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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

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November 10, 2022

9:00 a.m. EST

PANEL MEMBERS:

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| Neil Bressler, MD | Chair/Member |
| Emily Chew, MD | Member |
| Bennie Jeng, MD | Member |
| Jose Pulido, MD | Member |
| Michael Repka, MD, MBA | Member |
| Jayne Weiss, MD | Member |
| Thomas Freddo, OD, PhD | Consultant |
| David Glasser, MD | Consultant |
| Young Kwon, MD, PhD | Consultant |
| Samuel Masket, MD | Consultant |
| Todd Durham, PhD | Consumer Representative |
| Rajesh Rajpal, MD | Industry Representative |
| Jennifer Schwartzott, MS | Patient Representative |
| Jarrod Collier, MS | Designated Federal Officer |

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FDA PRESENTERS:

Linh Lo, PhD
Regulatory Advisor, Office of Product Evaluation and Quality, CDRH
"Device Classification Overview"

Elissa Wong, PhD
Division of Ophthalmic Devices, OHT1, OPEQ, CDRH
"Classification of Ophthalmic Dispensers Under Product Code LXQ"

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CALL TO ORDER

Dr. Bressler: I would like to call this meeting of the Ophthalmic Devices Panel to order. I'm Dr. Neil Bressler, the chairperson of the Panel. I'm an ophthalmologist specializing in retinal diseases and a professor of ophthalmologist at the Johns Hopkins University School of Medicine. I'm also Editor in Chief of JAMA Ophthalmology.

I note for the record that the members present constitute a quorum as required by 21-CFR Part 14. I would also like to add that the Panel members participating have received training in FDA device law and regulations. For today's agenda, the Panel will discuss and make recommendations on the classification of ophthalmic dispensers, which are unclassified preamendment devices to Class I, subject only to general controls. This will include a discussion of the known risks and safety/effectiveness concerns and a general classification recommendation for ophthalmic dispensers.

Before we begin, I would like to ask our committee members and FDA attending virtually to introduce themselves. Committee members, turn on your monitors if you haven't done so and unmute your device before you speak. When I call your name, state your area of expertise, your position and affiliation. We'll start with Dr. Emily Chew.

INTRODUCTIONS

Dr. Chew: Hi, my name is Emily Chew, I'm a board-certified ophthalmologist medical retina specialist. I do clinical trials at the National Eye Institute. I'm the Director of the Division of Epidemiology and Clinical Applications.

Dr. Bressler: Thank you. Dr. Bennie Jeng.

Dr. Jeng: I'm Bennie Jeng, I'm a cornea specialist by trade. I'm practicing at the University of Pennsylvania, where I'm a Professor and Chair of the department and Director of the Scheie Eye Institute

Dr. Bressler: Thank you. Dr. Jose Pulido.

Dr. Pulido: Hi, Jose Pulido. I'm a vitreoretinal specialist and the Chair of Translational Ophthalmology, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania.

Dr. Bressler: Thank you. Dr. Michael Repka.

Dr. Repka: Dr. Michael Repka. Professor of Ophthalmology at the Wilmer Eye Institute, which is at Johns Hopkins University in Baltimore Maryland, I do ophthalmology and pediatric ophthalmology.

Dr. Bressler: Thank you, Dr. Jayne Weiss.

Dr. Weiss: I'm a cornea and external disease specialist at LSU Health Science Center, New Orleans. I'm Chair of the Department of Ophthalmology and a Professor of Ophthalmology, Associate Dean of Clinical Affairs and Chief Medical Officer, LSU Medical Network.

Dr. Bressler: Thank you. Dr. Thomas Freddo. We may not have Dr. Freddo here. I'm going to go on and let you know if he comes back on. Dr. David Glasser.

Dr. Glasser: Hi, I'm David Glasser, I'm a cornea specialist at Wilmer Eye Institute at Johns Hopkins in Baltimore.

Dr. Bressler: Thank you. Dr. Young Kwon.

Dr. Kwon: Hi my name is Young Kwon, I'm an ophthalmologist specializing in glaucoma and a Professor of Ophthalmology at the University of Iowa.

Dr. Bressler: Thank you, Dr. Samuel Masket.

Dr. Masket: Good morning, I am Dr. Samuel Masket. I'm a Clinical Professor of Ophthalmology at the Stein Eye Institute at UCLA, and my primary area of interest is anterior segment surgery, lens-based surgery in particular.

Dr. Bressler: Thank you. Dr. Todd Durham.

Dr. Durham: Good morning, this is Todd Durham. I'm with the Foundation Fighting Blindness. I'm trained as a biostatistician and outcomes researcher.

Dr. Bressler: Thank you. Dr. Rajesh Rajpal.

Dr. Rajpal: Hi, I'm Raj Rajpal. I'm a cornea cataract refractive surgeon practicing at See Clearly Vision in the Washington, D.C. area. I'm a Clinical Professor of Ophthalmology at George Washington University. And on this panel, I'm the industry representative as the Chief Medical Officer for Johnson & Johnson Vision.

Dr. Bressler: Thank you. Ms. Jennifer Schwartzott.

Ms. Schwartzott: Hi I'm Jennifer Schwartzott, I'm your patient representative.

Dr. Bressler: Thank you. Dr. Tieuvi Nguyen.

Dr. Nguyen: Hi, good morning, everybody. I'm the Director of the Division of Ophthalmic Devices at FDA.

Dr. Bressler: Thank you. And Mr. Jarrod Collier.

Dr. Collier: Hi, yes, Jarrod Collier. I'm the Designated Federal Officer for today's Ophthalmic Devices Panel meeting. Thank you.

Dr. Bressler: Thank you, everyone. Again, I'll let you know if Dr. Freddo joins us. Now, Mr. Jarrod Collier, the Designated Federal Officer for today's Ophthalmic Devices Panel, will provide the conflict-of-interest statement for today's meeting. Jarrod.

## CONFLICT OF INTEREST STATEMENT

Mr. Collier: Thank you Dr. Bressler and good morning everyone. I'll now read the conflict-of-interest statement.

The Food & Drug Administration is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC section 208, are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 USC section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have financial conflicts when it's determined that the Agency's need for a particular individual's services outweighs his or her

potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this panel who are special government employees or regular federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for the purpose of 18 USC section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, cradas, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda the Panel will discuss and make recommendations on the classification of ophthalmic dispensers, which are currently unclassified preamendment devices to Class I (general controls). This will include a discussion of the known risks and safety and effectiveness concerns and the general classification recommendation for ophthalmic dispensers. Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict-of-interest waivers have been issued in accordance with 18 USC section 208.

For the duration of the Ophthalmic Devices Panel meeting on November 10, 2022, Dr. Todd A. Durham and Ms. Jennifer A. Schwartzott have been appointed to serve as temporary nonvoting members. For the record, Dr. Durham serves as the consumer representative to the Dermatologic and Ophthalmic Drug Advisory Committee at the Center for Drug Evaluation and Research. Ms. Schwartzott serves as a patient representative, consultant to the Cellular Tissue and Gene Therapies Advisory Committee at the Center for Biologics Evaluation and Research. These individuals are special government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. The

appointments were authorized by Mr. Russell Fortney, Director of the Advisory Committee Oversight and Management Staff on October 13, 2022.

Dr. Rajesh Rajpal is serving as the industry representative, acting on behalf of all related industry. Dr. Rajpal is employed by Johnson & Johnson Vision. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue. A copy of this statement will be available for review and included as part of the official transcript.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak. Thank you all for much. I will now turn the meeting back over to Dr. Bressler. Thank you.

OPEN PUBLIC HEARING

Dr. Bressler: Thank you, Mr. Collier. At this time we will proceed with the Open Public Hearing portion of the meeting. However, no open public hearing speaker requests were submitted for this meeting. A written submission was received from Genentech, from which I'll read excerpts for the public attendees. The complete letter will be available on the meeting announcement page for the Ophthalmic Devices Panel of the Medical Devices Advisory Committee. I quote from the letter:

"Dear Mr. Collier, Genentech, a member of the Roche Group, appreciates the opportunity to submit comments regarding a notice of meeting of the Ophthalmic Devices Panel of the

Medical Devices Advisory Committee on November 10, 2022." Close quote. The letter goes on to say, quote, "Primarily, we ask that FDA clarify that the term 'ophthalmic dispensers' is limited to lower-risk, non-invasive, and non-implanted ophthalmic dispensers and will not encompass implantable drug delivery ophthalmic devices or pre-filled ophthalmic syringes that are intended to penetrate the eye. Products that are intended to be implanted into the eye or to penetrate the eye have different risk considerations from those for lower-risk ophthalmic dispensers not intended to penetrate the eye. Consequently, implantable drug delivery ophthalmic devices and ophthalmic syringes are likely to require additional regulatory controls to provide a reasonable assurance of safety and effectiveness, vis a vis ophthalmic dispensers not intended to touch or penetrate the eye." Close quote.

The letter goes on to say the following, quote: "We ask that the Agency make clear that it is not proposing for this class I classification discussion to encompass any ophthalmic dispensers that are intended to be implanted into the eye or to penetrate the eye." Close quote. Finally the letter states, quote, "We also request that in addition to the committee recommendations on the classification of ophthalmic dispensers, FDA should, in response to the committee meeting discussion, publish a more precise and complete regulatory definition of the term, quote, 'ophthalmic dispenser,' close quote, for purposes of any potential Class I classification rulemaking to make it clear that this term does not include more complex ophthalmic drug delivery devices, such as implantable drug delivery ophthalmic devices and prefilled syringes that deliver ophthalmic drugs." Close quote. The letter is signed by Eric Olson, Vice President and Global Head Product Development Regulatory Policy for Genentech.

The Panel may discuss the content of the letter while we are having our panel

deliberations.

So now I'm going to proceed to the FDA presentation. And I would like to invite the FDA representative, Dr. Linh Lo, to begin. I'll remind the public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate, except at the specific request of the Panel Chair. The FDA representative will have ten minutes to present, and so you may now begin your presentation. Thank you.

## FDA PRESENTATION — CLASSIFICATION OVERVIEW, DR. LO

Dr. Lo: Hello, my name is Linh Lo, and I'm a regulatory advisor within CDRH's Office of Product Evaluation and Quality. Today I'll be providing a high-level overview of the medical device classification process, which forms the basis of our discussion today.

The purpose of this panel meeting will be regarding the classification of devices that are currently unclassified. Specifically, for one pre-amendment unclassified device type, the Panel will be asked to provide input to the FDA on the appropriate classification: Class III, Class II, or Class I.

We begin by explaining the different classes of medical devices. Devices are classified based on the controls necessary to mitigate the risks associated with the device type. Class I devices are only subject to general controls. Class II devices are subject to both general and special controls, and Class III devices are subject to general controls and premarket approval. These regulatory controls will be discussed in greater detail in the following slides. Importantly, a device should be placed in the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

Now, let's go into more detail about each of the classes. As mentioned previously, Class I devices are those devices for which general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. General controls are basic requirements that apply to all medical devices and are outlined in the Federal Food, Drug, and Cosmetic Act. Some examples include meeting establishment registration and device listing requirements, following good manufacturing practices, adhering to recordkeeping and reporting requirements, and ensuring that devices are not misbranded or adulterated. Most Class I devices do not require FDA premarket review prior to being marketed. On the right-hand side of this slide you can see a few examples of Class I devices. These include ophthalmic retractors, visual acuity charts, stereoscopes, and keratoscopes.

