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Exploring Policy Options for Establishing Cannabidiol Safety Surveillance

Washington, DC | July 17 & 20, 2020

Introduction

Since the passage of the Agriculture Improvement Act of 2018 (2018 Farm Bill), consumers have experienced increased access to products containing cannabidiol (CBD). CBD is one of the many cannabinoids found in the cannabis plant, along with tetrahydrocannabinol (THC) and others. Since 2018, many products containing CBD have been produced and sold in the U.S.; however, there remains a lack of information about the safety of CBD products. Establishing a CBD safety surveillance system would help regulators, public health officials, and healthcare providers collect data to advance understanding of CBD product hazards and enable them to quickly identify and respond to emerging CBD-related public health concerns.

Despite the fact that many of these products violate the Federal Food, Drug, and Cosmetic Act (FD&C Act), currently available CBD products traverse the many FDA-regulated product categories, including drugs, foods (including dietary supplements and animal feeds), cosmetics, and medical devices. Although marketed to consumers, the products are not commonly represented in healthcare databases or registries. In addition to safety concerns arising from indiscriminate consumer access and potential exposure to multiple products across multiple regulated categories, CBD content may not be accurately communicated on labeling or standardized batch to batch, and products may contain THC or contaminants.

To date, no single approach to monitoring the longitudinal safety across different CBD product types has been developed. Given the potential emergence of products with other substances that exhibit many of the general features of CBD products, lessons learned in evaluating the safety of CBD products may inform future approaches.

On July 17 and 20, 2020, the Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), convened a private workshop to explore opportunities to develop CBD safety surveillance systems and approaches. This document summarizes the workshop presentations and discussion, with the goal of informing policymakers and public health professionals interested in establishing a CBD safety surveillance system.

Session 1: Introduction to CBD and Monitoring Risks of Consumer Products Regulated by FDA

This session provided an overview of emerging trends in the consumer use of CBD products, as well as foundational challenges and opportunities around the monitoring of such trends. Recent experience with products such as e-cigarettes informed parts of the discussion surrounding CBD. Discussion also considered how safety is assessed in non-drug products, such as dietary supplements. Participants also considered an international case study thatexplored CBD and cannabis regulation in Canada.

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Regulation of CBD Products in the United States

Regulation of CBD was a key topic in the first session. As an opening presentation noted, states have taken different approaches to the sale of CBD, which has expanded and evolved widely following the passage of the 2018 Farm Bill. Twenty states permit CBD to be sold as a dietary supplement or food additive, twenty states have no direct laws, and ten states have prohibited the sale of CBD in such forms.

Speakers in this first session described adverse effects that are known to arise from CBD use, including sedation, somnolence, liver damage, and interactions between CBD and other drugs. Even though there are some existing studies related to these safety concerns, speakers in the session called for additional research on the effects of CBD.

Participants in this session discussed issues related to the regulation of CBD products, including lack of standardization in the product form, labeling, contaminants, and dosing. Some participants in this session believe there is a growing body of evidence that CBD products are safe at levels typically found in currently marketed CBD products, there still remains widespread inaccurate labeling of THC or CBD content and a small amount of product adulteration with heavy metals. Speakers also noted that dosing is especially challenging to assess if consumers are using multiple CBD products; however, dosing is also a crucial factor in understanding risks of CBD use. Acetaminophen was mentioned as a product that faced, in the past, similar challenges in assessing dosing.

Industry associations and other stakeholder groups are advocating for more guidance from U.S. FDA on how states should regulate CBD to improve consistency of regulatory frameworks across states.

International Regulation of CBD Products

International regulators have taken different approaches in regulating CBD. For instance, the UK has allowed CBD to be marketed as a natural food and has a suggested daily maximum dose of 70 milligrams for adults. Australia has similarly identified a suggested maximum dose of 60 milligrams or less of CBD, even though CBD is only available with a prescription. In this session, Health Canada presented a detailed case study of the regulation and surveillance of CBD and cannabis in Canada.

Under Canada's regulations, CBD is considered a cannabis product and is not treated differently than other cannabis products such as THC. In 2018, Canada legalized the use of cannabis for non-medical purposes. This legalization was done in phases, with the first phase in 2018 allowing fresh, dried and oil products, as well as full plants to be sold. Additional product categories were brought into this legal framework, including edibles, extracts and topical oils. These product categories are what remain on the market today.

