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Clinical Laboratory-Based Drug Checking Services and the Overdose Crisis

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Introduction: The Overdose Crisis and Emerging Harm Reduction Strategies

Accidental substance poisonings and related deaths have risen significantly in North America over the last 10 years. The year 2020 alone saw 69 710 lives lost in the United States (1), and 6214 deaths in Canada (2) due to opioid-related overdoses. In Toronto, Canada, the number of deaths increased by 78% compared to the previous year, whereas the number of non-fatal overdoses and paramedic calls also continued to grow steadily (3). This trend highlights our need to respond effectively to a very serious problem.

"Harm reduction" is a term collectively used to describe strategies aimed to help mitigate negative consequences associated with substance use. In response to the overdose crisis, harm reduction services have been utilized to help reduce drug poisonings and overdose deaths. These strategies can include overdose response training, naloxone distribution, supervised consumption services, safer opioid supply programs (i.e., providing individuals with prescribed hydromorphone or heroin) (4), and distribution of safe supply equipment. Apart from offering a safe supply, these strategies are considered reactive measures, since they help lower the risk of death but do not necessarily prevent the overdoses themselves.

Drug checking services (DCS) are gaining popularity as a key component of the harm reduction toolkit. The overall goal of these services is to reduce harms associated with overdose by providing an end user (or associated medical support community) with an understanding of the composition of substances obtained from the unregulated "street" drug supply. Opioid overdoses and deaths are mainly attributed to the toxic and highly unpredictable nature of the unregulated drug market. Drugs obtained illegally are highly contaminated with a variety of novel psychoactive substances (NPS) at varying concentrations (5). Although people who use drugs (PWUD) often understand their own level of drug tolerance, they are typically unaware of the true contents of the substance they have acquired, and the hope is that by providing an accurate breakdown of the compounds and quantities of drugs in the sample that many users will be able to make informed decisions and modify their behaviors accordingly (e.g., use with a friend, use at a safe consumption site, and/or have medical assistance available).

How Does Drug Checking Work?

Drug checking is a free and anonymous service offering analysis of both drug substances and/or used paraphernalia. Drug checking can be performed using a range of analytical technologies and can be offered either "on-site" (i.e., at the point-of-use) or "off-site" in a clinical or forensic laboratory. Since first becoming available in Europe in the 1990s, drug checking has been effective at determining the composition of illegally obtained drugs to identify the presence of unexpected or dangerous contaminants. Recently, DCS have risen in popularity in Canada in response to the opioid crisis and have expanded their scope to include tailored consultation offering harm reduction strategies along with the drug checking results. In addition, DCS allows for monitoring and surveillance of the unregulated drug supply that can inform paramedics, clinicians, and hospitals—helping them to better respond. It also provides data to policy makers

Inside...

