I was just -- and I was like, "Do  
12 you have a syringe at home? You're used to syringes."  
13 Well yeah, talk to us in syringes, kind of syringe  
14 language. I was more than happy to do that. And  
15 again, I'm sharing the story with you so this tells  
16 you how happy I was with the story.

17 DR. MEYERS: So I just want to add to  
18 that. So Rachel Meyers, pediatric pharmacist, again,  
19 so I love that. I think one thing FDA could do to  
20 help us with that is stop labeling the medications for  
21 5 ML. All the antibiotics, like Amoxicillin, 400

1 milligram per 5 ML.

2                   That is from the era of when we dosed  
3 in teaspoons, and that era is gone. And that is one  
4 of my biggest wishes. It needs to be just per ML.  
5 Nobody cares how much per 5 ML anymore. It's not  
6 relevant information.

7                   DR. PARBUONI: Too much math. And this  
8 would apply to over-the-counter products also. Not  
9 just the antibiotics. But the Tylenols, the  
10 Ibuprofens, all that stuff over the counter.

11                   Yes, in the back?

12                   UNIDENTIFIED SPEAKER 4: So we've had  
13 some interesting suggestions about packaging and  
14 things like that. And, you know, just reminded me  
15 something from the past and I was wondering. Does it  
16 make sense in the context of supplements and, you  
17 know, nonprescription medications in general, to have  
18 some kind of a symbol that makes it very easy to  
19 communicate?

20                   You know, like back in the day there  
21 was a radioactive symbol that would be put on a lot of

1 things. It was a very clear indication that, you  
2 know, this is something that's dangerous. And, you  
3 know, to just highlight the fact that, yes, you're  
4 using it as a supplement, you're using it as  
5 something, you know, which is over the counter, but  
6 there are consequences.

7 DR. HOYTE: I will say, without naming  
8 the substance, but being from the State of Colorado,  
9 and I'm not talking about mushrooms, that being from  
10 the State of Colorado, exactly what you're saying on a  
11 particular product where people have now gone off and  
12 made things that look like candy or energy drinks or  
13 all sorts of things, by law now we got passed that you  
14 have to put a particular symbol that denotes that kind  
15 of substance it is so that when people go to take it  
16 they know exactly that, hey, just FYI, there is this  
17 particular substance here, just in case you didn't  
18 know that.

19 And so I think, you know, we don't want  
20 to do too many symbols, I think, because then there's  
21 a confusion to that, but to your --

1 UNIDENTIFIED SPEAKER 4: No, just one  
2 universal symbol that basically says this can be a  
3 drug and could be toxic, you know, something.

4 DR. HOYTE: Right. Yeah, no, I think  
5 you're making a good point. It's another potential  
6 deterrent upstream to, you know, reduce the risk of  
7 somebody getting something that they didn't really  
8 want to or not knowing the risk of what they were  
9 taking or whatever it is. So it seems to have worked  
10 in Colorado at this point.

11 DR. DOYON: I think that suggestion is  
12 going to have to be refined a little bit because the  
13 dose is the poison. Water, in enough quantity, will  
14 kill someone. Do we need labels on water? I'm being  
15 facetious here, obviously, but I think it's a little  
16 bit more complex than just sticking a logo and doing  
17 something like that, so.

18 DR. PARBUONI: I think I found one  
19 question I might have skipped over earlier. Focusing  
20 on the OTC drug product market, what are the most  
21 common drugs involved in poisonings? And I think we



1 focused maybe on gummy earlier, but I guess OTC drugs  
2 overall, the most common in poisonings.

3 DR. DOYON: So -- some of the Ibuprofen  
4 product, Naproxen products, but mostly Ibuprofen, and  
5 then Acetaminophen. We've seen quite a decrease in  
6 cough and cold preparations. If you look at data from  
7 the year 2000 to 2007, 2008, you have quite a few  
8 pediatric exposures to cough and cold preparations.  
9 The multi-symptom cough and cold preparations. But  
10 they've gone down tremendously, and we have plenty of  
11 data to show that.

12 The reason they went down so much is  
13 because of the voluntary withdrawal, based on an FDA  
14 recommendation, but the voluntary withdrawal of these  
15 cough and cold preparations for children under the age  
16 of four.

17 You're going to have trouble right now  
18 going to a retail pharmacy and finding a cough and  
19 cold product for your one-year-old or two-year-old or  
20 whatever. They are no longer available, so they're  
21 not bought by parents. They're not found in the

1 household. Children don't get into them, and  
2 therefore we have less calls and less ED visits.

3 So cough and cold preparations used to  
4 be quite high up on the list, but no longer. So it's  
5 back to our over-the-counter nonsteroidals or  
6 Acetaminophen products, and then maybe our  
7 antihistamines. And yes, Diphenhydramine was  
8 mentioned, but there's a lot of Loratadine and, you  
9 know, the second-generation antihistamine, so to  
10 speak. A lot of that being used in children as well.  
11 They have a lot of children formulations of these. So  
12 again, children get into those.

13 DR. PARBUONI: Any other questions from  
14 the audience? That's all I have. Thank you, all,  
15 very much for your time, and thank you for the panel.  
16 I'll leave it up to Brandon to close us out.