Cannabis products had already been available for medical use for roughly twenty years as a result of a series of court decisions, including a key decision by the Supreme Court of Canada.

Presenters in this session noted that as a result of CBD's regulation as a cannabis product, there are three access pathways for CBD products in Canada, including a pathway for medical purposes, a pathway for non-medical use, and a pathway for health products that contain cannabis or are used with cannabis. In Canada, if a cannabis product makes a health claim, its use must be authorized by a medical

practitioner, and patients can take this authorization to a licensed medical seller to obtain the product. However, Canada is currently gathering evidence and public comment regarding a potential change to this restriction. The non-medical access pathway is overseen by the provinces and territories, which are responsible for licensing the retail environments in their respective jurisdictions.

Representatives from Health Canada described the country's vigilance framework for cannabis products. Several forms of data are included in this framework, including reports from product license holders, who must disclose serious adverse events, and reports from consumers, providers, retailers, and regional health authorities who voluntarily disclose adverse events. Health Canada's definition of adverse event is similar to FDA's, and the term describes an untoward medical occurrence associated with a medical product that does not signify a causal relationship between the event and the product. Health Canada's Canada Vigilance Database, an established tool used for other products, collects these reports of adverse reactions for both medical and non-medical cannabis products.

After receiving case reports, Health Canada assesses serious adverse reactions and medically significant cases to determine if they were caused by CBD products. Additionally, if there is evidence of a case cluster, or product quality issues, other investigations might occur. Data is also analyzed annually. Canada also proactively studies cannabis through national surveys, sentinel surveillance, and registries of medical cannabis patients.

Session 2: Existing Efforts to Track CBD Utilization and Potential Health Safety Risks

This session explored the current landscape of efforts to track the utilization and safety of CBD. Discussion focused on key trends in consumer behavior around these products as well as product distribution, which provided context around the formative research requirements of surveillance activities underway. This formative research lays the foundation for CBD surveillance by characterizing CBD users and their behaviors related to CBD use, as well as the factors that influence that use. Attendees also discussed approaches being developed to detect signals, refine signal strength, and evaluate potential adverse events.

Surveillance Activities in Colorado

Colorado has emerged as a model of state-level surveillance of cannabis products due to the state's extensive experience with marijuana. Colorado's surveillance focuses on marijuana products and collects information primarily from two data sources: hospital emergency department data and poison center data. While Colorado does not currently track CBD-specific health outcomes, this information does sometimes show up in their surveillance data of the related cannabinoid THC through consumer confusion about cannabinoid consumption or ICD-10 codes that lack specificity in differentiating between THC and CBD. The Colorado Department of Public Health contracts with local poison centers to collect enhanced data about the marijuana-related calls, including the product name, purchase location, label information, percentage THC, and other information. Poison centers must report regular information within 48 hours, and clusters, which are exposures including two or more people at a time, within 24 hours detailing unusual or severe outcomes related to that exposure.

A speaker highlighted challenges with Colorado's system of tracking hospitalizations associated with cannabis products. Colorado examines ICD-9 and ICD-10 billing codes related to cannabis to track hospitalizations related to marijuana use. In 2016, Colorado hospitals switched to using ICD-10 billing codes, which have a higher level of specificity compared to ICD-9 codes; however, these codes still do not differentiate between different types of cannabinoids. Limitations with the data sources include the lack of specificity in ICD codes (they do not distinguish between types of cannabis such as CBD and THC), general confusion about nomenclature of CBD and cannabis products, issues with sensitivity and specificity of ICD-10 codes, and incomplete data.

A speaker noted that the widespread lack of knowledge about cannabinoids can be a problem for data collectors at poison centers or hospitals. Consumers who are unfamiliar with the differences between THC and CBD, for example, can cause difficulties as they attempt to relay adverse reactions or other information about product use. This lack of nomenclature knowledge, the speaker noted, is likely a result of the emerging nature of the cannabis industry in Colorado.