There is also an alternative pathway to determine that a device is Class I. Class I devices could also be devices that cannot be classified into Class III because they are not life-sustaining, life-supporting, or of substantial importance in preventing impairment of human health, and they do not present a potential unreasonable risk of illness or injury, and these devices cannot be classified into Class II because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness.

Class II devices are those devices which cannot be classified into Class I because general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. There are many types of special controls, but some examples include performance testing, sterilization validation, and device-specific labeling requirements. These special controls, in combination with the general controls previously described, provide a

reasonable assurance of safety and effectiveness for Class II devices. Examples of Class II devices include daily wear soft contact lens for vision correction only, optical coherence tomographers, and cornea electrodes.

Typically, Class II devices require a premarket notification, generally referred to as a 510(k), prior to being marketed in the U.S. Within these 510(k) submissions, companies must also provide evidence demonstrating how the special controls for the specific device type are met.

Class III devices are those which cannot be classified into Class II because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and the devices are life sustaining or life supporting, or are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval through a premarket approval application, or PMA, prior to being marketed. Examples of Class III devices include intraocular lenses and excimer laser systems.

Here is a flow chart that walks through the general decision-making process for each of the classes just discussed. We start with determining whether general controls are sufficient. If so, the device can be appropriately regulated in Class I. If not, we ask whether there is sufficient information that allows us to be able to develop special controls. If so, the device can be appropriately regulated in Class II. If not, then it would be Class III if the device is life-supporting or life-sustaining or if it is of substantial importance in preventing impairment of human health or if it presents a potential unreasonable risk of illness or injury. If the device is not life supporting or life sustaining or of substantial importance in preventing impairment of human

health and does not present a potential unreasonable risk of illness or injury, then we end back up at a Class I designation.

Now, we will shift our focus to the classification process for ophthalmic dispensers, a pre-amendments unclassified device type, which will be discussed today. Before we walk through the process, here are a few quick definitions. First, what is a pre-amendments device? A preamendments device is a device which was introduced into interstate commerce prior to May 28, 1976, or the date of enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act.

An unclassified device is a pre-amendments device which was not classified by the original classification panels. Therefore no classification regulation currently exists for these devices. This brings us to the purpose of this panel meeting: to formally classify these unclassified devices. Please note that while these devices are not classified, they are currently brought to market through the 510(k) process.

Pre-amendments unclassified devices will be classified once the FDA has taken the following steps. First, FDA will solicit input and a recommendation from the device classification panel, which is the purpose of this meeting. Second, FDA will publish the Panel's recommendation for comment, along with a proposed rule outlining FDA's proposed classification for the device. Finally, after taking into account public comments, the FDA will publish a final rule classifying the device.

What we ask from the Panel today is to provide input on the classification of ophthalmic dispensers and whether they should be classified into Class III, Class II, or Class I. The input should include: an identification of the risks to health presented by the device type; a discussion

of whether the device is life supporting, life sustaining, of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness or injury. The Panel will also be asked to discuss whether general controls alone are sufficient to provide reasonable assurance of safety and effectiveness for the device type, and if not, whether sufficient information exists to develop special controls, and what those special controls should be to provide a reasonable assurance of safety and effectiveness for the device type.

Following this Panel meeting, the FDA will consider all available evidence, which includes the input received from this panel and the public. The FDA will then publish a proposed rule in the Federal Register, proposing classification of this device type and seeking public comment on the proposal. Finally, FDA will issue a final rule identifying the appropriate class. If FDA determines that the devices can be appropriately regulated as Class I or Class II devices, the devices may continue to be marketed. If, however, FDA determines that they fall into a Class III designation, a separate call for PMAs will also be published. Existing devices may remain on the market until a specified date, at which point a PMA should be submitted in order to continue marketing. If this PMA is not approved, existing devices will be considered misbranded and must be removed from commercial distribution. I hope this has provided you with sufficient background to set the stage for the forthcoming discussion. Thank you for your time and attention.

FDA PRESENTATION — OPHTHALMIC DISPENSERS (LXQ), DR. WONG

Dr. Bressler: Thank you, Dr. Lo. I just want to note in the interim, Dr. Thomas Freddo who is at Boston University School of Medicine, a panel member, also has joined us and will be participating in the Panel deliberations. We will now proceed to the second FDA presentation. I

would like to invite the FDA representative Dr. Elissa Wong to begin, and the representative will have 30 minutes to present. And you may now begin the presentation.

Dr. Wong: Good morning. My name is Dr. Elissa Wong, and I am a biologist in the Division of Ophthalmic Devices within the Office of Ophthalmic, Anesthesia, Respiratory, ENT, and Dental Devices in CDRH's Office of Product Evaluation and Quality. Today, I will be presenting information regarding the effort to classify ophthalmic dispensers under product "LXQ." These devices are currently unclassified, and we are seeking your thoughts and recommendations on the appropriate regulatory classification for these devices. Here is an outline of today's presentation. These are the topics that we will be discussing.

Ophthalmic dispensers are manual devices used to deliver ophthalmic liquids to the eye, either to irrigate the eye or to deliver medication to the eye. There are many different types of ophthalmic dispensers. Eye cups are the one type of ophthalmic dispenser, as shown in the photograph on the left part of the side. Eye cups are cup-shaped devices that are used to temporarily hold liquid, such as saline solution or other ophthalmic medication. An eye cup is filled with liquid, fitted and inverted over the eye to allow the solution to irrigate, wash out, or flush the affected eye. Other types of ophthalmic dispensers are droppers. As shown in the middle of the slide, some droppers have a squeezable pipette bulb, and may consist of the pipette and bulb only, or may be designed as a closure for a storage container. As shown on the right side of the slide, some droppers are squeezable bottles with a tapered tip and cap.

The indications for use identifies the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. Here, we show representative indications for use statements for ophthalmic dispensers,

such as: intended to hold and place liquids such as eye wash solutions over the eye to allow the solution to wash out or flush the affected eye; intended for instilling ophthalmic medication dropwise to the eye.

In terms of regulatory history, ophthalmic dispensers, including eye cups and droppers, are pre-amendment devices. This means that these devices were marketed prior to the Medical Device Amendments Act of 1976. Ophthalmic dispensers were not classified in the original classification panels. Currently, ophthalmic dispensers are unclassified, and there's no regulation associated with the "LXQ" product code. To date, FDA has cleared 5 eye cups under the "LXQ" product code. Table 1 in the Executive Summary summarizes the 5 eye cups that have been cleared to date.

There are a wide variety of optical conditions that are treated using ophthalmic dispensers. Dispensers are used to administer liquids as drops or in larger volumes. These can administer the liquid as drops to accommodate the very limited volume capacity of the ocular surface. The dispenser can also help to maximize the concentration of liquid in the eye while minimizing the exposure of that liquid to the rest of the body. Ophthalmic dispensers are also used to administer larger volumes of liquid to flush debris or foreign material off the ocular surface whose presence may cause ocular pain or discomfort.

We conducted a systematic literature review to identify information published on the safety of ophthalmic dispensers. The literature review was conducted using PubMed and Embase databases. The time range of our search was between January 1, 1976, and May 11, 2022. We included a variety of general search terms to capture potentially relevant literature, such as different spellings of eye cup and eyedropper, droptainer, eye drop dispenser, and other similar

terms. The initial search excluded nonclinical studies, case reports on 9 people or fewer, economic and cost-effectiveness analyses, narrative reviews, conference abstracts or proceedings, commentaries, and editorials. The initial yield was 185 articles after duplicates were removed. After review, 15 articles were determined to be relevant to the safety of ophthalmic dispensers. For additional information about the literature review process, please see the Executive Summary.

In the next few slides, I'll summarize the findings of our literature search. First, 11 cases of bacterial keratitis associated with bacterial contamination of ophthalmic dispensers were reported in 3 articles. The tips of the bottles, and in some cases, also the inside of the bottle caps, were found to be contaminated with the same bacterial culture cultivated from corneal scrapings. Also, some patients have a known event of ocular trauma, such as an abrasion with a mascara brush. Some patients experienced serious adverse events or needed serious interventions. These included significant corneal scarring, the need for corneal transplantation, enucleation, and a blind, painful eye requiring retrobulbar alcohol injections for pain relief.

6 studies evaluated microbial contamination of ophthalmic dispensers, either by culturing the droptainers used by patients, which was done in 5 studies, or by directly inoculating eyedroppers and droptainers in the laboratory, which was done in 1 study. The droptainers were sourced from a wide variety of settings, including clinics, patient homes, and long-term care facilities. Contamination was found in 8-28% of droptainers.

In a study of 194 droptainers from asymptomatic glaucoma patients by Geyer et al., 40% of droptainers that had been open for more than 9 weeks were contaminated, compared to 19% of those that had been open for 8 weeks or less. This difference was statistically significant. In a

laboratory study by Coad et al., tips of eyedropper pipettes and droptainers were inoculated with bacteria. it was found that bacteria can be detected from droptainer caps, but not eyedropper bottle caps, after 24 hours. The authors suspected that design of this dispenser might also play a role in the contamination. They noted that for the preservative in the solution to be effective, it must come in direct contact with the contaminating bacteria. An eyedropper bottle can achieve this more easily than a droptainer because the continuous re-immersion of the eyedropper's pipette tip into the sterilizing effects of the ophthalmic preservative decreases the risk of bacterial contamination and growth. They also noted that the caps of droptainers can serve as a potential reservoir for microorganisms.

Next, Solomon et al. reported a series of 12 patients with acute conjunctival inflammation caused by nonintentional contact of the droptainer tip to the conjunctiva during the self-administration of topical ophthalmic solutions or ointments. These 12 patients had at baseline corneal conditions, such as herpetic keratitis, or were status post-ocular surgery, such as cataract extraction, penetrating keratoplasty, laser in-situ keratomileusis. They presented with sudden onset of painful red eye and were observed to have corneal epithelial erosion in the lower bulbar conjunctiva with surrounding hyperemia and conjunctival edema.

After performing clinical examinations and requesting patients to replicate their method of self-administration, the authors found that these events were self-induced injuries from inappropriate use of the droptainer. Notably, none of the patients had been aware of the possibility that their injuries were self-induced.

Recognizing that inadvertent touch of an ophthalmic dispenser tip to the surface of the eye can lead to contamination of the tip, we found five other studies that use this as an indicator

of inappropriate device use. These studies evaluated the use of various eye drop guides fitted to droptainers by various patient populations. The sample sizes were generally small, but a variety of patient populations are represented, from healthy adults to patients with glaucoma or rheumatoid arthritis. In these studies, inadvertent tip touch with the eye was found to be common. The proportion of participants who experienced inadvertent surface eye touch prior to any use of the droptainer, with or without an eyedrop guide, ranged from 22-76%.

In summary, there was very little literature available specifically about ophthalmic dispensers. The literature shows that inadvertent contamination and self-induced ocular trauma is possible with the use of ophthalmic dispensers. Secondary infection is also possible, but it appears to be uncommon, since the case reports on infection involves a very small number of patients and were published greater than 30 years ago, with no similar case studies identified since. Therefore, it may be concluded that ophthalmic dispensers are generally low in risk.

The next few slides provide background information for medical device reports, or MDRs. Medical device reporting is one of the post market surveillance tools the FDA uses to monitor device performance, detect potential device related safety issues, and contributes to benefit risk assessments of these products. MDRs can be submitted by patients, healthcare professionals, consumers, and mandatory reporters. MDRs can be used effectively to establish a qualitative snapshot of adverse events for a specific device or device type; to detect actual or potential device problems using a real-world setting or environment. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including under-reporting, data quality issues, like the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. The incidence or prevalence of an event cannot be determined from

this reporting system alone, due to potential under reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Due to these limitations, MDRs are only one of the tools the FDA relies upon to assess device performance.