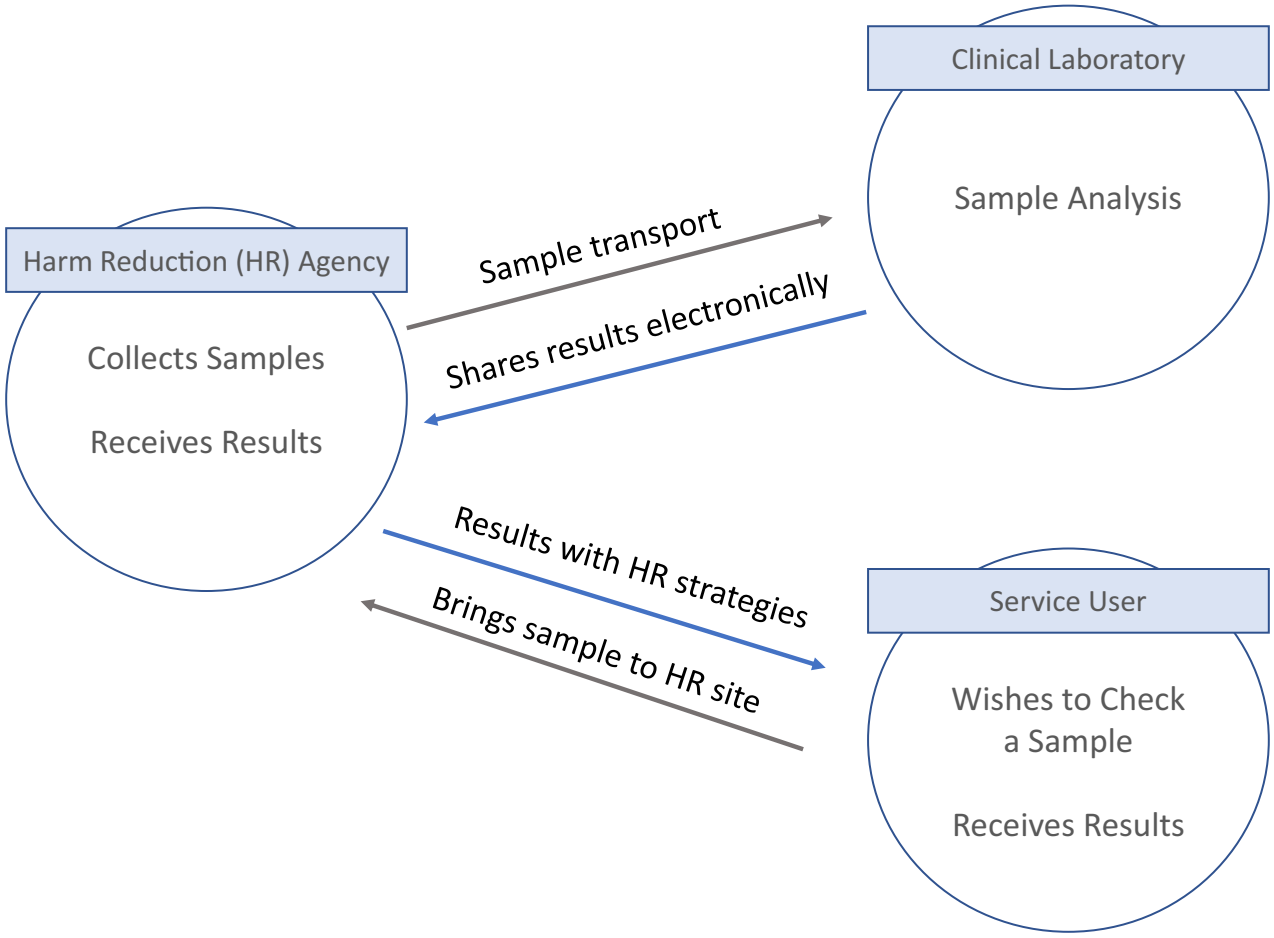


Fig. 1. Toronto's drug checking service model.

at the provincial and national level, enabling a deeper understanding and more appropriate response to a situation that is constantly changing.

What Does Toronto's DCS Do?

Toronto's DCS is a pilot project funded by the Government of Canada's Substance Use and Addictions Program and the St. Michael's Hospital Foundation in Toronto. Since its inception in October 2019, it is the first project of its kind to offer DCS using gas and liquid chromatography-mass spectrometry-based testing in a clinical laboratory setting. This service offers PWUD timely and detailed information about the contents of their drugs to help them make informed decisions about their use. As part of the project, Toronto's DCS makes information publicly available, sharing data on the contents of the unregulated drug supply to help assist harm reduction workers and clinicians tailor their care. This data sharing comes in the form of bi-weekly reports as well as "alerts" when a novel or extremely dangerous drug begins to circulate in the supply. Based on the data generated from the project Toronto's DCS can advocate for increased access to harm reduction services and safer alternatives, such as increasing the availability of safe supply programs.

Fig. 1 shows the model used by Toronto's DCS. Drug samples and used paraphernalia are collected from 5 frontline harm reduction agencies in Toronto. These government sanctioned sites also offer supervised consumption services (referred to as "safe injection sites") that allow for the use of unregulated substances under the supervision of medically trained staff with on-site life-saving measures such as naloxone and oxygen. Once the samples are collected, they are transported via courier to 1 of 2 clinical laboratories for analysis. Results are available within 48 h of receipt to the laboratory and communicated back to the harm reduction agency via electronic reporting. The harm reduction staff relay the results to the PWUD in person or by phone. Personalized harm reduction support and health care referral services are also provided.

A minimum of 10 mg of a drug substance is required for analysis. Examples of drug substances include powder, crystals, rocks, a portion of a pill, blotter (typically used as a sublingual drug delivery method), or liquid. Used paraphernalia is also

accepted through the service including remnants from a syringe, a used cooker (the container used for mixing and heating up a drug), or a used filter (used to eliminate insoluble impurities in a drug solution).

Methodologies Used in Drug Checking

There are 2 types of DCS: "on-site" and "off-site" testing. On-site testing implies that samples are tested at harm reduction locations (i.e., at safe consumption sites) or elsewhere at the point-of-use, whereas off-site testing is typically performed in a clinical or forensic laboratory.

Testing modalities that are commonly used at on-site DCS include Fourier-transform infrared (FTIR) spectrophotometry and fentanyl test strips (FTS); however, mobile mass spectrometry (portable ion scanner) and gas chromatography (GC)-, liquid chromatograph (LC)-, and paper spray (PS)-mass spectrometry (MS) can also be employed on-site (6, 7). For DCS that utilize a combination FTIR and FTS, identifying fentanyl and fentanyl analogues in drug samples or used paraphernalia is the primary focus of the service. FTIR is an attractive technology for DCS since it allows for drug analysis within minutes and preserves the sample to be returned to the client. While this testing modality is considered favorable for PWUD, it has limited utility for detecting novel substances not included in FTIR spectral libraries and has relatively low sensitivity (unable to detect substances with a concentration less than 10% by weight). The high limits of detection of FTIR have necessitated the use of a second-line method, FTS, which can detect concentrations of 100 ng/mL (8). Recently, an on-site method using PS-MS has been developed to quantitate 49 target compounds with an untargeted full scan to help delineate the composition of drug checking samples. This development has certainly offered benefits over the existing on-site FTIR and FTS analysis performed through other DCS sites (7).