Another surveillance effort in Colorado explored during the discussion was the Rocky Mountain Poison & Drug Safety (RMPDS) center, a Division of Denver Health, an acute care academic safety net hospital and community health system in the Denver Area. The center implements the Research Abuse, Diversion, and Addiction-Related Surveillance System (RADARS), which monitors prescription drug abuse, misuse, and diversion and tracks other non-prescription substances (e.g., over the counter (OTC) medications, consumer products, and kratom). Another survey source, the NMURx online national survey of non-medical use (NMU), tracks prescription drug use and illicit drug use among US adults age 18+ the center has developed. RMPDS applies state-of-the-art methods to RADARS and NMURx survey sources along with national poison center data, which is discussed in the next section, to triangulate Sentinel event detection and syndromic surveillance.

Poison Center Data

The national network of poison centers is a useful data source for understanding some aspects of CBD safety, and many states, including Washington and Colorado, use poison center data for cannabis surveillance. Codes exist for CBD-related calls; however, there are also less-specific cannabinoid codes, and there is likely variation in how codes are selected. Advantages of the National Poison Data System (NPDS) include the ability to detect sentinel events (e.g., clusters of cases or similar cases in different locations that require additional investigation), conduct syndromic surveillance (e.g., setting up triggers in the system to track patterns of exposures), and centralize data from all 50 states on a near real-time basis.

From January 2020 to the date of this convening, there were 924 CBD-related cases captured nationwide. Of these cases, some high-risk populations have been identified, with children under 5 being a particularly notable at-risk group. Cases involving children under five accounted for almost 40% of cases recorded thus far in 2020, and 12% of cases were coded as adverse reactions, including reactions to the drug on its own and drug-drug interactions.

A speaker noted that poison center data has the capability to detect events such as geographic clusters or closely-related cases across different geographies that necessitate further investigation. In particular, data collectors can detect patterns of exposure in poison center data and construct a trigger that will

create an alert within the system when new, related cases come through. Data collectors can use these alerts to monitor these patterns of exposure more efficiently.

The NPDS is used for additional surveillance activities with data collection methodologies that could be relevant to CBD surveillance. NPDS can track longitudinal data and trends over time to evaluate a change in the marketplace. For example, the NPDS was used to track the impact of flow restrictors to prevent accidental ingestion of OTC medication in children (10.1016/j.amepre.2018.12.015). NPDS data also noted acute changes in the number of exposures to liquid laundry packets (e.g. Tide pods). This allowed for public health interventions to decrease adverse exposures.

CBD as a Prescription Drug

Side effects of CBD as a prescription drug have been studied in clinical trials of Epidiolex, the only approved treatment that includes CBD as the active ingredient. With the exception of Epidiolex, Marinol, and Syndros, no product containing cannabis or cannabis-derived compounds (either plant-based or synthetic) has been approved as safe and effective for use in any patient population, whether pediatric or adult.

The Epidiolex trials provide an important base of evidence for post market surveillance of adverse events and risks associated with CBD. Epidiolex is therapeutically indicated for Lennox-Gastaut and Dravet Syndromes, two rare epilepsy disorders that largely impact children. (Note: After the meeting, FDA added a third indication for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older). While the Epidiolex clinical trials provide an important source of data about adverse events related to CBD, it is important to note that the experience of children with rare epilepsy disorders may not be generalizable to broader adult populations.

In the Epidiolex trials, several side effects were identified, including somnolence, gastrointestinal issues, and elevated alanine and aspartate aminotransferase levels. In another study focused on children with Dravet Syndrome, about 15% of children experienced treatment-related side effects while using CBD leading to withdrawal of medication compared to only 1% of children who were assigned the placebo treatment. About 16% of children in the study experienced serious treatment-related side effects compared to 5% of children receiving placebo. Side effects in this study included somnolence, diarrhea, decreased appetite, and convulsion.

Of particular note is the interactions between CBD and the drug clobazam, which is used in combination with other medications to treat seizures caused by Lennox-Gastaut syndrome. A speaker noted that CBD when combined with clobazam can lead to excessive sleepiness, which may be related to a drug interaction. CBD when used with valproic acid (Depakote), a common epilepsy drug, has also shown to lead to abnormal liver function in clinical trials due to a possible drug interaction. Patients in another trial saw an eleven-fold increase in risk of elevated aminotransferase levels when taking CBD in conjunction with Valproate as compared to placebo.

