Fentanyl Quantification and Messaging

Summary

- Current drug checking technologies used at point-of-care (FTIR) can help give us an idea of how much fentanyl is present in a sample, but at the moment, these methods can only give ranges that are imprecise at best.
- There are potential harms associated with providing individuals inaccurate quantification information, but providing wide ranges to account for inaccuracies is of limited use to people who use drugs.
- Confirmatory testing provides both accurate and precise fentanyl quantification but is hard to access and results may take weeks to be returned, if available at all.
- Methods to provide accurate and precise quantification information with point-of-care FTIR analysis are still in development but offer some promise and should continue to be pursued.
- Aggregate fentanyl quantification information is of value to share publicly to highlight the wide variation in fentanyl concentration of available drugs.
- The way quantified results are delivered to service users is important to convey the most accurate results possible within limitations of the technology, and messaging needs to be consistent across technicians to help prevent misinterpretation of results.

Description

The ability of drug checking services to accurately and precisely provide service users with quantification information is not only important, research shows it is a major driver for people to access drug checking services.[1,2] Particularly in a drug market heavily saturated with fentanyl, quantification can provide individuals with utilizable information that can directly lower their risk of overdose.

It is important that technicians who are providing quantification information at point-of-care services fully understand how quantification methods work using FTIR, their strengths and limitations, and how to best explain quantified results clearly to service users. This document is intended to provide information and guidance for drug checking services about how to understand and present quantified results and suggests ways to be responsible when sharing fentanyl quantification or concentration information publicly.

Methods for Quantifying Fentanyl

FTIR methods

There are two main methods for quantifying fentanyl at point-of-care using FTIR: mixture analysis and Bruker Quantitative Analysis 2. A report produced by the BCCSU compares these fentanyl quantification methods and highlights the strengths and weaknesses of each method using drug sample data collected from community sites verified with confirmatory analysis. Some of these findings are summarized below.

1. Mixture analysis: mixture analysis is an algorithm that attempts to recreate the spectrum of the drug sample using library reference entries to best represent it, and therefore can report the ratio of components as a percentage make-up. For more information on how a mixture analysis is conducted please see the BCCSU Drug Checking Webinar Series. Mixture analysis has never been validated for use in drug checking, however, this method has been used for quantification consistently in British Columbia since the inception of FTIR drug checking in 2017.[3]

   In samples where fentanyl was confirmed with laboratory testing to be below 20% concentration, mixture analysis on FTIR failed to detect fentanyl 34% of the time.[3] When mixture analysis did return a fentanyl result, the average difference from the true value was -5.2%. As mixture analysis results are returned with a visualization of the concentration estimate (see Figure 1), with further development, manual quantification using the generated spectrum may aid technicians in refining mixture analysis results. For now, estimating quantification using mixture analysis needs to rely on a triangulation of methods, described below.

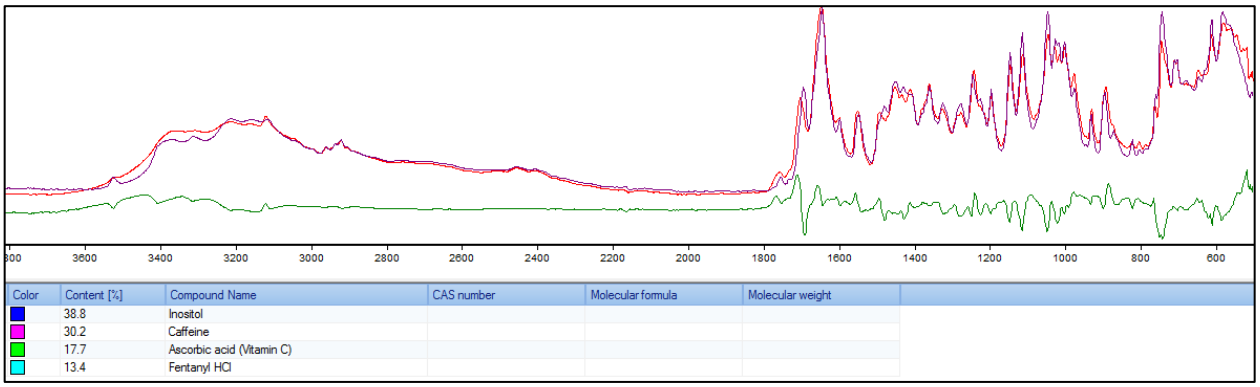

Figure 1. A mixture analysis output. The purple and green spectra visualize how the measured sample (red) is different from the algorithm's estimation. Further development of methods may make better use of these visualizations for more accurate estimations.