To further contribute to the benefit risk assessment of ophthalmic dispenser devices, the Agency reviewed medical device report databases. The search included all available data up to August 15, 2022. To capture as many potentially relevant MDRs as possible, the search terms were broad and included the product code "LXQ," 510(k) clearance numbers for this product code, and general terms such as eye cup, eyedropper, eye drop, droptainer, eye dispenser, ophthalmic dispenser, ophthalmic, dropper, and similar terms. Initially, 1,674 unique MDRs were identified. FDA evaluated each MDR and reviewed each report for manufacturer name, brand name, generic name, product code, premarket submission number, if provided or applicable, and narrative report. Based on this review, only 3 MDRs were identified as relevant to ophthalmic dispensers.

One MDR, reported in February 2015, was from a patient taking glaucoma and tissue rejection drugs who was concerned that plastics used in dropper bottles posed risk to patients if they were opaque, because he could not see whether he needed to obtain a replacement supply of medication. This MDR appears to be a general concern about droppers used for ophthalmic medications.

One MDR reported in March 2021 was from a patient reporting that there were quote, “sharp plastic corners on either side of the dropper which makes it very hard to maneuver,” quote, and that, quote, “the dropper is hard to use.”

The last MDR, reported in July 2022, was from a pharmacist on behalf of a patient prescribed a biologic for neurotropic keratoconjunctivitis of the right eye. The publicly available labeling indicates that this is a self-administered medication that comes in a specially designed vial, an ophthalmic dispenser. The dispenser is a pipette with a plunger that is designed to connect to the vial top, uptake the medication from the inverted vial, detach from the vial top, and deliver the eye drop to the eye when the plunger is pressed. The patient complained that when he pushes the plunger, “the medication squirts out,” and quote, “it's difficult to control how much medicine gets into the eye,” quote. For additional information about these MDRs, please see the Executive Summary.

This slide provides background information for recalls in the Medical Device Recalls database. This database contains Medical Device Recalls classified since November of 2002. Since January 2017, it may also include the correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall, and again when a recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its consumers about the recall. Therefore, the recall information and posting date identified on the database indicates the date FDA classified the recall and it does not necessarily mean that the recall is new.

A search of the Medical Device Recalls Database through August 15, 2022 was done using general search terms such as eye cup, eyecup, eye dropper, eyedropper, eye drop, eyedrop, droptainer, eye dispenser, ophthalmic dispenser, ophthalmic, and other similar terms. This search did not identify any relevant recalls.

To identify the risks of these devices, we reviewed MDRs, recall information, and literature analysis as previously discussed, and the information available to FDA regarding cleared devices. We have identified 4 risk categories for ophthalmic dispensers. Infection. This can result from a new device that has microbial contamination as packaged or a device that becomes microbially contaminated because it is improperly cleaned and re-used. This can result from the microbial contamination of the ophthalmic dispenser and ophthalmic medication because the dispenser tip has touched the eye or touched another unintended surface. Adverse tissue reaction. This can result from the use of device materials that are not biocompatible. This can also be caused by interactions between the device and ophthalmic medication, for example, chemicals from the device leach into the ophthalmic medication. Compromised treatment. Treatment can be comprised as a result of a damaged or defective ophthalmic dispenser. This can also result from inadequate instructions, and the device not being used as intended. Design of the dispenser may cause incorrect dosage of medication to be dispensed to the patient. Mechanical injury. Unintended direct physical contact with the eye can result in injury to the patient.

We propose these risks will be sufficiently addressed by general controls and do not require special controls as part of the medical device regulation process. We recommend that ophthalmic dispensers be regulated as Class I devices.

Here is our proposed classification regulation for ophthalmic dispensers. Part A of the regulation defines ophthalmic dispensers as manual devices that are intended to irrigate the eye or provide controlled instillation of ophthalmic medication. We are proposing these devices be classified as Class I exempt devices with general controls. This concludes our presentation. Thank you so much for your time, attention, and thoughtful feedback on the following panel

questions.

PANEL DELIBERATIONS

Dr. Bressler: Thank you, Dr. Wong. We are now going to start the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel chair. Additionally, we request that all persons asked to speak identify themselves each time. This helps the transcriptionist identify the speakers. So I'm going to open it up to the Panel now for questions that they may have on the presentations that we heard, and we will go around and discuss some of the specific items, probably for the next 45 minutes, before we address the FDA questions. I'm going to start with Dr. Jayne Weiss.

Dr. Weiss: I had a few questions, one, with the number of reports, I assume we have no information, whether the infections or any other events have changed over the course over time. But if we do have any information on that, I would appreciate that. Two, over this period of time, are the same plastics being used in the drop bottles? Maybe some have more antimicrobial properties than others? And then the third part --

Dr. Bressler: Jayne, I'm going to interrupt you. I'm going to have them take one at a time, if that's okay. In case you have a follow-up on it. Okay, Dr. Wong or others, do you want to take the first question to clarify?

Dr. Nguyen: Hi, Tieuvi Nguyen, FDA. So Dr. Weiss your first question was, I think you were referring to the -- were you referring to the literature and those infection cases? Okay, so um... --

Dr. Weiss: Either one.

Dr. Nguyen: For the literature, I don't know that we have that information. The literature, as said in the executive summary, I think, just reported on exactly what we had written in the executive summary. So we don't have a lot of information about those patients. The MDR searches, as Dr. Wong explained, most of them had to do with complaints of use of the droppers themselves. I don't recall that it specified any types of infections that resulted from those occurrences.

Dr. Bressler: And I think her second question was if the plastics or the chemical makeup of the dispensers had changed over time. Is that correct, Jayne?

Dr. Weiss: That's correct.

Dr. Bressler: Do you have information on that, from the FDA?

Dr. Nguyen: As specified in the executive summary and in Dr. Wong's presentation, we have cleared five dispensers, and they have all been eye cups. And so to my knowledge, if they do change materials, because those devices do still require a 510(k) currently, they would likely have come in with a 510(k) submission to receive those changes. So, what is in our 510(k) database now should specify the materials with the names. But it's part of the quality systems that if you do change materials, design, or something that could affect the safety and effectiveness of the device, that currently, they would have to come in with the submission to the agency, since they are unclassified, requiring a 510(k).

Dr. Bressler: And Dr. Weiss, I'm going to get to your third question before I move on. Go ahead, Dr. Weiss.

Dr. Weiss: In terms of the compromised treatment and the size of the drop, as I recall,

the size of the drops are a lot larger than what the fornix can hold. So some of the drop, there's wastage… increasing the chance of infection or decreasing? Might this be the opportunity to suggest to manufacturers to make the drop size more in keeping to what the eye can actually hold?

Dr. Nguyen: You cut out a little bit, Dr. Weiss. So I think your question was regarding the drop sizes and whether or not the companies would re-evaluate the volume from the drop sizes to make sure the volume was appropriate for the eye, was that your question?

Dr. Weiss: That was most of it. And part of it was, is drop size at all associated with infection risk, or we don't have that information?

Dr. Nguyen: Okay, I understand. So, I would just say from a device perspective do have to follow good manufacturing procedures. As part of that, in the quality systems regulation, they would have to have internal documentations regarding the design specifications of the device, the rationale for that, and the risks associated for the design. So they have to have internal documentation to justify the design of the device, basically. And this could include the size of the drop. So your question specifically about the redesign, I think that's more of a drug issue, it may be drug-specific, so I wouldn't have a comment to that. Generally speaking, the company, as part of the quality systems, would have to have detailed information justifying the design of the device and the specifications that they use.

Dr. Bressler: So Dr. Weiss, we will come back to that as we have many recommendations for the FDA to consider and one of those may be from you, may not be, if it's being used as an ophthalmic dispenser to the cul-de-sac, should it be specified as a range. Now, if you'll put your hand down so I can keep track. I'll go in order of the hands. Dr. Repka.

Dr. Repka: Thanks. Michael Repka. I wanted to ask if GMP, or good manufacturing practices, in the design that would be enacted over a Category I, does that cover the glass pipette or plastic pipette having smooth edges? Second part of that is that if you did a design of a droptainer or an ampoule, how do we know that with the tear-off tops you don't get a sharp edge that could cause mechanical injury? Or is that part of the GMP required of the manufacturer to show in their design?

Dr. Nguyen: Yes, the GMP should cover that. Design controls are an aspect of the GMPs. So they would have to have specifications to ensure -- they have to do a risk assessment, number one, and justify all the design characteristics of the design. So your question about surfaces and smoothness, yes, those all have to be taken into consideration. And that is also true for issues such as bottle caps and how easily they come off, if there's sharp edges that could have potential safety concerns. Those are all parts of the quality systems and internal documentation.

Dr. Bressler: Thank you. Now we are going to go to Dr. Masket. And you'll have to unmute. Please.

Dr. Masket: Sorry about that. Sam Masket here. Given that the biggest concern is contamination, has anyone done a cost-based analysis of using individual drop dose dispensers, both in terms of dollar cost, as well as carbon footprint, with regard to certain medications that may have higher risks of contamination or for certain treatment conditions?

Dr. Nguyen: As stated in our executive summary and presentation, when we performed our systematic literature review, we did exclude cost analysis type studies as part of our analysis. We focused really on safety of ophthalmic dispensers. So I don't know if I could answer that question for you.

Dr. Bressler: Thank you Dr. Masket, and I don't think the literature showed that, and correct me if I'm wrong, Dr. Nguyen, we don't know if there was less contamination if these were single drop sort of dispensers. But obviously it would cost more, I would think so at least. Dr. Pulido.

Dr. Pulido: Just a question and observation, and that's. in my mind when I think of a dispenser, I think of my little you know, bottle of Dorzolamide, and you take the cap off, put it on. I was intrigued by what that pharmacist wrote, so I did look it up. There's a new drug on the market that comes in a glass vial. You put on this basically syringe, or needle, on it and attach a syringe, and then you attach a syringe, they call it a pipette but it's a syringe, and then you take the syringe off and you use the syringe yourself without the needle to instill it in your eye. That's not what I think of when I think of an eye bottle dispenser. How is the FDA putting that in the same category as all the others?

Dr. Bressler: Dr. Nguyen? Do you want to comment? This gets to, we've combined eye cup dispensers, ophthalmic pipette dispensers, and now this more complex description that Dr. Pulido just gave us.

Dr. Nguyen: Sure, again, these are unclassified devices and the devices that we are aware of are the ones that have gone through the 510(k) clearance, which again, have all been eye cups. Ophthalmic dispensers, as Dr. Wong described within the presentation, and the ones we are considered to be classified under one regulation, would have to be the type of devices for which we believe have the same level of risk and same considerations for safety and effectiveness.

Dr. Bressler: Dr. Pulido, did that address your comment?

Dr. Nguyen: So if I could just clarify a little bit. So again, the five clearances are what we are aware of. The examples that Dr. Wong included in the presentation are the devices for which we believe have the same level of risk. So, assuming that the Panel agrees that this would be a Class I device subject to just general controls, if a device such as the one that Dr. Pulido just described were to want to come into the market under this regulation, the limitations of exemptions are when we believe that a device may fit into a regulation of the same risk and category, but for which the intended use or technology may require that, even though most devices may be exempt from premarket review, if they trip the limits of exemption, they still have to come in with a 510(k). FDA would still have to review and determine if it's appropriate to be within this category. And then if FDA were to clear that device, any similar type devices would then be exempted under the regulation.