Drug interactions are concerning because CBD inhibits CYP 2C19, an important drug metabolizing liver enzyme that helps clear medications from the body. Therefore, CYP 2C19 inhibition slows the elimination of clobazam metabolites, diazepam, and tricyclic antidepressants among others. This is thought to be a potential source of side effects as such as sleepiness with clobazam use among other drug interactions. Pneumonia and acute respiratory failure were reported in some children with Lennox-

Gastaut Syndrome as serious side effects of CBD use when taken with clobazam. Other concerns arise when patients do not disclose CBD use to physicians or take forms of CBD that include contaminants. Unlike medicinal grade CBD, commercial CBD is not tested for concentration of contaminants.

Other Limitations in Data Collection of CBD Adverse Events

Stakeholder participants acknowledged the general lack of population-level data available on CBD use (mode of use, reasons of use, use with other substances) on both federal and state levels. There are Federal and State-based surveys including the National Survey on Drug Use and Health (NSDUH), the National Health and Nutrition Examination Survey (NHANES), Monitoring the Future, and CDC's Behavioral Risk Factor Surveillance System (BRFSS), that collect important information on a range of health behaviors that could partly inform trends with CBD use and potential adverse events, however, they are not currently designed or equipped to do so. These limitations and lack of data has rendered CBD product surveillance challenging. There is a need for funding to add questions to these surveys, as well as validate survey questions. Consumers are not accurate reporters of what products they use, specifically in the confusion between CBD and THC products. In one study, about half of individuals in US states could not report whether they were using a CBD or THC product, and about a third of individuals could not report what type of product they were using.

Monitoring Policies that Influence CBD Usage

One speaker discussed the regulatory differences in how states treat CBD and marijuana. These areas of difference include testing, access, labeling, point of sale education, advertising, types of products allowed, and licensing. The speaker emphasized that these differences may also influence health outcomes related to CBD use, and that instead of monitoring just adverse events, monitoring policy and its implications on adverse health events could be useful in future approaches to CBD safety surveillance. The speaker mentioned that advertising in particular has the capacity to greatly influence how consumers view both CBD and marijuana products. In the future, the speaker noted, policy divergences should be an area of focus when considering solutions to improving CBD surveillance.

Research Questions for a CBD Surveillance System to Answer

Surveillance systems need to address two types of questions: formative questions that help identity what data should be collected, and ongoing surveillance of critical information. Formative research questions include the "who, what, why, and how" of CBD use. Some of these can be articulated as "What types of adverse effects might be expected?" and "Who might experience these effects?" among others. One speaker noted that the "who" aspect, concerning the population that is actually using CBD, seems to be particularly important for informing safety discussions, which is currently missing from much of the data collected surrounding CBD.

Other important data points include frequency of use, quantity, and duration of CBD use and exposure. Speakers noted that many of these questions are not yet addressed for marijuana products, and THC monitoring should work in tandem with CBD monitoring due to confusion about products or concomitant use. Panelists closed out this session by noting the need to keep up to date with the expanding evidence base to refine research questions as consumer experience accumulates with these products.

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Session 3: Leveraging Potential Data Sources to Assess CBD Safety

This session explored data sources that could be leveraged to gain better understanding of CBD safety surveillance. Both traditional public health data sources (e.g., surveys, poison center data, claims data) and non-traditional surveillance data sources (e.g., social media data and websites that track illicit substance abuse) were discussed. Both the strengths and weaknesses of each data source were explored as well as the types of insight that could be derived from these data sources to inform key surveillance questions.

Poison Center Data

Poison center data from the NPDS were again discussed as a data source that could be further leveraged to understand CBD safety. NPDS currently uses around 15 cannabis-related codes for tracking exposures and adverse events related to cannabinoids. According to NPDS data, CBD exposures have modestly increased in 2019. CBD-related exposures were more likely to be observed in youth and older adults compared to other cannabis products, but were linked to fewer serious health outcomes. Also, there are a relatively greater share of women reporting CBD exposure cases as compared to non-CBD cannabinoid exposures.

