

Guidance Document for Implementing Comprehensive Toxicological Testing of Drug Products and/or Paraphernalia Suspected to Contain Opioids or Stimulants

1.0 Background

During 2021, 106,699 drug overdose deaths occurred in the U.S. Increases were driven by large and increasing numbers of deaths involving opioids, especially illicitly manufactured fentanyl and fentanyl analogs (IMFs), and/or stimulants.¹ Public health response to high and growing levels of fatal overdose deaths is limited by a lack of timely and localized data on the substances in illicit drug products. Timely data on drug products and/or drug paraphernalia, including those involved in overdoses, are critical to help:

- Track the spread of IMFs in the illicit drug supply.
- Identify and track trends in the use of emerging novel psychoactive substances (NPS)² such as synthetic opioids (e.g., fentanyl analogs and nitazenes), illicit benzodiazepines (e.g., clonazepam, etizolam, flualprazolam), and synthetic cathinones (e.g., eutylone and N,N-dimethylpentylone) in drug products.
- Determine the extent to which non-opioid drug products such as cocaine and methamphetamine also contain IMFs.
- Track harmful adulterants in IMFs and heroin drug products including xylazine and tramadol.
- Determine the substances contained in counterfeit tablets such as IMFs.

2.0 Intended Use

This document provides draft guidance to recipients regarding comprehensive toxicological testing of drug products and/or paraphernalia to support applicants design proposals and workplans to test drug products and/or paraphernalia as part of OD2A:LOCAL. CDC will provide updated guidance to recipients when funding begins. Through workgroup meetings with recipients, CDC will work to maintain requirements that are both feasible and comprehensive.

Recipients will need to adapt the CDC testing guidance to their context. Flexibility is necessary to address geographic variations in drug availability. **This guidance will be updated as needed in response to changes in drug prevalence, national toxicology testing standards, and new analytical technologies.** Updates will include ongoing identification of: 1) new fentanyl analogs and other synthetic opioids, 2) drugs commonly mixed with fentanyl such as xylazine, 3) non-opioid NPS including synthetic cannabinoids and cathinones that often co-occur with opioids and other stimulants, and 4) illicit benzodiazepines.

3.0 Forensic Toxicological Testing Parameters

For purposes of this funding announcement, the minimum level of toxicological testing for drug products and drug paraphrenia should include confirmatory testing for commonly prescribed opioids; illicit opioids such as fentanyl and heroin; illicit stimulants including cocaine, methamphetamine, other amphetamines, and cathinones; and drugs commonly co-occurring with opioids and/or stimulants, such as (but not limited to) benzodiazepines (See *Table 1* for full list). Testing for commonly co-occurring substances is important because these substances may impact overdose risk and public health co-morbidities (e.g., skin lesions). Finally, a key goal of drug product and/or paraphernalia testing is to identify and track NPS drugs in the illicit drug supply, especially those that might become more commonly distributed. Thus, toxicologic drug product and/or drug paraphernalia testing programs must test for NPS common to their region and are encouraged to test for the complete list of NPS listed in Table 1.

¹ <https://www.cdc.gov/nchs/data/databriefs/db457.pdf>

² <https://www.unodc.org/LSS/Page/NPS>

Due to the rapid shifts in the types of NPS detected and involved in drug overdose deaths across different US regions, recipients should consider guidance on testing scope found [here](#). The following drugs are recommended for inclusion in comprehensive testing for NPS as of the winter of 2022 and will be updated at time of funding.

Table 1: Substances included in testing protocol*	
Opioids	Stimulants/Cathinones/Hallucinogens
Natural and semi-synthetic opioids	2F-Deschloroketamine
Codeine, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone	3-OH-PCP/4-OH-PCP
6-Acetylmorphine, 6-Acetylcodeine, Heroin	Alpha-PHP/alpha-PiHP
Synthetic opioids	Amphetamine, MDA, MDEA, MDMA, Methamphetamine
Buprenorphine	Cathinones (Eutylone, N,N-Dimethylpentylone, Pentylone)
Methadone	Cocaine
Tramadol	N-Cyclohexyl Butylone
Fentanyl and fentanyl analogs*	N-Propyl Butylone
4-ANPP [^]	
Acetylfentanyl	Benzodiazepines
Carfentanil	Alprazolam, Clonazepam, Diazepam, Nordiazepam, Oxazepam, Temazepam
Fentanyl	Illicit benzodiazepines (Bromazolam, Clonazolam, Etizolam, Flualprazolam, Flubromazolam, Phenazolam)
o/m/p-Fluorofentanyl	
Other illicit synthetic opioids*	Other relevant substances*
2-Methyl-AP-237	Gabapentin
Borophine	Levamisole
Nitazenes (Etodesnitazene, Isotonitazene, Metonitazene, N-Desethyl Isotonitazene, N-Pyrrolidine Etonitazene, Protonitazene)	Natural and synthetic cannabinoids
	Xylazine

*This list will be updated as needed to reflect newly identified substances.

[^]Despropionylfentanyl, also known as 4-anilino-N-phenethylpiperidine (4-ANPP), is a fentanyl compound that can serve as a marker for illicitly manufactured fentanyl and fentanyl analogs because it is both a precursor and a metabolite of these illicit products (but not pharmaceutical fentanyl), while having low pharmacologic activity that does not contribute to overdose toxicity.

If results from the above comprehensive testing of a drug product or paraphernalia are negative and there is strong belief that a drug was present (e.g., drug product involved in an overdose), further probative testing may be considered to assess whether a fentanyl analog, other synthetic opioid, and/or other NPS was involved. This may require discussion with the lab to clarify their capabilities beyond the range of NPS listed above.

4.0 Purity (quantitative) testing (Optional)

Applicants may propose to conduct quantitative testing to better understand the purity of drugs and other substances in drug products and/or paraphernalia. If pursuing this option, recipients are strongly encouraged to assess the purity of fentanyl and fentanyl analogs, methamphetamine, cocaine, and heroin, if feasible. Rapidly assessing the purity of emerging threats such as the nitazenes is also encouraged.