Dr. Bressler: That was very helpful. Thank you. We are going to go in order and go to Dr. Freddo next and then Dr. Jeng.

Dr. Freddo: Apropos to Dr. Weiss' comment, I'm surprised I haven't heard anything about this new nanodropper attachment that you screw on to a standard eye drop bottle dispenser that reduces the volume from the standard drop of 20 microliters to somewhere around underneath 10. They currently claim, at least online, that they are Class I approved by FDA and 510(k) exempt. I'm just wondering how that all fits into this mix that we are discussing today. Thank you.

Dr. Bressler: Okay. Thank you. Dr. Nguyen, did you or other FDA staff want to address that, the nanodropper attachment?

Dr. Nguyen: Yes, I think I'll ask Dr. Elissa Wong to comment on this.

Dr. Wong: Hi, this is Elissa Wong. As you mentioned, we are aware that the nanodropper is under -- they have registered and listed under Class I product code KYX, which is KYX is defined under 21 CFR 880.6430. KYX is defined as liquid medication dispenser. So to my understanding, the products under KYX are intended for oral use. So essentially, what we are basically saying is the nano dropper for ophthalmic shouldn't be under KYX, that's for oral use. We believe that devices with the specific intended use to deliver ophthalmic liquid to the eye would be a different intended use than products under this, under KYX. I hope that answers part of your question. I'll let Dr. Nguyen comment further.

Dr. Nguyen: One thing I do want to clarify is that when manufacturers believe they are Class I, because these are exempt, they do self-designate to be Class I. That doesn't mean the Agency agrees with that. And if situations come up with people, if it's brought to our attention that they are not appropriately classified, then I think that we would consider that and take action as needed. But as Dr. Wong said, we want to clarify that the KYX category is for oral dispensing of medications.

Dr. Bressler: Thank you. I'm going to turn it over next to Dr. Jeng and then Dr. Kwon.

Dr. Jeng: This is Bennie Jeng. I have two materials related questions, one is follow-up to Dr. Weiss's regarding the material, specifically regarding the rigidity. I know you talk about the components and type of the material, but is the rigidity of the bottle, let's say the eyedropper bottle, tested or made in consideration? That's the first question.

Dr. Bressler: Yeah, let's do one at a time. Great.

Dr. Nguyen: Yeah, I appreciate that, one at a time. Yeah, so this goes back to the

quality systems. And as part of following GMPs, good manufacturing processes, you do have internal documentation to justify the design of your device. So a consideration is if the device is designed to be used as intended. So if the intention is that the material has to be pliable enough to distill a drop at a time, they would have -- a company would have to have internal documentations why they set the specifications and why the materials they've chosen meet their design controls.

Dr. Jeng: Thank you. The second part of the question, I don't know if this is outside the purview, but I guess it's a comment. The opacity of the bottle that was made as a complaint at one point is actually one that we really need to consider. This is akin to the MDIs, especially the ones that are used for rescue medication, where you don't know how much medicine you have in the inhaler. For chronic use medications, patients run out all the time because they don't know how much medication they have in it. I think it's important that we consider, especially for chronic use medications, but probably for all, that they are in bottles that are transparent so patients can see how much is in there. Shaking up a volume of 1cc doesn't really tell patients how much there is left. Patients run out because of the lack of consistency in drop size and wastage, and then they end up without medications for a while.

Dr. Bressler: Dr. Nguyen you or your staff are welcome to comment on that, and I would expand, Dr. Jeng, I'm not sure if any of those are also trying to block out light to the medication itself. But Dr. Nguyen I'll turn that over to you or your staff if you have any comment on this concern or recommendation in general.

Dr. Nguyen: Sure. Yeah, Dr. Jeng, that's an important point. From a device perspective, again, I do think that companies do, as part of their internal processes, have to consider all risks

and perform a risk assessment. If a company does feel that's a risk with the use of their dispenser, they would design the device accordingly.

Dr. Bressler: Okay. We are going to turn to Dr. Kwon, then Dr. Rajpal.

Dr. Kwon: Thank you for the presentation. I have a question about the definition of ophthalmic dispensers under the product code "LXQ", and I'm not quite sure what that means. My question is, are there other ophthalmic dispensers under a different product code? The reason I ask is because it seems like this definition encompasses the eye cups, droptainers, and also the pipette type of eyedropper. And, as other panel members have mentioned, there are other types of topically applied medications available. For example, those single use, individually packaged preservative-free formulation drops, they are not specifically mentioned. Then of course, there's the earlier Genentech letter addressing a very different type of, more invasive type of formulations. I have no connection to Genetech but I think this all points to the fact that we need to have a more precise definition of ophthalmic dispensers under the product code "LXQ."

Dr. Nguyen: So again, you know, the only code for ophthalmic dispensers currently is "LXQ". And just to explain further, under regulation, there may be multiple product codes for devices that fall under the regulation. "LXQ" is defined as eye cups which are unclassified and under 510(k), and there's no product code or regulation defined for other dispensers such as the eyedroppers or droptainers that you had mentioned. So we acknowledge that. And part of this classification effort will be to, again, group the dispensers for which we believe fit within this category based on risk and intended use. The comment you made about Genentech, we agree with the letter from Genentech. We would not believe that dispensers such as those that penetrate the eyes such as syringes and implantable devices fit within this category. Those are very

different. There's an existing regulation for syringes, and within that regulation, there is a separate product code for ophthalmic syringes. But those types of devices are outside of scope of what we are doing today.

Dr. Bressler: So we will put those aside, but Dr Nguyen, if I could just expand or clarify what Dr. Kwon asked. Is there a rationale to lump, let's say, eye cups with these pipette dispensers? Based on minimal risk to both? Or can they be separated when you're preparing this classification? I don't mean necessarily today, but I think Dr. Kwon was implying you're lumping what appears to be different things. Putting aside the things that penetrate the eye. You've clarified those are not included here. But as far as the eye cup versus a pipette dispenser…

Dr. Nguyen: Sure. So, the identification as specified in the executive summary, we believe that those different types of devices such as eye cups and those droptainers have a similar intended use with similar risks. Right now, again, we just have one product code, "LXQ", for eye cups. But you know, when the regulation is finalized, it's possible that other product codes could be developed that fit within the identification of the regulation. But overall, from a risk perspective and intended use, we do view them as being similar and appropriate to be classified together.

Dr. Bressler: Okay. Dr. Rajpal.

Dr. Rajpal: Thank you Dr. Bressler and thank you FDA for the review. I have a similar question to Dr. Kwon, and I have two parts to this. The first one, is it appropriate or possible to clarify the definition with exclusions for those products that are not going to be considered in this droptainer category? I'll give two examples: one is ointments. Are they part of this or not? Are the tubes part of this, I should ask. And second, it seems that preservative-free

droppers are, that are multiple use -- sorry, single-use. But what about multiple use, single-bottle, preservative-free containers. Are those part of this? I think we are all expressing that there's some confusion, at least on our part, in understanding what falls into this category.

Dr. Nguyen: So let me just take one at a time. Regarding the identification, I think we would like suggestions from the Panel as to whether you believe additional clarification language should be included within the identification. I'll read what we proposed, where we have identified ophthalmic dispensers as manual devices that are intended to irrigate the eye or provide controlled instillation of ophthalmic medication. So based on the presentations today and the scope as we have described, we would like to hear from the Panel whether you believe additional language should be needed. I think your other part of the question was what types of solutions, is that right, are considered within scope here?

Dr. Bressler: Go ahead.

Dr. Rajpal: Actually, more the container. When we have single use preservative-free droppers, it seems to me from the discussion that those are falling into this category. But I'm asking also whether the multiple use bottles that are preservative free fall into this? Do they have a separate classification for approval?

Dr. Nguyen: Yes, I would say that those are all within scope.

Dr. Rajpal: Okay. Can I --

Dr. Bressler: We will have you do the second question, and we will come back to the language clarification for discussion with the Panel before we actually get to the FDA questions so we can make sure the Panel has had an opportunity to discuss what the language currently is,

or clarifications needed. Dr. Rajpal, we'll go to your second question next.

Dr. Rajpal: Please tell me if you want to defer to later. I think we would all agree that the risk of infection from a safety perspective is paramount for all of us. Is there going to be a requirement for the containers to be supplied sterilely, which is, I think, the way it is done now? And does it have to be stated or listed? I didn't see that in the document. So just understanding how that is generally managed and handled.

Dr. Nguyen: I'll just bring you back to, we have only cleared 5 devices under this category. All of them are eye cups, so far. And some of those eye cups have been cleared as non-sterile. So we would look to the Panel to discuss and recommend whether you believe that these devices must be sterile and provide your rationale for those.

Dr. Bressler: So we will come back for the Panel deliberation for us to discuss about whether they should be sterile when they are providing controlled instillation. And also whether any labeling should be on that. So I'm writing these down to make sure we come back to them for everybody. But I'll turn to Dr. Durham and then to Dr. Glasser. I encourage everybody for a second and third question so we can clarify all this.

Dr. Durham: Thank you. Todd Durham. Can you remind us: what is the process in place for surveillance? Say the profile or additional product complaints come in for some of those dispensers and that gives you more information. How might the classification be revised, or the suggested controls?

Dr. Nguyen: Just to make sure I understand your question: you're asking about post market tools that we have to monitor safety of these devices?

Dr. Durham: Correct.

Dr. Nguyen: Dr. Wong noted that we do have a system, that MDR system, where there are some mandatory reporters, such as the manufacturers, importers, that must report on complaints or malfunctions. And we do get a lot from consumer, patients, and other voluntary reporters. So we did list some of the limitations of some of those, I think they give you very good information. As you can see, we haven't received very many. We noted 3 MDRs related to ophthalmic dispensers. That's one system by which we would monitor safe use. Companies do typically have internal systems for which they review these complaints, take action on them, and reanalyze the risk assessments.

From a practical standpoint, if a company is marketing a medical device, they would have to register and list, as part of the general controls which is applicable to all medical devices, and as part of that they do have to keep within their internal systems all these types of information, the risk analysis, the CAPAs, Corrective Actions that they take. FDA does routinely inspect these manufactures, and as part of the inspection, we do make sure they are keeping their documentation up to date in analyzing any risks that come in adequately.

Dr. Bressler: Okay. Dr. Glasser, Dr. Chew, and then Dr. Freddo, and Dr. Kwon.

Dr. Glasser: Thank you, David Glasser. This perhaps belongs in deliberations, but I was going to make some suggestions regarding wording to clarify that these are for external administration and also comment on the one thing versus splitting of the different types. I'll defer to you if I should hold the comments for later.

Dr. Bressler: I would like you to make the comment with any question now and I'm

going to list it and I'm going to come back to the comments people had to see if anyone else on the Panel wanted to emphasize something. I think that's a good way to get our points across. But do one at a time. You had two items there.

Dr. Glasser: In terms of the wording under identification, devices that are intended to irrigate the eye or provide controlled instillation of ophthalmic medication, if you just inserted "external" in the right spot, I think that would clarify and differentiate between these types of devices, those injecting medicines, or slow-release devices. That's number one, I don't know if folks want to comment on that or if I should move on.

Dr. Bressler: Any comment, Dr. Nguyen?

Dr. Nguyen: Yeah, so Dr. Glasser, you would suggest somewhere saying dispensers are manual devices, for example, that are intended to irrigate the eye or provide controlled instillation externally? Or how would you phrase that?