Speakers in this session noted some limitations with poison center data. For example, in non-serious cases people might use other methods such as Google rather than calling the poison center. This means poison center data likely undercounts the true level of adverse events related to CBD. Poison center data are primarily a tool for health care providers to manage cases and inform care for people who need access to health care, but with modifications these systems could also help inform key research studies based on trends observed in this data source In addition, health care providers can call poison centers for consultation on the treatment of patients. One worry is that case numbers may decrease as health care providers no longer need advice for issues they are now familiar with treating. Trends in use can be impacted by other regulatory measures (e.g., the state of Washington mandated the poison center number to cannabis edible packaging). Poison center data often has a cost to use as well, which can present a barrier in obtaining this information.

A speaker noted that poison center data is most effective when used to understand the characteristics of CBD-related adverse events and to assess changes and short-term patterns of reported exposures especially when linked to other data sources to triangulate potential signals of adverse events.

National Surveys

National public health surveys are a powerful tool for collecting population level data on substance abuse and health. While no survey yet focuses on behaviors surrounding CBD use specifically, stakeholder participants at the meeting thought surveys could nonetheless provide potential and there could be opportunity to develop and embed specific CBD questions. Limitations of survey data generally include the fact that it is challenging to add new questions to the survey quickly due to the long and expensive process needed to validate questions for soliciting accurate feedback.

The National Survey on Drug Use and Health (NSDUH), one survey mentioned in this session, seeks to generate insight into the misuse or abuse of certain products such as alcohol or nicotine. It has several

potential strengths as a contributing data source for CBD surveillance due to its large national sample, face to face data collection method, and ability to relate potential new CBD questions to use of other drugs such as opioids. Key weaknesses of the data source include excluding certain populations such as active military members or long-term hospital residents, and it is unclear whether the target population for this survey uses CBD products enough to provide helpful information.

The Drug Abuse Warning Network (DAWN) was another national survey considered. One of the DAWN survey's mentioned strengths is that it includes data from emergency department visits, chart review, and inclusive case definitions that capture ED visits related to any substance use. A limitation is this survey may only capture a small number of CBD-related adverse events, as many would not result in an emergency department visit. In addition, many patients might need to be prompted to disclose CBD as a concomitant medication due to the nature of the substance, meaning that some events might not be detected.

The Monitoring the Future national survey, funded by the National Institute on Drug Abuse (NIDA), solicits input on a range of issues from approximately 42,000 adolescents annually. One strength is that it surveys adolescents about drug and alcohol use in a large national sample with room for early detection of spikes in activity. A limitation is that it is difficult to add new questions quickly, and it remains unclear whether CBD usage can be picked up in the population surveyed.

The National Health Interview Survey (NHIS) has a large sample size, covering about 27,000 adults and 9,000 children each year, and gathers large amounts of health information. This information could also be used to detect trends in CBD use, especially among populations such as the elderly.

The National Drug Early Warning System (NDEWS) has strengths in its diverse sample with twelve sentinel spots and that epidemiologists review local data, so there is a network of experts attached to the project. This survey, similar to other surveys, has the capability to track trends in CBD use. Similar to other surveys mentioned, it is difficult to add new questions quickly, and CBD is likely not captured currently.

Electronic Health Record Data

Electronic health record data can be useful in CBD safety surveillance. EHR vendors assist in developing this data source in support of CBD surveillance activities through stitching EMR data and creating longitudinal records. One challenge, however, noted during the workshop to fully leverage EHR data is the lack of clinical standards for identifying and documenting Cannabis or CBD use or related health outcomes linked to using these products. Significant research effort would be needed to investigate relevant terms and data relationships that could help stitch together different data elements within the EHR. This effort would become even more complex when trying to leverage data sources from multiple EHRs given the substantial fragmentation of different records systems within and across health systems (for example, the average health system uses 4.5 different electronic medical records). While EHRs would provide a more accurate depiction of CBD use and better track adverse events, significant challenges would remain in developing the needed data structures and terminology to quickly search EHR data for risks and outcomes associated with CBD use.

Nielson and Consumer Insights

Nielson Consumer Insights is another source of data for surveillance; Nielson has longitudinal panels of about 100,000 adults in the US and Canada. Through these platforms, they can deploy surveys on cannabinoids, including CBD. These households use a scanner to track every product they buy. Other information is available about demographics and health information. These panels are constructed to be closely aligned with US Census data to have a representative mix of consumers. Consumer panels can try to overcome terminology confusion by including definitions of terms to participants during studies. Nielson is conducting formative research about CBD including incidence of use, frequency of use, barriers to use, reasons for use, motivators, and interactions with other drugs.