2. Bruker Quantitative Analysis 2 (QUANT 2): QUANT 2 is a validated prediction model that allows for multivariable calibrated analysis, and similarly to mixture analysis, is designed

to quantitatively analyze spectra to determine component concentrations. To do this, QUANT 2 utilizes a partial least squares fit method which correlates spectral intensity in specified wavelength regions with values that were generated from reference entries (i.e. point-of-care FTIR scans later quantified by confirmatory methods).

The BCCSU used the QUANT 2 software to build an in-house model using fentanyl confirmatory testing quantitative data: the BCCSU Fentanyl Quant Model.[3] The BCCSU Fentanyl Quant model returns a result for every sample, but does not visualize the results like mixture analysis does (see Figure 1). This means that there is no way to evaluate how accurate the prediction is in the absence of other sources of data to triangulate the result with.

In the evaluation of quantification methods performed by the BCCSU, the average difference from the true value of fentanyl concentration for the BCCSU Fentanyl Quant Model was -1.1%.[3] The model is particularly useful for running large numbers of samples at the same time, as performed in a retrospective of fentanyl concentrations in the unregulated drug supply in Vancouver.[4]

	Mixture Analysis	BCCSU Fentanyl Quant Model
Average difference from true value	-5.2%	-1.1%
Detection failure rate	34%	0%

Table 1. A summary of the key indicators for the two fentanyl quantification methods offered by FTIR.[3]

Additional qualitative detection method

Fentanyl test strips can detect fentanyl at levels lower than the FTIR, however they do not provide any quantitative information (i.e., the faintness of the test line does not infer concentration).[5,6] Although it may seem deductive that a sample without fentanyl detectable by FTIR yet has a positive test strip result may be "below 5% fentanyl," since the detection limit of the FTIR is "about 5%",[5] a positive test strip alone does not indicate that regular fentanyl is present at a low amount. See "Limitations of quantified information" below.

Confirmatory testing

Currently, the only accurate determination of quantification is through confirmatory testing. Health Canada's Drug Analysis Service (DAS) provides gold standard results for quantification using quantitative nuclear magnetic resonance spectroscopy (qNMR) that are highly accurate and precise. Under a partnership with DAS, the BCCSU can send a subset of samples from point-of-care drug checking sites to DAS to be analyzed with their technologies.

The qNMR method developed by DAS is state-of-the-art and is the basis for the BCCSU Fentanyl Quant Model used at point-of-care drug checking.

One challenge of using confirmatory testing results for fentanyl quantification is the fact that the results are not immediately available, potentially taking weeks to be returned. Results may be made available to the person that provided the original sample, but because of the required analysis time, real-time information is not possible.

Key quantification concepts

To best describe quantified results to others, it is important to understand some key concepts related to quantification and drug checking.

Precision and accuracy

Fentanyl quantification results have two qualities that must be considered. The first is accuracy, which can be described as how close the estimate (point-of-care result) is to the true value. The second, precision, refers to how narrow of an estimate is provided (e.g., a range of 5–10% is less precise than reporting 7.5%).

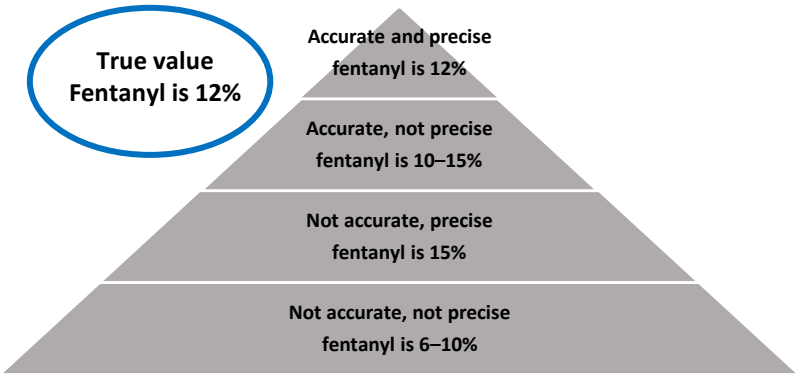

Figure 2. Pyramid hierarchy depicting increasing accuracy and precision using example fentanyl quantification results. For the purpose of this illustration, the "true value" of fentanyl was determined by confirmatory testing to be 12%.