Toronto's DCS employs off-site testing in 2 clinical laboratories using LC-Orbitrap high resolution (HR) MS- and GC-MS-based analysis. The laboratory using LC-Orbitrap HRMS uses both untargeted and targeted methods, although the other laboratory employs targeted GC-MS testing with a regularly updated mass spectral library containing more than 20 000 compounds, including emerging NPS. Both sites can detect known/expected drugs or new drugs (and their analogues and/or metabolites) to effectively characterize complex drug mixtures found in drug substances and/or used paraphernalia. This approach enables the detection of fentanyl (and its analogues), non-fentanyl synthetic opioids, benzodiazepines (and related drugs), synthetic cannabinoids, and other potentially potent or dangerous drugs or contaminants. When a novel substance is detected via untargeted analysis, it is reported presumptively then confirmed by running standards (when available) and sent for GC-MS for additional verification. Collaboration with the clinical laboratory provides the added benefit of analytical oversight and expertise to allow for more robust analysis compared to DCS that provide FTIR and FTS testing options.

How Are Drugs Reported?

As of mid-April 2022, Toronto's DCS has analyzed a total of 5606 samples (3750 substances and 1856 used paraphernalia). The program reports both qualitative and quantitative drug composition analysis. Since it is difficult to accurately quantify every possible drug or adulterant that comes into our service, we decided to only quantify the most frequently observed drugs in the Toronto market. All other drugs identified are reported qualitatively from the highest to lowest relative abundance in the sample. This type of reporting was decided in collaboration with our partners in the community and with PWUD.

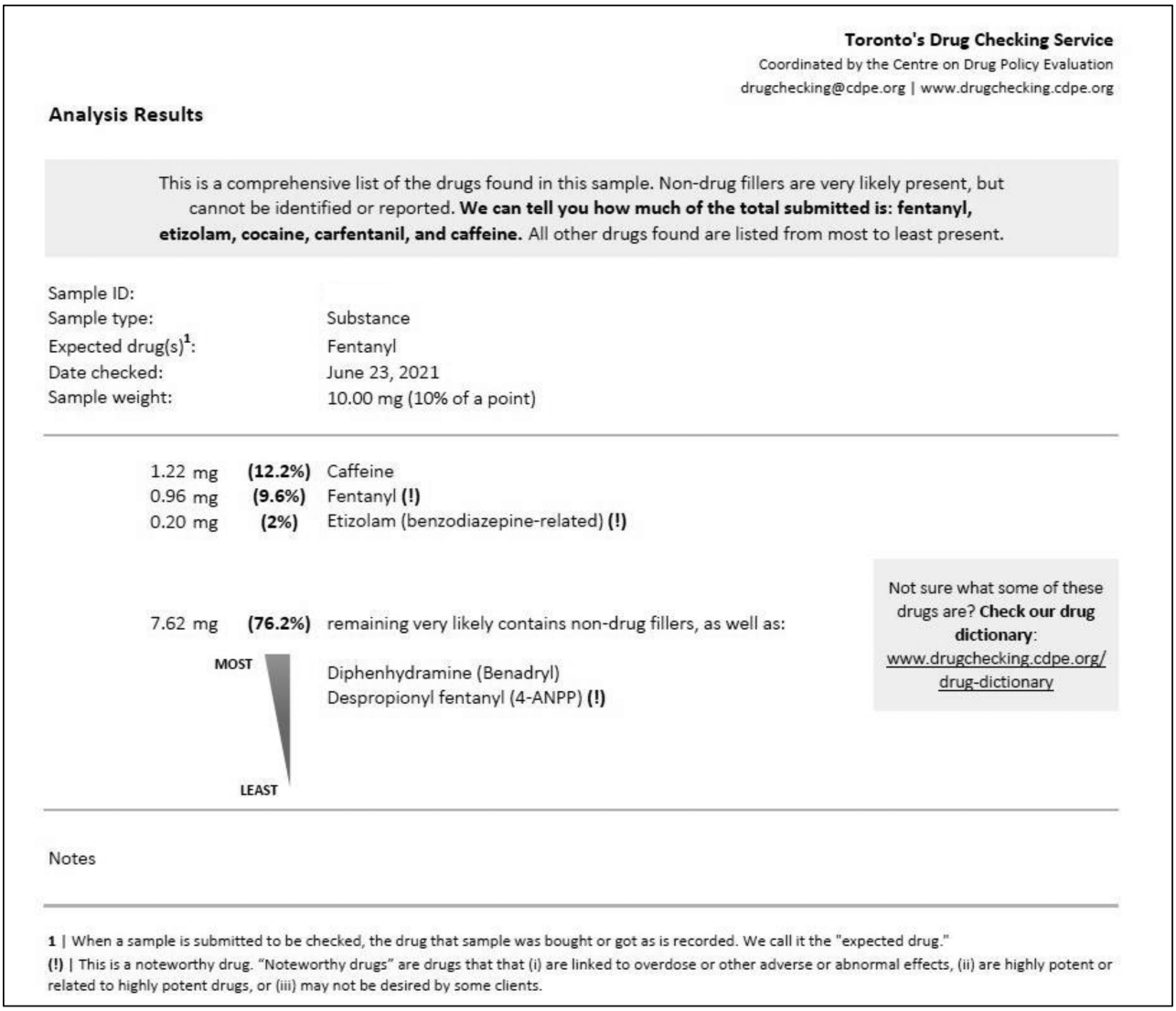
Quantitative analysis of fentanyl, carfentanil, cocaine, etizolam, and caffeine is performed in powders or pills submitted, whereas residual drug from used paraphernalia will only be reported qualitatively. If the sample submitted is a pill or powder, the report will indicate the weight, sample type, expected drug provided, and quantitative and/or qualitative drug analysis (Fig. 2). Samples submitted as used paraphernalia (e.g., cookers, pipes) will not include the weight or quantitative analysis. All reports include a disclaimer indicating that there are non-drug fillers that our analysis may not detect. These fillers commonly include sugars and mannitol; however, it is possible that other harmful fillers exist that we cannot detect such as microbes, pesticides, or trace metals.