Dr. Glasser: Controlled external instillation, maybe put it in there. That would be my suggestion. As to the lumping and slit splitting, I'm hearing several different categories. Eye cups, I'm not concerned about the sterility of eye cups. Bottles with medications inside them, that’s obviously a different story. And Dr. Rajpal brought up the issue of single versus multiuse preservative free medications. And that's something we may need to look at more carefully. I think patients tend to use single-use preservative-free dispensers more than once. I think that's probably already happening, so we maybe want to take that into consideration as we deliberate.

Dr. Bressler: So Dr. Glasser, I'm going to bring each of those up for the group as we potentially split versus lump, and then if we do split, to talk about this single versus multi-use

preservative-free versus preservative-containing products. Dr. Nguyen, I'm going to go back to the panel for a consensus or a goal for consensus on those issues.

Dr. Nguyen: I think you can go back to the panel. I would like if the Panel could discuss further, I'm interested in a couple things: the sterility issue Dr. Glasser discussed with the eye cup versus dispensers, if folks have any comments on that and what that distinction is and the rationale behind that distinction. I want to focus, just remind the panelists that we are talking about, for purposes of this classification, we are talking about stand-alone dispensers, not those that are pre-filled with the drug. So within that context, if anyone has any comments regarding any splitting of issues due to sterility, I would appreciate it.

Dr. Bressler: Understood. And I'm going to bring those up, each one, I just want to go through questions to clarify from the FDA first, or comments to bring up. And then I'm going to try to organize these with the Panel. I understand that you want feedback on that, so we are planning it and we will discuss each of these. Let me go to Dr. Chew and then I'll have additional questions or comments from Dr. Freddo and Dr. Kwon.

Dr. Chew: This is Emily Chew. I just wanted to follow up with Dr. Weiss, talked about the amount that the eye can actually hold. Is there any concern to make sure the pediatric group might have a smaller amount of it, for example a drug that might be likely absorbed systemically, is there a need to differentiate between adults and pediatric? Or is that a moot point, at this point?

Dr. Nguyen: You know, I think that may be more of an issue for the drug labeling than the dispenser itself. I don't know that I could answer that question. If certain dispensers, if they are labeled for pediatric use, I would assume the Panel would know better than me, those would

probably come in pre-filled dispensers as part of the drug product. That's outside of scope of this discussion today. Although, you know, those are considered combination products, and the same considerations that we would have for these stand-alone dispensers would still apply to combination products. But I believe that may be more of a drug labeling issue.

Dr. Bressler: Thank you. Dr. Freddo.

Dr. Freddo: One comment and one question. My comment apropos to Dr. Kwon's and Dr. Bressler's discussion of the issue of transparency of the bottle and potential concerns about light sensitivity to the product contained therein. I'm aware of non-ophthalmic dispensers that are designed in such a way that the majority of the bottle is opaque, but there's then left a transparent vertical strip at one side of the bottle that would allow for light protection for most of it and still have there be a strip of transparency that the patient could use to monitor the volume left in the bottle. My question for the FDA folks is: how do contact lens related products fit into this? Say, a contact lens rewetting drop, for example, that are often sold in droptainers that commonly have larger volumes than would a medication we'd prescribe. How do those fit into the mix in your view? Thank you.

Dr. Nguyen: Thank you for the question. So those type of contact lens solutions are currently regulated as medical devices. And so you know, the bottle in the solution is considered as one product. So currently we review those, and all the risks associated with the bottle and the solution, together.

Dr. Bressler: And we will come back to that in just a minute. Dr. Kwon.

Dr. Kwon: Hi. I just want to follow up on what Dr. Rajpal said earlier about

preservative-free and multi-dosing medication bottles. My understanding is that that is a bottle that is of substantially different technology than for the current droptainers available in the United States. And these bottles are specifically designed to prevent the ingress of outside fluid back into the bottle, specifically using membranes or with one-way valves. And I believe it's not yet available in the United States, but it is available outside the United States, in Canada and Europe. Given that it's a substantially different technology than existing droptainers that we currently have in the United States, do you think that that scope falls under the same category of Class I, without premarket notification, or is this substantially different technology that requires 510(k) submission?

Dr. Nguyen: I would remind the Panel, if the product is prefilled with any type of solution, again, that would be outside of the scope of the Panel meeting. But back to what I mentioned earlier, if there's certain types of technologies that trips the limits of exemption, meaning that the intended use or there are technology differences, even if we classify this as a Class I exempt device, if there are certain types of technologies that we believe are differences in technology, we would require the company to come in with a 510(k) submission so we can evaluate the device to ensure that it was safe and effective.

Dr. Bressler: And Dr. Repka.

Dr. Repka: I wanted to make sure, because I sense a lot of confusion here. This prefilled issue that has come up, and I recognize this is not about combination products, that the definition here probably needs to say "not prefilled" or "empty" or something, as well, in the classification. So just making the classification clearer to its intent. Thank you.

Dr. Bressler: Thank you, yeah, that may come to part of the classification language.

Okay. Dr. Masket I think you had additional comments?

Dr. Masket: So sorry. Given again the concern about contamination and a study that we heard earlier that indicated the longer the bottle was around, the greater the likelihood of contamination, should we also be considering size of the dispensing bottle?

Dr. Bressler: Dr. Nguyen, you can or cannot comment with your staff? Or I can discuss it with the Panel when we have more discussion on these comments that came up.

Dr. Nguyen: Yeah, maybe I can ask Dr. Masket to clarify what he means. Are you suggesting certain sizes of dispensers would be outside of scope? Or the size of the dispenser itself would inherently have different levels of risk?

Dr. Masket: The concern is, if we're talking about the longer bottle is available, or open or used, the greater the likelihood of contamination, if we look at a 5mL versus a 15mL bottle, chances are we are looking at a lower likelihood of contamination. I'm questioning, has this been a consideration, or should we consider the maximum size of the bottle in terms of reducing the risk of contamination?

Dr. Nguyen: So again, I would say that we would -- that should be a question to the Panelists if you would like to discuss that, if you do believe that should be a consideration. I'll remind you that from our literature search in our executive summary, where it seems to suggest that that becomes an issue is inadvertent touch of the eye, where that could contaminate the tip that could go into the cap, or something like that. And so, I would like to hear the Panel's thoughts on that. And as part, again, of our GMPs and the quality systems, and under general controls, there are provisions for adequate directions for use. So these dispensers should have

adequate directions for use to ensure safe use of the device. But you know, I would ask the Panel if you have any other comments about whether or not, to Dr. Masket's point, if those considerations are something that you believe need further clarification within the regulation.

Dr. Bressler: We will bring that up within the other comments that we had on some of those controlled installation devices. Maybe I could bring up the first issue that came up with the questions for further, just deliberations right now. These are not questions from the FDA, but just from the Panel. There was some -- I sensed discussion or concern, maybe even… The risks, there are very few identified in the literature from FDA's review with either irrigation devices like these eye cups or these controls instillation devices. Dr. Glasser emphasized that perhaps we should be separating these out, because at least the perceived risk may be different. Like, putting some solution, Dr. Glasser, into an eye cup and you splash it on there is a little different than putting some solution into an eye drop dispenser and dispensing it today, next week, and 3 months from now. Am I interpreting your comment correctly?

Dr. Glasser: Yes, that's what I was thinking.

Dr. Bressler: Okay. Any other comments? Dr. Glasser is suggesting these perhaps be separated out. That the whole considerations and the risks are different for filling an eye cup versus an ophthalmic dispenser. Dr. Weiss. Please.

Dr. Weiss: I agree with Dr. Glasser.

Dr. Bressler: Anyone feel that's overdoing it? As they are so far as being suggested to be lumped together? I think, again, Dr. Glasser is suggesting, and Dr. Weiss is concurring, that perhaps these be separate. Let's talk about --

Dr. Nguyen: If I could just ask clarification to Dr. Glasser and Dr. Weiss on their comments. Are you suggesting that these different products should be under a different regulation? Or do you still believe that, you know, the intended use and risk would still be under the same regulation and should be categorized under Class I? If you could just please specify if you believe the risk puts it into a different class, that would be helpful to us.

Dr. Glasser: You know, I'm not convinced at the moment that the risk difference is enough to classify it differently. But I think we need to talk about it as two different things and consider them separately.

Dr. Bressler: I could concur that they sound both potentially like Class I devices, but there are other Class I devices out there, and I think there's a little concern for the public safety, a little concern about whether it's appropriate to think about the infection risk from filling an eye cup and splashing it somewhere. Is that really the same risk, albeit both low, both falling into to Class I, as filling a dropper and putting those drops in, whether it's preservative-free or has preservative in it, over some time. I think that is the discussion. And whether there's value to sort of keep those separated out.

Dr. Nguyen: Thanks. That's helpful. Just to remind you, if we do believe, for example, that they are within the same risk category, and if we do feel that we could create an identification or regulation that could encompass both, this is just a reminder that under the same regulation, you could still create different product codes to differentiate the different types of dispensers. I wanted to make that clear. If the Panel did feel strongly that they should be two different regulations, then we would need input from you all what the difference in the description should be, any comments you would have on the different risks to public health.

Because then we would have to create two separate regulations.

Dr. Bressler: Okay. Dr Rajpal, then Dr. Repka.

Dr. Rajpal: I was going to follow up on that same issue of whether we really need to split. It's really more a question for whatever processes, at least in my mind, are easiest or best from the FDA perspective. The discussion came about, which I agree with, that the cups can be nonsterile, but the others need to be sterile. So perhaps it doesn't have to be split, but rather just clarified from that perspective, if everybody agrees with that.

Dr. Bressler: I want to bring that up as a follow up issue in a minute, Rajpal, just to keep it separate, about whether the ophthalmic dispensers need to be sterile. And we will go around the group for that. Hang on to that thought for just a minute. Dr. Repka.

Dr. Repka: It seems to me that the big premise here is that the IFU for the two different approaches for what the patient sees would differentiate the product. And what I'm curious is, do you need a separate classification if you're allowed a different IFU for the open eye cups versus the sterile dispensers? Because the patient who refills an eye cup, no problem. But as was brought up, the droptainer that's filled, the patient assumes it's sterile when in fact it may not be, and that's potential bigger risk. If a single regulation in this class works, that's fine. If you can have different IFUs, that would be better.

Dr. Bressler: Dr. Nguyen, that seems to be similar to the comments I heard from the other doctors.

Dr. Nguyen: Anything that has to do with regulation has to fit the identification of that regulation and the intended use. To your point about labeling and separate indications for use,

indications for use can be different. I do believe, creating different product codes to differentiate the different types of dispensers within the same regulation, there can be different expectations. But I would ask our policy advisor on the call, Jismi Johnson, for anything she has to add on the logistics of separating these out products within the same regulation.

Jismi Johnson: Hi, this is Jismi Johnson, I agree with what Dr. Nguyen said. If we see that the technology and intended use of the droppers and the eye cups are similar, the risks to health are similar, we can keep them under one regulation, separate them out by product code for tracking purposes and categorization. But if the Panel does agree that droppers have different risks that need to be mitigated, whether in Class I or Class II, we could separate them out into different regulations. And additionally, we can talk about adding additional language to the identification language in the proposed classification reg that we have identified to add additional information to clarify droppers and eye cups.