Another Nielson survey with about 4,000 participants explores side effects of CBD use, and asks about what form of product was taken, what the symptoms were, and what actions were taken. There is an ability to follow up with respondents to gain additional information. Nielson collects point of sale data from 200,000 retail locations that may be leveraged to track CBD sold in stores as well.

Social Media Data

Social media data, which includes data that come in short-form tools like Twitter and long-form social media outlets like Reddit, have been used in different research efforts on pharmaceutical use. Social media data analysis has been used to identify side effects that have informed FDA label changes, by assessing side effects people report that may not be listed on the label. In one example discussed at the meeting, an analysis of social media forums uncovered changes in how social media users discussed side effects after a label change. A diabetes case study was presented during the discussion, in which social media was harnessed to help researchers understand side effects that patients tend to attribute to certain diabetic drugs. The speaker noted these methods could provide interesting approaches for determining CBD use and risks that consumers associate with these products. The major drawbacks of using social media data is the lack of experience with the methods used for these analyses, which depend on artificial intelligence tools to mine large amounts of unstructured data. This is especially important in the context of informing potential regulatory actions taken based in part from the results of generated by these methodologies.

Session 4a: Establishing Key Goals and Capabilities for Establishing a National CBD Safety Surveillance Network

This session explored opportunities for linking data assets and resources. Panelists considered how to generate research methodology that can be used to address those gaps and generate insight into CBD safety and health related risks. Different approaches discussed in this session include utilization of person-generated health data, use of real world evidence, interagency collaboration, and linkage of data sources through a mosaic approach.

Person-Generated Health Data

In Session 4a, speakers put forth proposals for ways to generate data for CBD safety surveillance. One option discussed was using person-generated health data. A presenter in this session provided one approach for the utilization of person-generated health data in CBD safety surveillance. In this framework, volunteers would participate in an online survey. In this approach, the person generated

data could be anonymously linked to pharmacy data and other health information through a process called "tokenization." This method of evidence generation builds on previous work conducted by IQVIA on person-reported medication use. Researchers found that people were largely accurate reporters of the medications that they took, and also disclosed sensitive topics, such as illegal drug use, or substance abuse during pregnancy.[1]

The tokenization process used to link records is a sort of broad surveillance that allows for participation from a large variety of subgroups of special interest. This work, as the presenter noted, requires very active and adaptive data curation to avoid errors and identify bad actors. The time needed for curation leads to slight delays, meaning the system is near real-time and cannot be an adequate substitution for poison center data.

Signal Evaluation

One challenge in conducting CBD surveillance is the need to determine whether a causal link exists between CBD use and any adverse events that may be detected. One speaker suggested opportunities for using real world evidence (RWE) comparator arms in CBD research to establish these causal relationships. The speaker noted the emerging literature that shows the effectiveness of observational studies and their capability to capture similar average treatment effect estimates when compared to randomized clinical trials, using a "target trial" approach in which observational data is analyzed in a manner that mimics how a clinical trial might be conducted.

To carry out this approach, researchers would start with defining a "target trial" that they seek to emulate. Researchers would have to identify data that could be used to mimic the inclusion and exclusion criteria for the "CBD intervention" and the trial endpoints. Machine learning could be useful in predicting and extracting information from unstructured data for CBD-related adverse events. Machine learning, as the speaker noted, is quite adept at handling complex data structures, which could be relevant to the use of electronic medical records in surveillance. Propensity score matching or Inverse Probability Treatment Weighting (IPTW) could be used to balance the comparator against the intervention group. Finally, multivariate analyses could be used on both groups to address residual confounding. This approach would provide an alternative or even complementary source of evidence to randomized controlled trials to study potential signals of adverse events or risks related to CBD.