What Has Toronto's DCS Found in the Unregulated "Street" Drug Supply?

The causes of overdoses in Canada are related to 2 main issues: high potency opioids with varying amounts of drugs found between samples, and dangerous drug mixtures or drug adulteration.

At this point, fentanyl is the most used drug for the population we serve; 50% of the drugs submitted for analysis are expected to be (or acquired by the user as) fentanyl, followed by cocaine (10%), and methamphetamine (8%). On average, expected fentanyl samples are composed of approximately 5% fentanyl relative to the total sample weight submitted but can range anywhere from 0.1% to 83% of the sample. Due to this large range in fentanyl concentration, nearly 15% of the fentanyl samples submitted to the DCS are associated with an overdose.

Fig. 3 (9) shows the range of noteworthy drugs detected in fentanyl samples between October 10,



Toronto's Drug Checking Service
Coordinated by the Centre on Drug Policy Evaluation
drugchecking@cdpe.org | www.drugchecking.cdpe.org

Analysis Results

This is a comprehensive list of the drugs found in this sample. Non-drug fillers are very likely present, but cannot be identified or reported. **We can tell you how much of the total submitted is: fentanyl, etizolam, cocaine, carfentanil, and caffeine.** All other drugs found are listed from most to least present.

Sample ID:
Sample type: Substance
Expected drug(s)[1]: Fentanyl
Date checked: June 23, 2021
Sample weight: 10.00 mg (10% of a point)

1.22 mg **(12.2%)** Caffeine
0.96 mg **(9.6%)** Fentanyl **(!)**
0.20 mg **(2%)** Etizolam (benzodiazepine-related) **(!)**

7.62 mg **(76.2%)** remaining very likely contains non-drug fillers, as well as:

MOST
LEAST

Diphenhydramine (Benadryl)
Despropionyl fentanyl (4-ANPP) **(!)**

Not sure what some of these drugs are? **Check our drug dictionary**: www.drugchecking.cdpe.org/drug-dictionary

Notes

1 | When a sample is submitted to be checked, the drug that sample was bought or got as is recorded. We call it the "expected drug."
(!) | This is a noteworthy drug. "Noteworthy drugs" are drugs that that (i) are linked to overdose or other adverse or abnormal effects, (ii) are highly potent or related to highly potent drugs, or (iii) may not be desired by some clients.

Fig. 2. An example of a quantitative drug checking report from Toronto's drug checking service.

2019, through March 25, 2022. Of particular note are the benzodiazepine-related drugs, nitazene opioids, and xylazine found in a significant proportion of samples.

The mixture of fentanyl and high potency benzodiazepine-related drugs (e.g., etizolam and flualprazolam), sometimes referred to as 'benzo-dope,' are one of the leading causes of death in this population. This is also evident in British Columbia (BC), Canada, where illicit drug toxicity deaths involving a benzodiazepine drug increased from 15% in July 2020 to 43% in February 2022 (10). From the Toronto DCS data, at least 1 benzodiazepine-related drug is present in in over 70% of fentanyl samples submitted to our service.

More recently, there has been a significant raise in benzimidazole nitazene opioids, including metonitazene, isotonitazene, and etonitazepyne found in fentanyl samples—representing a new and dangerous trend in the unregulated drug market. At least 1 nitazene opioid was found in 19% of all fentanyl drugs checked in March 2022. These nitazene opioids are approximately 10 times more potent than fentanyl and represent a significant risk for overdose in combination with fentanyl and/or benzodiazepine-related drugs (11).

Lastly, the detection of xylazine, a tranquilizer only approved for large animal veterinary use, in fentanyl samples is also increasing (found in 19% of fentanyl samples in March 2022). Symptoms of ingestion can include sedation, vomiting, miosis, central nervous system depression, respiratory depression, and potentially severe hypotension. In combination with fentanyl or benzodiazepine-related drugs the subsequent risk of overdose and death is significantly increased (12).

Relevance to the Clinical Laboratory

Aside from directly supporting harm reduction efforts through drug checking in a clinical