The FTIR methods described above should not be used independently to portray individual sample results as either accurate and precise. Validation of the methods has shown QUANT 2 to be more accurate, but when taken together, the results may offer an ability to triangulate the true value and offer a more precise result. It is important to remember that FTIR analysis may not represent the proportions or concentration of the whole sample accurately as samples can be unevenly mixed and heterogeneous.

Further, two point-of-care technologies aligning well does not necessarily mean the concentration estimate is accurately representative of the whole sample. In samples sent for confirmatory testing, there has been substantial differences in fentanyl concentration between qNMR results and well-aligned point-of-care results. This may be because heterogenous (poorly mixed) mixtures sampled on the FTIR do not represent the entirety of the sample well. At DAS, fentanyl samples are homogenized before being measured, evenly spacing and distributing the fentanyl throughout the sample—a step not taken at point-of-care.

Purity vs. percentage

An important distinction that needs to be made when referring to drug checking quantification is the difference between purity and percentages:

- Purity is proportion of active ingredients (for example, cocaine) against *contaminants* (e.g., tropacocaine). Drug checking with FTIR cannot identify contaminants all too well in things like cocaine or MDMA (it can in heroin though, e.g., 6-monoacetylmorphine or noscapine). Contaminants are present from the synthesis of the drug, not added with the intention to dilute the sample as an adulterant would be.

- Percentage is the relative proportion of active ingredients against *adulterants*. For example, if a mixture analysis result is 80% cocaine 20% inositol, that result is percentage because the cocaine itself might only be 85% pure, meaning the sample is actually 68% pure (80% x 85%). Percentage is something that can be approximated with FTIR, while purity may not.

Percentage determined at point-of-care can vary significantly from the purity determined by confirmatory testing. For example, cocaine with no adulterants detected by FTIR can vary from 75%–95% in purity determined by qNMR. Fentanyl with “no adulterants detected” has varied from 60%–95%. This is the main reason to avoid the term ‘pure’ when delivering drug checking results. Additionally, there is always the chance that things are present in the sample under the detection limit of the FTIR.

Reporting Quantification Results to Service Users

Determining quantification results is a skill that is developed over time with experience and exposure to drug checking the unregulated drug supply; with experience, drug checking technicians may gain more confidence determining quantified results and confidence relaying the information to service users.

When a technician has learned how to use mixture analysis and combine the results with other methods and knowledge to quantify results, it is important that the technician and other

support staff know how to relay this to the service user. Depending on the technician's comfort level providing quantification information in the results of a drug check, they can use any of the following methods to relay fentanyl concentration to service users:

Approach	What to say	Strengths	Weaknesses
Provide a range on either side of the estimated value	"I believe there to be somewhere between 8–12% fentanyl in this sample."	• While imprecise, providing a range allows for a wider scope of accuracy.	• Different technicians have differing levels of confidence in determining fentanyl quantification. • Ranges may not be standardized (e.g., <5%, 5–10%, 10–15%, etc.) and instead be further narrowed based on technician confidence (e.g., 8–12%, 13–15%). • For potent drugs like fentanyl, the difference between minimum and maximum of a range is substantial.
Compare the sample to what is considered 'normal.' If the technician knows what is usually found in the local drug supply and there is a sense of what shows up in a typical sample, the technician may be able to assess if the sample is above, below, or typical of the normal quantity of fentanyl detected in similar samples.	"Your sample has an above-average amount of fentanyl in it."	• Easy to figure out with our technologies (accurate).	• Limited information conveyed (very imprecise). • What do people consider normal? "Normal" can be subjective and vary across different sites and/or technicians.
Do not provide percentages with drug checking results	"Your sample contains caffeine, mannitol, and fentanyl."	• Correct by omission. • Best practice for technicians who are still gaining experience with drug checking and have not yet been trained in or comfortable using quantification methods.	• Percentage estimates are an important driver for people to access drug checking services in BC. • People who previously received fentanyl percentages will be unhappy to have them withheld.

		• An appropriate answer for some samples when quantification analysis is not recommended or results are too uncertain to provide confident quantification	• This method does not promote behavioural change as drug checking merely functions to identify adulterants (fentanyl is no longer considered an adulterant).

Limitations of quantified information

No matter which of the above techniques are used to relay fentanyl concentration information, it is critical that technicians clearly explain the limitations of the drug checking technologies to service users and engage conversations about how to use more safely.