Learning from Past Public Health Challenges: Opportunities for Interagency Collaboration

Past public health challenges can be useful in informing future approaches to CBD surveillance. E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) and similar conditions are difficult to capture in traditional surveillance systems, and the EVALI outbreak brought attention to the fact that

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[1] Laursen M, Hallgreen CE, Dreyer N et al. Comparison of electronic self-reported prescription medication use…**Pharmacoepid & Drug Safety** 2020;29:328-336. https://doi.org/10.1002/pds.4937
Dreyer et al. Direct-to-patient research: piloting a new approach to understanding drug safety…**JMIR Public Health & Surveillance** 2015; 1(2); e22. doi:10.2196
Richardson et al. An int'l study of…advertisement methods to facilitate study participant self-enrolment …. **JMIR Public Health and Surveillance 2016;** 2(1) e13: 1-10

there is a massive proliferation of cannabis-related products on the market. In the case of EVALI, identifying a growing threat to public health was largely an ad hoc process through passive surveillance data inputs. Lessons learned from EVALI and the current opioid crisis shows the need for CBD surveillance to be underpinned by interoperable systems and infrastructure that can access a diverse range of data sources with the ability to proactively take research questions to the data sources.

Also, based on the EVALI experience, stakeholders at the meeting considered the opportunity for how social media data analyzed through natural language processing along with survey data could support ongoing efforts at CDC to implement CBD syndromic surveillance. Relevant data sources linked across these agencies, combined with social media data, could play an important role for supporting CBD safety surveillance capabilities.

Experience with previous public health challenges has shown that interagency collaboration between FDA, CDC, SAMHSA, and NIDA could be an important tool to coordinate nationally representative survey research. Cognitive testing of survey questions is essential to ensure that people are answering the question as researchers intended. CDC is currently designing cognitive testing for marijuana and CBD questions.

Session 4b: Exploring Potential Policy Options for Establishing a National CBD Safety Surveillance Network

This session discussed next steps to establish a sustainable CBD safety surveillance system. Discussion considered the cost and feasibility of different surveillance system approaches, and explored the strengths and weaknesses of these approaches to answer different surveillance questions of interest.

Existing Surveillance System Models

Different surveillance programs evaluate consumer sentiment, case reports, registries, social media, observational studies, and clinical trials. Attendees emphasized the importance of bringing these different data sources together under a “mosaic approach”. The mosaic approach to surveillance largely describes a method of linking data sources that contain different populations, outcomes, or regions to gain a better picture of safety surveillance. The approach involves assessing the strengths and limitations of different data sources, and evaluating the overlap between the data sources as well. Health Canada, like other stakeholders, has experienced challenges with the mosaic approach to CBD surveillance, as linking data within its system has proven difficult. This is partially due to the large data sources that are not necessarily specific to cannabis.

One case study discussed was the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System. RADARS was founded with funding from Purdue Pharma, around a requirement to monitor oxycontin. It has changed quite drastically and is now an independent public entity with a broader focus, and funding from industry, government, and NGO sources.

RADARS’ experience highlights how an independent entity, using multiple data sources, can tackle a significant surveillance challenge. Monitoring opioids is challenging because patients are motivated to

hide the medication they take for fear of consequences such as losing access to medication or legal action. People were more willing to be open about their opioid use when entering treatment, and RADARS initial data came from these treatment centers. The program has since expanded to include other data sources, including anonymous sources that can provide a fuller picture of opioid use.

FDA's Sentinel System

Another case study presented was FDA's Sentinel system. Sentinel's creation was congressionally mandated in 2007 with the FDA Amendments Act (FDAAA). The development of the Sentinel program took place in three phases. The system development began with public consultation, then a Mini Sentinel was developed. Building on Mini Sentinel, FDA deployed the Sentinel system in 2016.

Sentinel has a coordinating center that helps organize the system along with several data partners. Engaging with data partners and academic scientists was highlighted as an important part of the development of Sentinel. Additionally, the privacy protections in Sentinel were seen as crucial.

Both the technical aspects of building a surveillance system and community around the system are important. The Sentinel structure now has three distinct centers: the Community Building and Outreach Center, the Sentinel Innovation Center, and the Sentinel Operations Center as a potential model to consider when establishing a network approach to surveillance.

Sentinel is FDA's post-market safety assessment signal management framework that allows the agency to conduct active surveillance at the population level. This active surveillance is a spectrum of phases that includes three steps: signal identification, refinement, and evaluation. Signal identification refers to a method used to identify associations between medical products and health outcomes of interest (HOIs). Signal refinement is a process for evaluating the significance and magnitude of a certain suspected HOI. Signal evaluation consists of the implementation of a formal epidemiological analysis of the causal relationship between the HOI and the medical product.