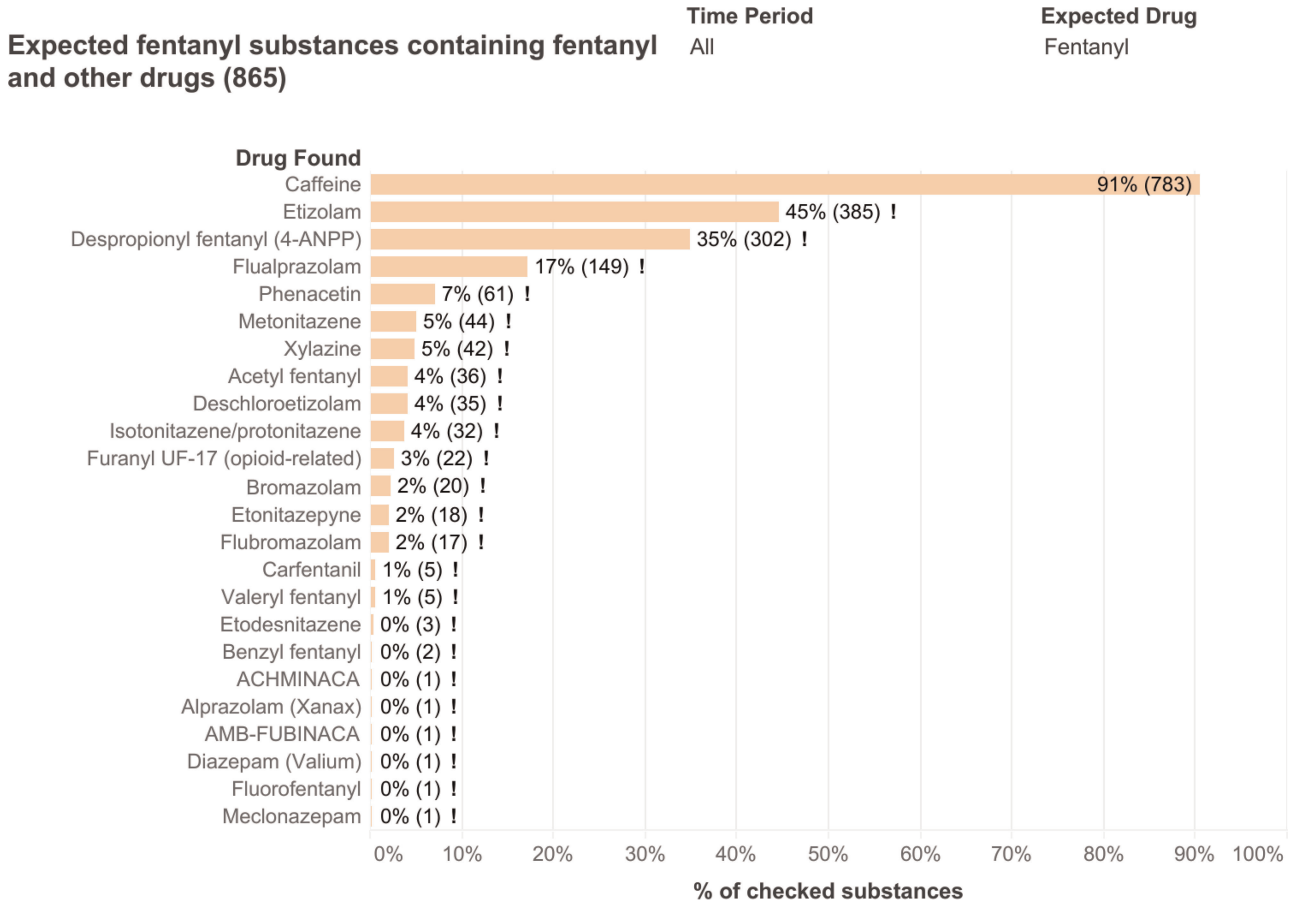


Fig. 3. What's contaminating Toronto's drug supply? Expected fentanyl substances containing fentanyl and other drugs.

laboratory, there are many other benefits to DCS that directly impact clinical testing and patient care. Laboratorians provide informed consults to clinician calls and queries, sharing awareness of what is circulating in the unregulated drug market. Potent and dangerous NPS contaminants emerging in the drug supply may not be detected by routine urine drug testing, either via immunoassay screens or targeted MS-based testing, which can complicate clinical care. Knowledge of local drug trends can facilitate important communication between laboratorians and clinicians to optimize patient management—especially in the overdose setting.

DCS data can also be used to keep drug libraries and test menus up to date. Monitoring local trends in positivity rates can help laboratories decide which drugs to include in MS-based targeted screen or panel-based confirmatory testing. These data may also be helpful when determining which drugs are no longer relevant for clinical drug testing and can be removed from test menus.

Limitations to Toronto's DCS

While Toronto's DCS offers important services to help reduce harms in PWUD, there are many limitations that are inherent to the service that are openly communicated to clients. First, due to limitations with MS-based technologies, some drugs may not be detected by the instrument (i.e., drugs that don't "fly" or are not included in the targeted spectral library) or may not be soluble in organic solvent. Specifically, Toronto's DCS does not identify or report non-drug fillers, largely due to analytical limitations. In addition, the sample that is analyzed through the service may not be representative of the entire drug substance being used. This is referred to as the "Chocolate Chip Cookie Effect," which can be resolved by mixing a powder or scratching off different sections of a pill before submitting a sample for analysis. This is the same for patients who submit used paraphernalia from multiple drug uses; the results are most representative from a single-use paraphernalia. Lastly, while drug analysis can offer more information about the composition of a drug and allow for informed decision-making, drug checking cannot guarantee that a drug is safe to use.

What Do You Need to Set Up a Drug Checking Service?

Setting up a DCS is feasible for clinical or forensic laboratories/laboratorians interested in finding new ways to support the drug overdose crisis.