17 DR. MCCLARY: All right. Thanks again,  
18 Dr. Parbuoni, for moderating this session.

19 So again, I want to thank our  
20 panelists. Amazing discussion. And now we'll close  
21 out the workshop with final remarks from Dr. Terri

1 Michele, and director of the Office of Nonprescription  
2 Drugs here at FDA.

3 DR. MICHELE: All right. Well, I think  
4 I have to start with just wow. This has been such a  
5 terrific workshop. Just really excellent  
6 presentations. I've been so impressed. And I think  
7 the audience will agree.

8 I would like to once again thank all of  
9 our speakers, panelists, moderators, for all of the  
10 terrific information that we heard, the opinions.  
11 Just so much good stuff.

12 I think all of you who were here in the  
13 room saw me taking copious notes, and certainly we'll  
14 all be taking this back and there will be lots of  
15 discussion on all of these topics here at FDA.

16 So just reflecting back on what we  
17 heard, we heard from three very different panels. The  
18 first one was focused on manufacturing. The second  
19 one was focused on issues related to adherence. And  
20 the third was really focused on risks.

21 So for panel 1, we appreciated the USP

1 definition of a chewable gel dosage form for dietary  
2 supplements. And about some of the manufacturing and  
3 stability issues that can come up with these dosage  
4 forms. We also heard about some of the tricks of the  
5 trade that formulators use to mask the bitter tastes  
6 of drugs and the feel of drugs. I mean, certainly all  
7 kinds of things about taste that I never even knew,  
8 and yet it all makes intuitive sense when you hear  
9 about it.

10 And finally, we heard about some of the  
11 creative options that are becoming available, some of  
12 the newer technologies with 3D printing, all kinds of  
13 things we can do with individualized dosage forms that  
14 can be particularly useful for particular patients and  
15 particular challenges in formulation.

16 So this panel was very helpful in  
17 comparing some of the characteristics of candy with  
18 the characteristics of a typical drug product. And we  
19 heard that candies generally have sweeter taste  
20 palates, they have stronger aromatic flavors, novel  
21 textures, novel forms, brighter colors, creative

1 packaging. All kinds of things.

2 And I hadn't really thought about it,  
3 but that color really does make a difference in how  
4 you think about the flavor of something. So something  
5 to keep in mind.

6 Then in panel 2, we heard a little bit  
7 on the flipside. You know, some of the unique and  
8 rare circumstances where candy-like dosage forms are  
9 helpful to achieve a therapeutic intent. Certainly  
10 the example from our dental colleague was very useful.  
11 And some of the benefits of other creative dosage  
12 forms, like mini tabs and orally disintegrating  
13 tablets, as well as the benefits of maybe encouraging  
14 kids to be able to swallow tablets, because that's, of  
15 course, the best taste masking is if it never really  
16 gets much in your mouth.

17 An important takeaway that I took from  
18 all of these examples that we heard was that they were  
19 all used in very controlled circumstances. Under the  
20 direct supervision of a healthcare provider. And  
21 that's really just not the case in the OTC market.

1           So when we start to think about where  
2 do these fit in, we're hearing some great examples  
3 from the prescription world and a direct supervision,  
4 but maybe less in the OTC space.

5           Then in panel 3, we sort of focused on  
6 the risks. And we heard from some of our colleagues  
7 with poison control experience. We started off with a  
8 fantastic historical example of some of the unintended  
9 consequences that can happen when a dosage form tastes  
10 too good. I mean, I certainly grew up with the  
11 concept of a St. Joseph's Aspirin. And I remember it  
12 was such a rare treat to get to take one.

13           So something that we need to kind of  
14 keep in the back of our mind as we are exploring  
15 what's going on with these new and more candy-like  
16 dosage formulations.

17           The other thing that I think came  
18 through loud and clear from this panel is that  
19 children will get into anything, and children will  
20 especially get into anything that tastes like or looks  
21 like candy. They'll find a way. Kids are incredibly

1 creative. I'm always amazed at the things that they  
2 do that we never would have thought of.

3 We heard about some of the things that  
4 we can do, some of the tool in our toolbox as  
5 regulators, as manufacturers, a formulators, to try to  
6 protect against some of these things, related to, you  
7 know, child-resistant packaging. What an incredible  
8 benefit that has been for public health. Some of the  
9 newer flow restrictors and the unit dose packaging and  
10 how they has made a difference in certain  
11 circumstances.

12 But I think the perception also makes a  
13 huge difference in the market. You know, we heard  
14 that OTCs as a whole, and we've known this for a lot  
15 of years, are perceived by the general public to be  
16 less harmful or less risky than a prescription drug  
17 product.

18 And then that gets multiplied with some  
19 of these more candy-like dosage forms like gummies.  
20 So we have to think about that perception factor and  
21 how do we factor that in when we're thinking about

1 these formulations.

2                   So again, thank you to our panelists,  
3 to our speakers. We'll be taking all this feedback  
4 back. I can hear the conversations already going on.  
5 There's going to be lots of them. And I wish all of  
6 you a very pleasant day. Safe travels. And thanks  
7 again for joining us for this very important workshop.

8                   (Whereupon, the workshop concluded at  
9                   3:54 p.m.)

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## CERTIFICATE

I, RICHARD LIVENGOOD, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

*Richard Livengood*

RICHARD LIVENGOOD

Notary Public in and for the

State of Maryland

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## CERTIFICATE OF TRANSCRIBER

I, NICHOLE RYAN, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



NICHOLE RYAN

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