Dr. Bressler: I think I heard from the Panel, but I'm going to open up for them to agree or disagree otherwise, that the risks are perceived to be different for eye cups versus ophthalmic dispensers. If that helps with what Dr. Johnson just mentioned… I didn't hear disagreements, so we are going to say that the Panel believes that the risks, while low in both from your literature review or reports or the experience of the ophthalmologists, while the risks are low for infection, they believe that they are different.

Ms. Johnson: If we can also, either now or later, talk about what those different risks are. What would be different than what we have already presented for these collectively?

Dr. Bressler: Does anyone want to comment from their experience, expertise? We don't have anything from the FDA's literature review to say that there's greater, let's say bacterial

infection, necessarily. Although, it has been seen that culturing those bottles, etc. have infection. I'll go to Dr. Weiss and then to Dr. Glasser so we can address Jismi Johnson. Are the risks perceived as different or likely different?

Dr. Weiss: I think the expectation of the patient is different. When one has a medicine filled bottle, the expectation is that it's sterile. When you're using an eye cup, the expectation for sterility is not the same.

Dr. Bressler: Dr. Glasser?

Dr. Glasser: I agree with Jayne. If we're talking about bottles that are coming empty and they're being filled by patients, the patient is not going to use sterile technique in filling the bottle. And I think there is a reasonable expectation, at least theoretically, that there could be bacterial contamination inside the bottle, even if it comes sterile. And if the bottle is used for many days, weeks, or months, the risk of bacteria growth, if it's a non-preserved solution, it's greater. That's all theoretical. I don't think there's been any published literature that shows that. But we just need to think about that when we decide how we classify these.

Dr. Bressler: The feedback to the policy experts, could you consider that the risks are different for infection, even though we don't have scientific information to confirm that? It's tough to prove the negative so far in this. Now I want to get to the sterility issue. Were there comments from the group that these ophthalmic dispensers that have this controlled instillation should be sterile? That's the first question for the group. Or could some be marked as sterile and some not sterile? I'm just expanding on the discussion here. Ms. Jennifer Schwartzott.

Ms. Schwartzott: I'm the patient representative, Jennifer Schwartzott. I have chronic

progressive septo-optic dysplasia, and I regularly use these drops throughout the day. I use all of the different kinds. I tend to stay away from the eye cups because of the lack of sterility. I also use the single use and I've never, ever overused those. When I'm done with that initial drop, I won't use it again. But I know other people do because they are expensive. I've always been concerned about how sterile they are in a bottle that is bigger that's been around for a little while. It goes in my purse; it sits in the house. You try to keep it under cooler temperatures, but it doesn't always happen. I think that's definitely something that needs to be addressed. I have had mystery eye infections where they have no idea how I got them or even what they were. I have never ever, did I ever remember, have I touched my eye with the dropper itself. So, I could see that people could do that if they had Parkinson's or arthritis or something. It has never happened to me that I remember. So, I don't think that's as big of a risk. But I do think that the sterileness is important.

Dr. Bressler: I'll expand to our panel of experts, if somebody has expertise just to make sure we covered this, and then I'll get to Dr. Masket's comment. If you take something that has preservative in it and you put it into one of these ophthalmic dispensers, does the preservative still work? So it came in a combined device, contact lens solution or something, which has preservative in it, and then it's put into one of these ophthalmic dispensers, does it remain doing its preservative thing? Or does the risk of infection go up? No comment there. Okay. Dr. Masket we are going to continue with your question or comment, and I'll come back to any other comments on whether these should be marked as starting as being sterile, although as mentioned, they may not stay sterile thereafter. Dr. Masket.

Dr. Masket: When we talk about sterility, I think we need to define what exactly is

supposed to be the sterile part. So, the contents, the cap, what is under the cap? And that differs for single use versus multiple use dispensers and devices. I think we need a little bit more clarity. Again, we are assuming that these are sterile, but I think we need to know specifically what part is sterile or is not sterile, or what we would like to be considered as sterile.

Dr. Bressler: Dr. Nguyen, do you want to comment? Are these sterile to begin with right now?

Dr. Nguyen: I'm assuming that Dr. Masket is talking about droppers and not speaking about eye cups within this context. So again, we in the Center for Devices have only cleared 5 eye cups as ophthalmic dispensers thus far. It seems like you may be speaking about situations or combination products that are prefilled. So, I won't speak too much on the combination products other than to say that no issues of sterility are assessed as part of the product evaluation. But again, from the device side, we have only cleared 5 eye cups, which have been both sterile and non-sterile.

Dr. Bressler: But are you looking for clarification for ophthalmic dispensers, let's say, that are empty and might be filled with something? Those right now have no classification, correct?

Dr. Nguyen: Yes, that is correct. And we are only talking about empty dispensers that may be prefilled with some type of ophthalmic solution.

Dr. Bressler: Dr. Kwon, please.

Dr. Kwon: I just want to clarify and ask the question, are we talking about ophthalmic dispensers here that include combination products? In other words, say take Altimolol, for

example, that comes in a dropper bottle that is multiuse. Whatever we decide in this panel, will that apply to those ophthalmic dispensers that are part of the combination product? The regulation? Are we talking about that? Or are we talking about stand-alone product that has no medication in it? Can you clarify?

Dr. Nguyen: Yes. You are correct that we are only classifying empty ophthalmic dispensers. Combination products are outside the scope of this classification effort, but what we can say is that the considerations for evaluation of a combination product on the device side would be similar. So however we decide to evaluate the empty ophthalmic dispensers, we would have the same considerations for a combination product from a device perspective.

Dr. Bressler: Okay, let's go to Dr. Weiss.

Dr. Weiss: I'm a little concerned we are on dangerous ground because we don't have manufacturing expertise. While, as an ophthalmologist, I would assume, presume… those words get to the danger that before you're putting something else inside, the inside of the bottle is sterile. But for someone that does the actual manufacturing, has knowledge about that, maybe that's never the case, maybe whatever is put inside, the ingredients are such that it's irrelevant whether the inside of the bottle is sterile. I would be concerned about making regulations or advisements in the absence of having that knowledge of what the manufacturing is currently, that basically gives us a pretty darn low infection rate.

Dr. Nguyen: So I think that to your point, I will ask Dr. James Bertram, who is the Center for Devices Product jurisdiction officer to comment on that.

James Bertram: This is James Bertram, making sure everyone can hear me. So I

think at the end of the day, as Dr. Nguyen mentioned, we are focusing on a standalone product. I think Dr. Weiss, to your question, in the context of manufacturing controls, I think you also mentioned if it was going to be filled with Altimolol, the appropriate drug manufacturing controls as well as device manufacturing controls would be in place. If that drug product is intended to be sterile, then there would be appropriate controls in that place as a combination product, either from the drug or the device GMP side, to ensure that product is appropriately sterile. I hope that addresses your point, and there may not be GMP experts on here, but I just want to assure the Panel that, in the context of a combination product, as a drug product, if that combination product is meant to be sterile, the drug and device GMPs would be in place to ensure the sterility in the context of the combination product.

Dr. Weiss: So this is a follow up. Do we expect any of the droptainers to be used in any setting besides a manufacturer filling it with medications? Do we expect that a patient could fill it up with something, or someone else aside from a manufacturer would fill it?

James Bertram: This is James Bertram. I defer to the group and to those more aware of the practice in this space. If there is a stand-alone product out there that may be utilized as you just proposed, that could be a consideration for the Panel. However, it may not be all that common, the fact that that question was just posed to everyone. I don't know, I don't have the expertise on that specifically, but I would say if that product is on the market for a patient to do that, then that is something that we would be speaking to or would want to make sure we consider appropriately in this discussion. But not dwell too much on I think, the former consideration of, if it is prefilled in a manufacturing context, I don't think we need to dwell too much in that, as the implications here, and I just want to try to reiterate that this may help inform

considerations, but not say if, for example, here we say eye cups should not be sterile, again, that may be a decision. If for some reason there's a drug product that includes an eye cup and it's determined to be sterile, that doesn't preclude it from being sterile. It takes in the context of that drug product and what that to-be-marketed product would be. I hope that helps.

Dr. Bressler: To expand on that, if there's a product, let's say it's a contact lens solution in a large bottle, and somebody gets a small ophthalmic dispenser because they want to travel and be TSA compliant, does the bottle specifically say, 'don't repackage this as a member of the public into one of these small bottles?'

Dr. Nguyen: So we do have Dr. Angelo Green on the line. He's the Assistant Director of the Contact Lens and Dry Eye Devices Team. So I'll let him comment on your specific example.

Angelo Green: Hi, so thanks for the question, Dr. Bressler. Angelo Green. When we clear these, they are cleared with certain size bottles. And some of them could be cleared as smaller bottles. And essentially the testing that is done takes into account the size of the bottle. We can't control what consumers do all the time, as you know. But the labeling and what we clear is really based on sizes of the bottle, which are tested as part of the review process. So, the fact that consumers do this, we can't necessarily control whether they switch bottles. But in certain cases, small bottles are tested, as part of the review process. I hope that answers your question.

Dr. Bressler: Perhaps, I don't want the beat a dead horse, but we are being asked for opinions on language for these ophthalmic dispensing bottles, so I'm trying to give a concrete example that could happen in the public where the public takes their bottle that they are convinced has preservative and safe, etc., to use for their contact lens. Now they have these

ophthalmic dispensers that you're now deciding how the classify. Does it need to be noted in the future that this is or is not, this little ophthalmic dispenser bottle, as a stand-alone, is or is not supposed to be considered to be used to repackage something from a preservative or a preservative-free material? I think that's what we are thinking about. Because we don't know if these ophthalmic dispensing bottles as stand-alone would necessarily serve the same function holding that contact lens solution. I'm just giving that as an example.

Dr. Rajpal: Can I comment on that?

Dr. Bressler: Yeah, please.

Dr. Rajpal: Sorry to interrupt on this topic, but I was able to check while we were talking about this on how the J&J Vision Care Team handles this. It says, “From the FDA guidance on contact lens care solutions, we are putting the following warnings: to avoid contamination, do not touch tip of container to any surface. Replace cap after using. To avoid contaminating, do not transfer to other bottles or containers.” It’s not my area of expertise in terms of the labeling, but to answer your question, I do believe industry is doing it that way, but again, the FDA can address it better than I can.

Dr. Bressler: Right, and maybe confirm that all are doing that, perhaps. Dr. Green?

Dr. Green: Yeah, Dr. Rajpal is correct. We have those recommended warnings for our bottle labeling. Whether that should extend to the stand-alone bottles, that's why we are here, and we would appreciate the Panel's recommendation on that.

Dr. Bressler: Okay. Dr. Pulido.

Dr. Pulido: Just clarify for me, so let's say I got some lye in my eye and then I used an

eye cup irrigating system, that doesn't have to be sterile? There could be pseudomonas on that?

Dr. Nguyen: So again, I'll just bring you back to the executive summary. For the purposes of eye cups, we have cleared a couple that were non-sterile and in the public 510(k) database where you can read the summary of the information, they were a long time ago, so I'll say they are not that detailed as they are today. But there are directions on rinsing out those eye cups prior to use. I don't know if that answers your question. Those are the situations that we're aware of.

Dr. Pulido: I don't know if that completely answers the question. Would the system, the way it is now, allow for a non-sterile eye cup to be placed on an eye for irrigation?

Dr. Green: As Dr. Nguyen states, we have cleared non-sterile eye cups for the purpose of irrigating the eye. That means you know, it would be allowed per our clearance, specifically for eye cups. Does that answer your question?

Dr. Pulido: Yes, it does.