While every jurisdiction may have different requirements for analyzing controlled substances, there are several general considerations to setting up both an on-site or off-site DCS. For Toronto's DCS, an exemption from the Government of Canada's Controlled Drugs and Substances Act was required for each clinical laboratory involved. General site information, description of the service/operating hours, and responsible person in charge must be appointed and included in the submission. In addition, due to the nature of the drugs being analyzed, a description of security measures including access control, storage of controlled substances, and floor plan should be submitted. A detailed description of how the controlled substances will be prepared, analyzed, and disposed of is also required for the application. Although the samples being analyzed are not biological specimens, and thus outside the scope of many regulatory requirements, thorough validation of MS-based laboratory developed tests should still be performed.

Conclusions

Although data on the impact of DCS on the rate of overdose or death are currently being evaluated, drug checking has been a valuable surveillance tool for the broader harm reduction community as well as clinical laboratories. Delineating dangerous contaminants found in the drug supply has helped provide data to support innovative harm reduction approaches that can move beyond the reactive strategies currently employed.

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Proposed FDA Regulation of LDTs and the Potential Impact for Toxicology Laboratories

By Shannon Bennett, MS, MBA, CM/QOE (ASQ)

Clinical laboratories often purchase test kits from in vitro diagnostic (IVD) manufacturers, which are required to submit their kits as medical devices to the Food and Drug Administration (FDA) for approval prior to marketing. There are circumstances where no IVD exists for an analyte or matrix of interest, or an IVD needs to be modified to meet the laboratory's needs. Under Clinical Laboratory Improvement Amendments (CLIA), laboratories are allowed to develop, validate, and implement such laboratory developed tests (LDTs). Although the FDA has historically claimed regulatory authority over LDTs, they typically utilize "enforcement discretion" and do not require clinical laboratories to submit documentation to the FDA. That paradigm may soon shift.

Congress has introduced the Verifying Accurate Leading-edge IVCT Development (VALID) Act, which creates a new class of product, In Vitro Clinical Tests (IVCTs) (1). This is an umbrella term that places IVDs and LDTs under the same regulatory construct, giving the FDA explicit authority to regulate the development, validation,

and marketing of IVCTs. Any entity developing an IVCT is considered a "developer." The legislation is lengthy and complex and continues to evolve as it works through the legislative process. Here are some of the core concepts.

Grandfathering

Any LDT on the market prior to passage of VALID is considered a grandfathered test. Laboratories would not need to retrospectively submit validation or other documentation to the FDA and could continue offering the test. The FDA would be tasked with creating a new IVCT database called the Comprehensive Test Information System (CTIS). Laboratories would have 1 year to provide listing information for all grandfathered tests after CTIS becomes available. For those laboratories with extensive LDT test menus, this could be a significant effort.

Listing element requirements are extensive, and likely duplicate the information already available in an individual laboratory's electronic test catalog or validation documentation. Listing elements are also required for all new IVCTs post-passage, and laboratories need to update CTIS if an IVCT is modified (including grandfathered tests) (Table 1).

Unlike CLIA, which focuses primarily on analytical validity (AV), VALID also requires documentation of clinical validity (CV). Although clinical laboratories are no doubt familiar with the concept of CV and may incorporate elements into their test information, VALID requires laboratories to explicitly document evidence of clinical validity for IVCTs they develop. Much like AV studies, laboratories must consider multiple variables when documenting CV: Is the test quantitative or qualitative? Is the test used for screening or confirmation? What is the target population? Availability of patient samples for the intended use population (2)?

Performing a clinical trial for every IVCT is clearly not feasible for most, if not all, clinical laboratories. However, this may not be necessary; VALID outlines multiple sources of support for "valid scientific evidence," including peer-reviewed literature, clinical guidelines, consensus standards, real-world data, and other options in addition to traditional clinical trials. It will be necessary for the FDA to provide additional guidance and education for laboratories on their expectations regarding adequate documentation of CV.

Test Classification

The VALID Act leverages a risk classification process to determine when a test needs to be submitted to the FDA for review. Note the binary nature of the classification model—there is no moderate risk category in the current legislation.

Low Risk

Tests where "an undetected inaccurate result . . . would cause minimal or no harm . . . or immediately reversible harm" to a patient. Low risk tests would not require submission to the FDA, though developers would be required to list such tests in CTIS and comply with other requirements such as adverse event reporting.

High Risk

Tests where an unidentified inaccurate result would "present unreasonable risk for serious or irreversible harm or death to a patient . . . [or] is potentially likely to result in the absence, significant delay, or discontinuation of . . . life-sustaining medical treatment." High risk tests would require a full submission to the FDA and compliance with additional quality management requirements.

The VALID Act allows for several exemptions from submission requirements.

Custom and Low Volume

Tests that are developed for a specific patient, or those that are performed on $\leq$5 patients per year, respectively. Such tests do not require submission or compliance with quality requirements; additionally, custom tests cannot be advertised or appear on a test menu.

Table 1. Required listing elements for IVCTs in Comprehensive Test Information System

Establishment Name	Analyte
Official correspondent	Method
Test name and listing number	Test purpose
CLIA number	Disease or condition
Approval pathway	Context of use (e.g., clinical lab)
Narrative description of test	Summary of AV/CV
Description of conformance with mitigating measures, restrictions, or standards	

Humanitarian Use

Tests "for a disease or condition" where <10 000 individuals would be tested per year. Note that this includes *all* testing regardless of result, so a screening test for a rare condition may not be eligible if the screening population exceeds the numeric limit. The definition also specifies disease or condition, not analyte, so it is unclear if a multiple-analyte toxicology panel could potentially count against the numeric limit.