COVID-19 Evidence Accelerator

The COVID-19 Evidence Accelerator was discussed as another potential model for CBD safety surveillance This evidence accelerator uses real-world data to understand the rapidly changing landscape of COVID-19. Much like CBD, work in the COVID-19 space is relatively nascent and evolving.

In establishing a surveillance system, it is important to select common data elements and agree upon the information that should be collected by the system at scale. There is a need for open communication, where different partners can ask questions and find consensus quickly across multiple groups. Qualitative and quantitative evidence must be combined and novel data analysis techniques must be applied on an urgent timescale. Combining these two types of data has been a critical task that has a parallel in CBD surveillance. In the case of the COVID-19 Evidence Accelerator, it was important to bring together stakeholders from academia, the public sector, industry, and the tech industry.

Other Topics

One stakeholder suggested that it may be important to focus initial safety monitoring on CBD users who use it frequently, have concerns about dosage, or who are at highest risk of side effects due to drug interactions or other factors. This type of narrowing of scope is needed for the creation of a minimum

viable product. At the same time, stakeholders noted that monitoring the general population is crucial to tracking changes in consumer behavior and use around CBD.

Funding will be essential to establishing a safety surveillance system. Stakeholders noted that RADARS was initially funded through work on opioids (an area where there is a large amount of public interest in research) and that the Sentinel System is well funded by Congress. Stakeholders suggested obtaining a better understanding of how much funding will be a constraint for any CBD safety surveillance system.

Additional considerations discussed include the need to not reinvent the wheel, and to learn from existing surveillance efforts.

The Role of Industry

Industry representatives shared that many brands are interested in partnering with consumers and regulators to create safe products. One speaker noted that there is a tighter loop of communication between brands and frequent users, which is important to consider in light of the fact that half of CBD consumers are using on a daily basis.

Specifically, because the CBD industry is fragmented, large companies might want to differentiate themselves from smaller ones and be able to make claims about their products being the highest quality on market. Such commercial incentives might drive companies to participate in safety surveillance data collection.

Stakeholders disagreed about the potential role for industry in safety surveillance. Some noted that stakeholders would be willing to provide funding for research and voluntarily share information about customers. New York State described some information about its collaboration with companies as it worked on designing and implementing new regulations around CBD and medical cannabis. This included discussion about products coming from out of state and controlling the distribution and safety surveillance of those products.

Others argued that while industry might be willing to participate, they would not be able to provide enough funding for the needed work. Building a robust community necessary for proper CBD safety surveillance would require adequate resources that may be hard to acquire.

Similarly, one academic stakeholder advocated for the creation of a voluntary registration program for CBD product companies. This registration would be on an opt-in basis and provide a corporate stewardship mechanism. Companies in the registry might be able to share some of the data on product use and adverse events with regulators, which could allow regulators to draw some conclusions from subsets of CBD users' data.

Foundational Questions for a Surveillance System

Building on the formative research questions articulated in the first day, and learning from both existing and potential surveillance efforts and tools that are becoming available, stakeholders at the meeting described a number of key questions that are foundational for the establishment of a CBD safety surveillance system and could inform policies moving forward.

- Who uses CBD?

- What products do they use?
- Where do they get the products?
- Why do they use them?
- How do these products affect consumers?
- What are the outcomes associated with CBD use?
- Should a surveillance system include adverse events related to the quality of CBD products (e.g. contaminants)?
- Why are manufacturers and retailers not providing reports on CBD related adverse events?
- What is the frequency of CBD use?
- What is the denominator of risk for adverse events in the population taking CBD (i.e., the counterfactual)?
- How can surveillance systems move beyond spontaneous reporting? How can rich data be collected in a passive way?

What specific product types or patient groups might have the highest CBD exposures?

Looking forward, these key questions will be useful in identifying important components for a CBD safety surveillance system, including data sources that will be necessary in conducting surveillance. In addition, these questions will be useful in building institutions and networks that will provide the necessary support and community to enable a successful and sustainable safety surveillance system.