Three limitations that are important to convey:

1. It is an estimate based on what the technician understands is in the sample from the FTIR analysis/test strips and their knowledge of the local drug supply.
2. It is a range, meaning that even the small end of the range may still have potentially harmful impacts on human health and that the technician cannot say whether it is likely to be the high or low end of that range.
3. Other toxic components may be present in the sample but not detectible with the technology. In particular, carfentanil can contribute to opioid toxicity at levels far below the detection limit of both the FTIR and fentanyl test strips. Therefore, in all cases, quantification of fentanyl or other detectible components does not rule out the presence of carfentanil, which is highly potent in small amounts, and when mixed with other opioids. Non-opioids such as benzodiazepines can also increase the risk of overdose and may be missed by drug checking technologies (e.g., etizolam can be missed by benzodiazepine test strips).

Other messaging to share with service user

- If sample can be sent to a lab, wait for confirmatory testing results if possible.
- Potency is not directly related to risk of overdose since opioid tolerance varies widely between individuals.
- Even between different cities in the same province, the fentanyl concentration differs.[9] What may be typical for a person in Vancouver's Downtown Eastside may seem extremely strong for someone from Cranbrook.

Reporting Quantification Results Publicly

Drug Alerts

When a particular drug poses a risk of overdose or other potential health harms, a drug alert about a checked substance may be issued by regional health authority or a notification may be sent out by a local drug checking organization to notify the public about a potentially toxic drug.

Wording for these alerts is important. Research has shown that alerts (or media reports) regarding purity information can have unintended negative consequences.[7,8] For these reasons, it is recommended that public drug checking alerts are framed in terms of toxicity, rather than purity. Because quantified information can be misconstrued as 'purity,' it is important that drug checking alerts highlight the variability and unpredictability of the unregulated drug supply, not act as a mechanism to inform people about highly pure drugs. Therefore, **it is recommended at this time that drug checking alerts to the public do not include quantification information to avoid misinterpretation about 'purity.'**

Public Reports

Whenever possible, public-facing reporting should resolve to use the most accurate and precise results and include confirmatory-level analysis if possible. For knowledge translation purposes, aim to use the most confident results available, but if only less confident results are available, consider using aggregate results when relaying quantification information.

For example, in monthly reporting by the BCCSU, no alerts or key messages contain quantification information determined by FTIR at the single sample level. If required, confirmatory testing-derived (qNMR) results may be shared as these are considered to be the gold standard of drug checking data. Starting May 2021, the BCCSU began including aggregate FTIR-derived (QUANT 2) fentanyl concentration information in the monthly reports. The aggregate data ensures that not only can results be misconstrued or linked to particular drugs or appearances, aggregate results also allow for the law of large numbers to suggest a more accurate result. Histograms of drug checking quantification data allow for the use of wide bins (5% ranges are used in the BCCSU reports) to additionally account for estimation error.

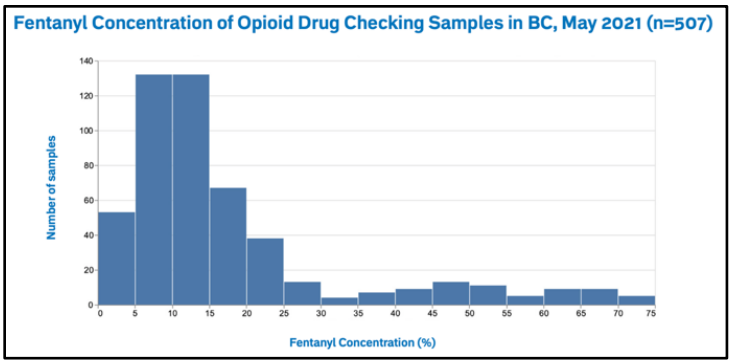

Figure 3. A histogram of fentanyl concentrations in drug checking samples presented in the May 2021 Monthly Public Health Report released by the BCCSU Drug Checking Project.[9]

Recommendations for improving quantification

1. Further evaluate point-of-care quantification technologies to assess accuracy, strengths and limitations.
    - Currently, different methods (may) operate better at varying concentrations
        - E.g., QUANT 2 works well when fentanyl is 5–20%, mixture analysis may work well 30%+
    - How do high levels of precursors affect fentanyl quantification attempts?
    - What happens when analogues become more common in the supply?
2. Develop training materials to bring technicians up-to-speed with senior-level technicians when it comes to quantifying fentanyl at point-of-care.
3. Seek alternatives to the Bruker software that may allow for more accurate quantification that is better suited to point-of-care drug checking in community settings.
    - E.g., machine learning models
4. Develop new methods and training materials for detection of commonly missed compounds such as carfentanil and benzodiazepines.

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