Law Enforcement or Employee Testing

Tests used solely for "forensic analysis, law enforcement activity, or employment purposes." While this exemption is particularly pertinent for toxicology laboratories, if a laboratory's IVCTs are used for law enforcement/employee testing and for clinical purposes, e.g., medication compliance programs, the exemption would not apply.

Manual

Tests that rely on "direct, manual observation, without the use of automated instrumentation or software." Such tests would most likely be quite simple, such as measuring pH or use of agglutination reagents.

Submission Requirements

When a laboratory is required to submit documentation to the FDA prior to offering a test, the breadth of information is substantial. The laboratory will need to provide:

- A description of existing alternatives to the test.
- An overview of validation studies and their conclusions (both AV and CV).
- Raw data from the validation studies.
- A risk assessment (e.g., a Failure Mode Effects Analysis or FMEA).
- A bibliography of all publications "reasonably known to the applicant" regarding the test/analyte.
- Information on the laboratory and the quality system used.

Most laboratories will already have much of this information, as CLIA requires that laboratories document test validation. However, the scope of validation studies and the level of detail expected by the FDA will likely be a significant shift for many laboratories. For example, in the author's experience, the FDA has expressed an expectation that laboratories follow Clinical Laboratory Standards Institute (CLSI) guidance when designing validation studies, and if those guidelines are not followed the FDA expects a documented rationale why.

Modifications

VALID defines a test modification as any change that has the potential to impact the analytical or clinical validity of the test; it is critical to note that this definition does not consider the *probability* of impact to AV or CV. If a test is modified, it becomes a new IVCT and would need to go through the classification process, followed by submission if required. This is particularly relevant for grandfathered tests, because modifying such a test makes it a new IVCT and may require submission.

Laboratories routinely look to optimize their tests to improve performance, accuracy, or other characteristics. The modification provisions may mean that laboratories are faced with a difficult decision:

- Continue using a non-optimal test or avoid updating a grandfathered test, e.g., decreasing required sample volume, to circumvent the FDA submission requirements, or
- Improve an existing test and risk losing grandfathered status and the possibility of being considered a developer under VALID.

Another scenario is modifying a purchased test kit, which laboratories routinely undertake due to limitations with commercial test kits. For example, a laboratory may purchase an ELISA kit for detection of methamphetamine in urine, then modify the kit for use with whole blood samples. Under VALID, the laboratory would now be a developer and need to comply with all listing and quality management system requirements, as well as submitting to the FDA for review prior to offering the test, if applicable.

Transition

The FDA would have 2 years after enactment to draft guidance documents for the specific processes, content requirements, and format of the new IVCT regulatory program. The CTIS system would likely be implemented during this time as well. After that, laboratories would have 2 additional years to come into compliance with the new regulations and guidance, for a 4-year total transition period. VALID would represent a dramatic change for clinical laboratories, so the FDA will need to devote significant resources to training and education on the new requirements for end users.

What's Next

The VALID Act has been attached as a rider to the Food and Drug Administration Safety and Landmark Advancements Act of 2022, which is expected for a vote in late August or early September of this year. Many stakeholders have been working behind the scenes for years, discussing elements of diagnostic reform legislation and providing feedback. As the bill continues through the mark-up and reconciliation process, expect continued advocacy and changes to the legislative language throughout the summer.

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The author has nothing to disclose.

Department of Transportation Proposes Changes to Drug Testing Rule 49CFR Part 40 to Include Oral Fluid

By Jennifer A. Collins, PhD

In the March 2020 issue, *Clinical and Forensic Toxicology News* reported on revisions to the Department of Health and Human Services (HHS) and Substance Abuse and Mental Health Services Administration's Mandatory Guidelines for Federal Workplace Drug Testing Programs using Oral Fluid (OFMG) effective January 1, 2020 (1). At that time, proposed revisions to the Department of Transportation (DOT) drug testing rule, Code of Federal Regulations 49 CFR Part 40 (Part 40), had not been published. On February 28, 2022, the DOT published a notice of proposed rulemaking on oral fluid testing in the *Federal Register* (87 FR 11156, Feb 28, 2022) (2). Like the revised HHS guidelines, the DOT proposed adding oral fluid as an alternative specimen type for workplace drug testing programs in the transportation industry. The DOT is required by law to harmonize with HHS guidelines on scientific and technical issues such as included drugs and cutoffs (Omnibus Transportation Employee Testing Act of 1991) (3). However, the DOT has discretion in many aspects of testing regulations governing transportation industries, and the proposed rule also includes updates and modifications to address issues that have arisen in practice over time.

The DOT drug testing rule, Part 40, was first published in final form on December 1, 1989, based on the original HHS Mandatory Guidelines for Federal Workplace Drug Testing Programs. The effective date was January 1, 1990, coincident with the implementation of the HHS Guidelines. Since the original implementation, Part 40 has been revised to harmonize with HHS changes in 1994, 2000, 2010, and 2018.