Dr. Bressler: There may be some comfort from other members, that doesn't mean it's right or wrong, of having the eye cups not necessarily be required to be sterile.

Dr. Pulido: Thank you.

Dr. Nguyen: Yeah, just to reiterate Dr. Bressler's point, we are here today to ask you, as the subject matter experts, whether or not you believe these products should be sterile. So if you have any comments on that and the justification, we'd appreciate any comments you have.

Dr. Bressler: And Dr. Nguyen, if I could expand to what Dr. Rajpal said, if there are products that are not intended to be put into these ophthalmic dispensing bottles, what is intended

to be put in them?

Dr. Nguyen: So I just want to make sure that we are not trying to suggest in any way that products that are clearly labeled to not be transferred, we don't want to suggest that these ophthalmic dispensers should be used to adulterate an approved or cleared product.

Dr. Bressler: Or repackaged, agreed.

Dr. Nguyen: That's a good question. What would these bottles be used for when empty? I think that Dr. Bertram was trying to allude to that. You all are the experts on what those uses are. I'll bring you to what we are aware of at the Centers for Devices, are those products are combination products and the dispensers we have cleared. I don't know if Dr. Elissa Wong wants to comment further on this.

Dr. Wong: Hi. So as Dr. Nguyen mentioned several times, for the eye cups, they have fallen under product code "LXQ", which made it easy for us to track which 510(k)s have come in, and there were only 5, and which devices those were, and what FDA had seen. There are many eye cups that are being sold without 510(k) clearance currently. We also needed, for this panel, to do research on droptainers, eyedroppers, none of which have come in to FDA, so we didn't have records on them, and they don't have product codes associated with them. We did do research to find out, are stand-alone empty droptainers, standalone empty eyedroppers, are they being sold direct to consumer as sterile? Non-sterile? So this is just information gathering. So what we found out is that in general, there are different companies that are selling direct to consumer both sterile and non-sterile droppers, including droptainers and eyedroppers. So that's what we found out. So, I guess that's kind of the state of what exists out there. I hope that is helpful.

Dr. Bressler: Very helpful. Yeah, let's go to Dr. Repka and Dr. Weiss and Dr. Pulido.

Dr. Repka: Two things. I just wanted to ask the FDA if the sterile cup is single use only, or if it's marketed for continued use, because that will relate to the sterility. And then I also wanted to ask, with respect to the droppers and the sterility, if a 503 (a) compounding pharmacy is touching the product, does that come under this jurisdiction, in which case, of course, we'd all want that product to be, or that device that they're purchasing empty to be filled, needs to be sterile. And if it doesn't fall under the purvey of this discussion, of course, that's important as well.

Dr. Bressler: Okay. Let's take the first one.

Dr. Nguyen: Yeah, can you remind me what that first question was again?

Dr. Repka: The single use versus multiple use, is there any marketing of that?

Dr. Nguyen: Yeah. I will turn it over to Dr. Elissa Wong to talk about those products, as she was the one that did the research on that.

Dr. Wong: Hello. So for the eyecups, the ones that have been cleared, the ones that have been cleared as sterile always specify for single use, disposable after one time. The other ones that were cleared as non-sterile were allowed to be reused, and there were cleaning instructions for in between use as part of the labeling. I can also dig up some of the labeling examples if that's helpful, and it will take me a little bit, if that's helpful. So maybe come back to me.

Dr. Nguyen: Yeah. And this is Tieuvi Nguyen, if I can answer Dr. Repka's second question that, you know, ophthalmic dispensers for use in compounding facilities are outside of

scope of this classification effort.

Dr. Bressler: Okay. Let's go to Dr. Freddo, and then Dr. Weiss. Dr. Freddo.

Dr. Freddo: I guess, for me, at least, and I'm sure there's not data on this, to the extent that we would worry about reuse on an eye cup, from my perspective, the thing I would probably worry about even more would be a device where you had an eye dropper that had a draw bulb at the top. And whether or not that would be a reusable device, whether purchased initially sterile or not. To me, I'm more concerned about something hiding up in that bulb on second use than I worry about really the surface of an eyecup. Both are a concern, but what's buried up in that draw bulb, to me, is potentially problematic.

Dr. Bressler: And Dr. Weiss.

Dr. Weiss: Yeah, so it seems like sort of following the discussion here, we have eyecups and droptainers. Eyecups are meant for the consumer. Regulations, I think, for the consumer are different. One could argue single use sterile, multi-use non-sterile, and that's a second question. I would say for the droptainers, there should be a stipulation or warning, this is not meant for consumer. If it's not meant for consumer, then I think we don't have to have the same concerns for sterility inside because it will be the company or someone who's familiar with pharmaceuticals in terms of following regulations. But I would, under what we're speaking about presently, it seems that there should be something for these standalone droptainers, that these are not meant for use by the consumer.

Dr. Bressler: Dr. Weiss, I'm not a legal expert. I'm just anticipating, if these are already marketed to consumers, for whatever reason, maybe somebody puts paint in them and uses it to

drip, you know, a little paint on or something, that it may be difficult to regulate that. But I just say that as an aside.

Dr. Weiss: Perhaps not to regulate it, but as a warning in terms of what could happen if you use it. Otherwise, we do get involved in having to regulate how the container, the sterility of it because we don't know that the [cutting out]. But I agree, we can't lawfully tell people [audio cut out].

Dr. Bressler: You may be suggesting not intended for repackaging something or other, but I understand. We'll bring that up. Okay. Dr. Pulido.

Dr. Pulido: Yeah, it's interesting that while you're talking, I see that one can get, online, these eye drop bottles, and it doesn't say anything about sterility. And one says, 'great for solvents, light oils, eye drops, saline, et cetera.' So I didn't realize that this is a significant problem, and if it does say for eye drops, it should be regulated and sterilized. That's my thoughts. Thank you.

Dr. Bressler: We'll come back to that, then, about the challenge of this. Maybe somebody uses it for tiny little drops of something while they're cooking, even, so I'm just pointing that out. Dr. Nguyen.

Dr. Nguyen: Those are really good comments. I just wanted to remind you that, you know, a dispenser would have to meet the definition of a medical device and has an intended use for medical purpose and that's what, you know, we should view all our comments within that context. But I think those are good comments.

Dr. Bressler: Okay. Are there other comments or clarifications before we end our

deliberations? Because we'll then have the FDA post specific questions to you. Dr. Freddo, I'm going to ask you to speak next, and I apologize. Your background happens to have almost the same color yellow by your blinds. But please, speak out if I miss you. So Dr. Freddo, and then Dr. Kwon.

Dr. Freddo: My question to the FDA group is it seems to me that we've opened a bit of a can of worms here in the sense of we're talking about eyedroppers as a panel. The reality is, I would assume, that everything we're discussing would have to be equally applicable to anything dispensing nose drops or ear drops. So is there a presumption that there will be across the board consistency in the FDA regs regarding those drops and droppers as well? Thank you.

Dr. Nguyen: So I would just say that, you know, we regulate products based on intended use, and then evaluate the risk based on that intended use. And if a dropper is used for different parts of the body, those would be separate evaluations. And so I can't really speak to, you know, those instances, but they would be separate regulations, and with their own risk analysis.

Dr. Bressler: And Dr. Kwon.

Dr. Kwon: Just switching gears a little bit to the eyedrop size. I think this was originally brought up by Dr. Weiss at the beginning of our conversation. I was wondering if the FDA, and of course the issue is that currently, the eye drop size from, say, droptainers, vary widely. I think my reading is that it comes anywhere from 25 microliters to 70 microliters per drop, and we know that the eye fissure, conjunctiva fissure, can only hold up to about 30 microliters. So anything greater than those is either waste, or even an overdose of whatever medication is being applied and suspended topically, may have systemic side effects. So is there

any regulation as to the appropriate drop size as we discuss this ophthalmic device?

Dr. Nguyen: I think that the issue that you're talking about regarding drop size and potentially dosage is really more of a drug issue within the context of that specific drug. So again, I would say that would be outside of scope from the device perspective. But I think that, you know, those points are valued as part of the evaluation of the drug product.

Dr. Bressler: Thank you, and if I could have one final deliberation from anybody who has expertise on the Panel, the FDA did their systematic search and found very little evidence of infections resulting from however people might be using these droptainers right now. And I just didn't know if there was any experience or otherwise expertise on the Panel to suggest otherwise, that there are infections in the cornea from somebody repackaging something and irrigating. So Dr. Jeng, I'll go to you first. I'm just deliberating here.

Dr. Jeng: Within the literature, I think we all know about it, obviously many more cases than have actually happened was reported. We see them at meetings, they're reported as abstracts. It's not so novel and so it doesn't get into the peer reviewed publication. So we know that it happens. It's not very common. We know that these containers are contaminated. I mean, studies over and over that have not been published have shown this. But actual clinical infection, it happens, but it's actually not that common.

Dr. Bressler: Okay. Thank you. I just wanted to have that for our deliberations as well. Dr. Kwon.

Dr. Kwon: If I can just add to that, it may be so, because of the preservatives that are in the bottle. And so, of course, they aren't commonly contaminated, I think after multiple use,

but they don't become a clinical infection as much because of the preservatives that are in those medications. That would be my comment.

Dr. Bressler: That's helpful for my deliberations, at least. Okay.

Any other comments in the group? Because we're going to consider having a refocus. I know we've been going a long morning here, but we definitely have to refocus to be able to address the FDA questions. And Dr. Tieuvi, I don't know if there's anything else you wanted for general discussion before we get to those questions from the panel.

Dr. Nguyen: No, I don't have anything else. Thank you. It's been a good discussion.

Dr. Bressler: Thank you. Dr. Pulido, I think you had one additional comment.

Dr. Pulido: Yeah. One last comment to the point of Dr. Jeng. Again, I think one of the exclusion criteria were single case reports. And so, these were at least eight or more, was what the review inclusions were. So, that would negate the vast majority of singlet cases.

Dr. Bressler: And I think as Dr. Jeng said, the novelty of this is not new. It's been reported. It can happen, so now people know it can happen, so it may not get in the literature, per se. That doesn't mean it wouldn't have been reported to somebody or a physician would not have taken care of it. Okay.

## PANEL Q&A

### Question One

Dr. Bressler: All right. So at this time, let's focus our discussion on the FDA questions to the panel. Panel members, copies of the questions have been sent to you electronically and

posted online for the public. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. And I'll now turn it over to Dr. Elissa Wong, who will read FDA question number 1. Dr. Wong.

Dr. Wong: FDA has identified the following risks to health for ophthalmic dispensers: infection, adverse tissue reaction, compromised treatment, and mechanical injury. Please comment on whether you agree with the inclusion of all the risks in the overall risk assessment of ophthalmic dispensers under product code "LXQ." In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these ophthalmic dispensers.

Dr. Bressler: Okay. And I'll ask the panel to comment on that, please, if somebody wants to start, if they agree or if they have additional risks that they think should be listed there. And I'll start with Dr. Repka and then Dr. Glasser.

Dr. Repka: So I think the FDA has identified the risks. I think we've enumerated some sub-risks, if you will, in the discussions. But these are the risks, and they seem to have been very low in the literature review. And should be low in the way these devices appear to be being used as medical devices.

Dr. Bressler: Thank you. Dr. Glasser.

Dr. Glasser: I agree with Dr. Repka. I think these are the relevant risks. I think they're appropriately identified, and I do think the risks are very low.

Dr. Bressler: So I'll turn to the panel if anybody has additional different comments in terms of are these risks listed adequate or are there additional risks? So we'll take those

additional comments then. Dr. Pulido.