Proposed Major Changes to 49 CFR Part 40

The most significant change is the addition of oral fluid as an alternative specimen for safety-sensitive transportation employees subject to drug testing under Part 40. The drugs and cutoffs (Table 1) mirror those implemented in the HHS OFMG effective January 1, 2020 (4). The DOT indicates that this change will provide employers flexibility, a means of performing observed collections on every test, and potentially reduced costs of compliance with Part 40. The proposed DOT rule is written to incorporate processes and procedures required for urine and oral fluid into a single document with language changes as applicable to the individual matrices. In the discussion section of the proposed rule, the DOT requests public comment on several specific topics. Highlights of the proposed revisions are provided below.

Specimen Collection

Oral fluid specimen collector training requirements and collection procedures relevant to oral fluid collection devices have been incorporated into the proposed rule. It is noted that not all oral fluid collection devices permitted in the HHS Guidelines would be allowed for DOT-regulated collections under the proposed DOT rule. The specific language requires that each collection includes a split sample that is subdivided from the original in the presence of the donor. This differs from the OFMG, which permits the use of 2 separate collection devices, either simultaneously or sequentially, as a means of obtaining a split specimen.

Significantly, the proposed DOT rule permits collecting an alternative specimen type when a donor does not provide a sufficient amount of specimen in the initial collection. The DOT requested public comment on who should be empowered to make such a decision during the collection process.

Another change to the collection process relates to the current requirement for a same-gender observer when an observed urine collection is required. The proposed rule permits the use of a licensed/certified medical professional to conduct an observed urine specimen collection when a same-gender observer is not available.

Laboratory Procedures

Laboratory procedures must incorporate the drugs and cutoffs currently approved in the HHS Guidelines for oral fluid (Table 1). Specimen validity testing, as specified in the OFMG, is permitted, but not required. Of some significance is a proposal

Table 1. Oral fluid testing cutoff concentrations.

Initial test analyte	Initial test cutoff[a]	Confirmatory test analyte	Confirmatory test cutoff concentration
Marijuana (THC)[b]	4 ng/mL[c]	THC	2 ng/mL
Cocaine/benzoylecgonine	15 ng/mL	Cocaine	8 ng/mL
		Benzoylecgonine	8 ng/mL
Codeine/morphine	30 ng/mL	Codeine	15 ng/mL
		Morphine	15 ng/mL
Hydrocodone/hydromorphone	30 ng/mL	Hydrocodone	15 ng/mL
		Hydromorphone	15 ng/mL
Oxycodone/oxymorphone	30 ng/mL	Oxycodone	15 ng/mL
		Oxymorphone	15 ng/mL
6-Acetylmorphine (6-AM)	4 ng/mL[c]	6-Acetylmorphine	2 ng/mL
Phencyclidine	10 ng/mL	Phencyclidine	10 ng/mL
Amphetamine/methamphetamine	50 ng/mL	Amphetamine	25 ng/mL
		Methamphetamine	25 ng/mL
MDMA[d]/MDA[e]	50 ng/mL	MDMA	25 ng/mL
		MDA	25 ng/mL

[a] For grouped analytes (i.e., 2 or more analytes that are in the same drug class and have the same initial test cutoff): *Immunoassay:* The test must be calibrated with 1 analyte from the group identified as the target analyte. The cross-reactivity of the immunoassay to the other analyte(s) within the group must be 80% or greater; if not, separate immunoassays must be used for the analytes within the group. *Alternate technology:* Either 1 analyte or all analytes from the group must be used for calibration, depending on the technology. At least 1 analyte within the group must have a concentration equal to or greater than the initial test cutoff or, alternatively, the sum of the analytes present (i.e., equal to or greater than the laboratory's validated limit of quantification) must be equal to or greater than the initial test cutoff.
[b] An immunoassay must be calibrated with the target analyte THC.
[c] Alternate technology [marijuana (THC) and 6-acetylmorphine (6-AM)]: The confirmatory test cutoff must be used for an alternate technology initial test that is specific for the target analyte (i.e., 2 ng/mL for THC, 2 ng/mL for 6-AM).
[d] Methylenedioxymethamphetamine (MDMA).
[e] Methylenedioxyamphetamine (MDA).

to reduce the retention period for nonnegative specimens from 1 year, as required in the current HHS and DOT Guidelines, to 90 days.

Medical Review Officers

Other than adding training specific to the oral fluid matrix, there are few substantive changes for medical review officers. One proposed change would permit medical review officer staff to make inquiries to pharmacies to verify declared prescription medication to assist in interpretation of results. Currently the medical review officers must personally contact the pharmacy for such information.

Substance Abuse Professional Remote Evaluations

The current rule requires an in-person assessment by a substance abuse professional before an employee can return to duty following a violation of the drug policy. A guidance document issued in April 2020 permitted remote evaluations for specific time periods during the COVID-19 pandemic. The proposed Part 40 includes amendments permitting a remote substance abuse professional evaluation as a permanent option given certain conditions are met.

There are additional changes throughout the document that revise or clarify existing requirements and incorporate necessary modifications specific to the individual matrices. The full document may be accessed at the DOT website: https://www.transportation.gov/odapc/frpubs.

In summary, a notice of proposed rulemaking for the Department of Transportation Procedures for Workplace Drug and Alcohol Testing Programs was published in the *Federal Register* in February 2022. While the most significant changes are consistent with those implemented by HHS, the DOT rule contains some policy and procedural differences that are specific to the transportation industry.

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