Dr. Pulido: Yes. So there is another risk in that there are case reports in the literature of super glue being put on the eye because the bottles looked similar to the bottle used for the drops. So similarity in bottle size, et cetera. So that should be added to that also.

Dr. Bressler: Understood that you want to have that taken into consideration, that it could look similar to things that are not ophthalmic droptainers, let's say. Thank you. Dr. Freddo.

Dr. Freddo: Apropos to the prior mention of the pediatric population, I wonder if there should be an addition as to variability among dispensers in terms of the volume or dose that they would administer on a single drop. That may be overdoing it, but I just want to bring it up, particularly relevant to the pediatric population. Thank you.

Dr. Bressler: Okay. So you want to at least consider taking into consideration that the pediatric population may have a different, let's say scenario, because of the size of the drops relative to the size of the pediatric eye or cul-de-sac, et cetera. Understood. Any other comments about additional risks, or what was said so far?

All right. I'll turn to questions from the FDA. So Dr. Nguyen, with regard to question 1, the panel agrees with the risks that were identified, and that they were appropriate, and that they should be interpreted as these should be quite low risks. So obviously there were reports otherwise that it was more than a very low risk, that does not make sense, and that there should be some consideration to whether these droptainers could mimic other devices that might get mixed up with them to at least take that into consideration, along with whether anything has to be considered regarding the size of the drops for pediatric population. But the risks do seem

appropriate as identified.

Dr. Nguyen: Thank you so much. No further clarifications needed.

Question Two

Dr. Bressler: Okay. If that's adequate, I'm going to turn to Dr. Wong to then read Panel Question Number 2 for us.

Dr. Wong: Question 2: Section 513 of the Food, Drug and Cosmetic Act states a device should be Class III if: Insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and, if the device is purported or represented to be for use in supporting or sustaining human life or for use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, and there is sufficient information to establish special controls to provide such assurance. A device should be Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness or insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, or establish special controls to provide such assurance, but is not purported or represented to be for use in supporting or sustaining human life or for use which is of substantial importance in preventing impairment of human health and does not present a potential unreasonable risk of illness or injury.

FDA does not believe that special controls will be required for ophthalmic dispensers

under product code "LXQ," and that general controls will be sufficient to provide a reasonable assurance of the safety and effectiveness of ophthalmic dispensers. As such, FDA believes that Class I is the appropriate classification for ophthalmic dispensers under product code "LXQ."

Please discuss whether you agree with FDA's proposed classification of Class I for ophthalmic dispensers under the product code "LXQ." If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification. This concludes the panel questions.

Dr. Bressler: Okay. We're going to ask for feedback on this. If I could turn to anyone on the panel that wants to comment on the classification, which is proposed as Class I classification and whether further clarification is needed within this classification. Dr. Weiss.

Dr. Weiss: I would agree and answer to the question with Class I classification. I would also agree with Dr. Glasser and others' proposal to split eyecups separate from droptainers. The question is also can we have a guidance or a warning in terms of droptainers are meant, if they're going to be if they're going to be used for something to be administered to the eye, they're not meant for patient use. I don't know if you can say that or not.

And then I would open it up to others' discussion in terms of do we mention sterility, or do we not mention sterility? I would feel comfortable not mentioning sterility if they're not meant to be used for patients, and they're only meant to be used for companies. I'd feel less comfortable with not mentioning sterility if patients, or we won't have an exclusionary guidance for patients. And for eyecups, I think I would probably feel comfortable not having them be sterile, but I'll leave that up for others to comment.

Dr. Bressler: So I'll open to the Panel to further comment on the question. We'll expand from Dr. Weiss, who summarized nicely. She's recommending, as an answer to the question from the panel, that it be Class I, but as was discussed, we have the FDA consider splitting out eyecups versus droptainers. They just seem to be too different to the panel with respect to risk, at least a perceived risk for infection. And part 3, though, from Dr. Weiss, is to say that perhaps there should be some guidance that those droptainers not be for patient use, or that there be some consideration of guidance regarding single, multiple use, preservative free, or preservative stuff.

So that's a lot, but I think you distinguished it well, and I'll open it to the panel to comment either if you disagree with the Class I or disagree with the eyecup versus droptainer separation, and then I'll open it up to any other further clarifications or comments regarding should it be indicated not for patient use or some guidance in that way or should it be indicated sterile/not sterile, single use/multiple use. So those are sort of two separate clarifications if we go down the splitting eyecup and droptainer. Any comments from the group on that summary so far, or suggestions? Dr. Rajpal, please.

Dr. Rajpal: I'll speak on behalf of the industry for a moment. I agree with the classification as Class I. The other topics that were just raised I think are important and do need to be addressed, and whether they're addressed as a splitting or whether it is clarity of the definition of which products, I think either way the FDA can certainly guide us and manage based on their internal processes, I would think. So I would be comfortable with that.

I think the other thing that we should just consider, and maybe I'll wait, Dr. Bressler, if you want me to, but it's kind of a continuation of the same topic, which, again, clarifying the definition, which I think Dr. Glasser had started with in terms of saying external. And as I was

thinking about how industry approaches this, maybe it should also include something about being topical, and unfilled. So that I think it would be clearer that those are the containers we're talking about. I think we've all expressed some confusion from that perspective.

Dr. Bressler: Very helpful. Topical or external, or whatever the appropriate definition is as used in FDA, let's say, regulations, but to also indicate unfilled. Dr. Repka.

Dr. Repka: Yeah. If I could suggest either whatever the correct regulatory term is, empty as opposed to or unfilled, whichever is an appropriate term to use there. I think that special controls, at least by the way I read the regulation, are not necessary here, that the general controls are the product, quality of production are what's going on here, and the special use that is going to be made for that application of a medical device would govern under general controls, what has to be done in terms of sterility.

Dr. Bressler: Okay. So Dr. Repka is providing some guidance that we consider these items of, you know, sterility or not sterility would fall under general controls. Yep. Okay. Dr. Kwon.

Dr. Kwon: I agree with the Class I classification of the ophthalmic dispensers we discussed today, and as was pointed out by earlier speakers. This is Young Kwon here. I have a question. If we're going to have the word "empty" or "non prefilled" to the definition of ophthalmic dispensers in this product category, what would be the implication of that if the product is a combination product, say filled with a glaucoma drug or steroid as the FDA is evaluating that new glaucoma drug that has a droptainer, would our classification and that definition that we're trying to change have implications on the combo side from the FDA perspective?

Dr. Nguyen: So again, I think that I stated earlier that obviously combination products are outside the scope, but yes, the considerations for combination products for the device constituent part would be similar.

Dr. Bressler: Okay. Do we have other comments from the group so far? I'm going to do a little pre summary first to see if there's any other comments from the panel before I present that to Dr. Nguyen as our proposed summary.

So I've heard so far that we have consensus that this should, indeed, be, in answer to their question, within Class I. That there be some consideration, however is most appropriate to think about perhaps a product code that's lumping eyecups and droptainers may need some clarification, that it's not exactly the same things, and that it may be of value for collecting adverse events or reporting or for understanding the whole area here and the risks, and that the general controls are probably sufficient to address the issues that were brought up during our deliberations about, you know, is this going to be preservative, preservative free, single versus multiple. And that while the FDA may take those comments in mind, the general controls should be sufficient, and that their comments that perhaps it could be considered as, you know, for external or topical, whatever the appropriate term is, to separate out that, you know, syringes or other things that are used to go into the eye, and that it be considered empty or unfilled, whatever the appropriate use is, recognizing that that shouldn't separate us out from when this is a combined, you know, product and device, you know, that's put inside of it. Obviously, it's not going to be empty anymore. So I'll open that up to any clarifications before I turn it over to Dr. Nguyen what we think. Dr. Pulido, please.

Dr. Pulido: So should it say it should be sterile if intended for eye use?

Dr. Bressler: I think that didn't come up as specific language, but I'll open that up to if you'd like to at least consider that, I'll open it up to other comments from the group. Did the group want to recommend that it if the FDA have this for ophthalmic use, that it be indicated that it be sterile? Dr. Masket?

Dr. Masket: Hi. The problem is, if it's going to be sterile in advance of being filled, then, you know, that doesn't really weed the end product. And then you're talking about then it's a combination product, and that might also cover the dosing, whether it's 30 microliters, 50 microliters, or what have you. So I think it's hard to mandate that something be sterile before it's filled, if we're saying this is an unfilled product, then how can we mandate that it be sterile. It's after it's filled, and that's a different ballgame there, I think.

Dr. Bressler: I think that's why we were considering that unfilled for that. Okay. Dr. Rajpal.

Dr. Rajpal: In follow up to those points, if we're getting into the sterility issue again, should it be only a single use then? Because we know that after something is put into it and used, it's no longer sterile. So I'm not, I don't have a suggestion. I'm just raising that as an issue.

Dr. Bressler: I would propose that we brought up this concern about once you fill it, is it sterile, who repackaged it, who's watching it, and that there's a general recognition that those bottles at least can be cultured with problems, so we did bring that up. Dr. Glasser, did you have another comment?

Dr. Glasser: I was just going to say what you just said, Neil. Nothing to add.

Dr. Bressler: All right. Any other comments? Because I want to try to get a summary to

Dr. Nguyen. So Dr. Nguyen, the panel generally believes, or there was a consensus, at least, that it be Class I. They generally believe that there should be some consideration of however you regulate or make your product codes that a consideration be recognized that eyecups are not necessarily the same as droptainers in terms of the risks for the individual, and so that perhaps there be some way that you can recognize, and the public can recognize the separation.

That the wording consider some way of indicating if this is for external or topical use, and that we're only discussing right now an unfilled or empty container because so many things happen after that we're not commenting on what could happen after that. And that some consideration be given as to recognizing what has to be done in these classifications that will recognize there may be preservative material put into these, preservative free, single use, multi-use, et cetera, and to just please come back to us or others in the field to address any safety problems that might be addressed by that.

So I think that was the general consensus from the Panel and the concerns that they had. So Dr. Nguyen, I'll open it up to you to clarify back to us what you might need.

Dr. Nguyen: Thank you so much for that. I do not think that I have any other follow up questions. I think that's very clear. Thank you.

FDA SUMMATION

Dr. Bressler: Very good. Okay. At this time, the Panel will hear some summations or comments or any other clarifications that the FDA may have. Dr. Nguyen.

Dr. Nguyen: Hi. Thank you, Dr. Bressler. So I just wanted to thank, first of all, all our distinguished panelists today, and including our consumer, our industry and our patient

representatives for joining us, for the really informative discussions, and, of course, a big thanks to our FDA team that he is on the line right now for all their hard work. There was a lot of research that had to go into this, so I thank them for their efforts.

So we'll certainly take all your feedback into consideration when we draft the final rule for the regulation for the dispensers, and as Dr. Linh Lo had stated in her presentation, the next steps will be to draft the final rule. It will be posted, and we will take comments on the language, so all your considerations hopefully will be incorporated into that final rule.

And then lastly just wanted to thank Dr. Neil Bressler again for chairing this classification panel. Thank you all so much.

## ADJOURNMENT

Dr. Bressler: Thank you, Dr. Nguyen. I also want to thank all the panel members for their input and expertise, the FDA and the presenters for their contributions to today's panel meeting. This meeting of the Ophthalmic Devices Panel is now officially adjourned. Thank you, everybody.

[Meeting adjourned at 11:33 a.m. Eastern Standard Time]