

Public Comment to the U.S. Sentencing Commission

Re: Proposed Amendments on “Fentanyl-Related Substances” (FRS)

To the Honorable Members of the Commission:

I appreciate the opportunity to comment on the proposed amendments addressing fentanyl-related substances (FRS) in the United States Sentencing Guidelines. I write as a chemist with training and expertise in molecular structure and function, and with professional experience advising and testifying on the chemistry and pharmacology of controlled substances, including through previous public comment and invited oral testimony before the US Sentencing Commission on two occasions in 2017.¹

The Commission’s effort to add fentanyl-related substances (FRS) to the United States Sentencing Guidelines is timely and appropriate. At the same time, I respectfully urge the Commission to consider three observations that can help craft guidelines that are fair, evidence-based, and proportional:

- Fentanyl analogues and fentanyl-related substances are not interchangeable categories.
- Potency and danger of specific drug substances vary widely across both categories.
- Proportional sentencing based on drug potency is achievable where pharmacology data exist.

I. There are Differences Between “Analogues” and “FRS”

The Guidelines currently treat fentanyl analogues as a specific category within the Drug Quantity Table. The proposed amendment would add fentanyl-related substances. There is substantial overlap between these two categories, and it is reasonable that they might be treated similarly, but it should be understood that they are not the same.

Analogue determinations are subjective and case-dependent

“Analogue” status depends on a contextual judgment about whether a substance is sufficiently “similar” to fentanyl in chemical structure (and in most contexts, the known or intended function). In practice, analogue determinations require subjective interpretation and are subject to inconsistent or contested determinations.

This subjectivity and lack of clarity can be especially problematic in cases where the analogue issue is not litigated or established at trial but only introduced at sentencing under relevant conduct. In such cases, the subjective analogue designation would have to be made at sentencing.

1. (a) Public Hearing on Alternatives to Incarceration Court Programs and Synthetic Drugs Washington, DC Tuesday, April 18, 2017. <https://www.ussc.gov/policymaking/meetings-hearings/public-hearing-april-18-2017>
(b) Public Hearing on Synthetic Cathinones Washington, DC Wednesday, October 4, 2017. <https://www.ussc.gov/policymaking/meetings-hearings/public-hearing-october-4-2017>

FRS is structurally defined but potentially broader and more mechanical

The HALT Fentanyl Act defines “fentanyl-related substance” through a list of allowable structural modifications relative to fentanyl, such as substitutions on the phenethyl group, piperidine ring, or replacement of the N-propionyl group with another acyl group. This definition is objective in form, but also potentially expansive: it can capture substances that do not meaningfully resemble fentanyl in pharmacological effect, abuse potential, or public health risk. As I have noted previously, the singular defining feature of FRS scheduling is molecular structure: “Structure is important, but function is the larger concern here.”²

Thus, while FRS are defined more objectively, they may also sweep far more broadly than what most scientists or clinicians would view as fentanyl-like drugs. For example, FRS designations can include fentanyl-derived vaccines under development to mitigate the harms of fentanyl and fentanyl analogues.³

II. Potency and Harm Vary Widely Across Analogues and FRS

A central scientific problem with treating all analogues and FRS identically is that potency is not uniform. Some fentanyl analogues and FRS are significantly more potent than fentanyl, while others are less potent, or even antagonistic (i.e., counteractive). As I wrote previously: “compounds that are chemically related to fentanyl can be more or less dangerous, more or less potent, or even counteract its effects...”² However, the current proposal provides only one direction of deviation — enhanced severity across the category — irrespective of whether a given substance is more or less potent than fentanyl.

The proposed categorical enhancement relative to fentanyl does not align cleanly with known pharmacology; structural relationships do not guarantee enhanced potency. Fentanyl analogues and FRS can produce widely differing effects.

Some substances captured by these definitions are less potent than fentanyl

Several fentanyl-related substances have been reported to exhibit lower potency in relevant studies than fentanyl itself.⁴ For example:

- acetyl fentanyl, butyryl fentanyl, and valeryl fentanyl, which differ from fentanyl in their acyl substituents;
- *meta*-fluorofentanyl, which differs from fentanyl in the aniline ring; and

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2. Dudley, G. B. US fentanyl rules are so strict they may prevent life-saving research. Invited Commentary in *New Scientist*; 19 January 2023. <https://www.newscientist.com/article/2355617-us-fentanyl-rules-are-so-strict-they-may-prevent-life-saving-research/>
 3. Barrientos, R.C., Bow, E.W., Whalen, C., Torres, O.B., Sulima, A., Beck, Z., Jacobson, A.E., Rice, K.C. and Matyas, G.R., 2020. Novel vaccine that blunts fentanyl effects and sequesters ultrapotent fentanyl analogues. *Molecular pharmaceuticals*, 17(9), pp.3447-3460
 4. Varshneya, N.B., Hassanien, S.H., Holt, M.C., Stevens, D.L., Layle, N.K., Bassman, J.R., Iula, D.M. and Beardsley, P.M., 2023. Fentanyl analog structure-activity relationships demonstrate determinants of diverging potencies for antinociception and respiratory depression. *Pharmacology Biochemistry and Behavior*, 226, p.173572.

- 4'-fluorofentanyl, which differs by substitution on the phenylethyl group.

These examples demonstrate the key scientific point that structural modification alone does not impart greater potency or imply heightened danger.

The breadth of the FRS category includes compounds without opioid agonist activity

FRS structural breadth is such that it can encompass substances under investigation for therapeutic or preventive purposes (e.g., fentanyl-derived vaccines³), underscoring that structural coverage does not necessarily correlate with abuse potential or potency.

Perhaps most strikingly, testimony by the Food and Drug Administration (FDA) during consideration of FRS legislation reported that at least one of a small group of FRS tested in preliminary screening appeared to function not as an agonist, but as an antagonist.⁵ This FRS, which has not been publicly identified to my knowledge, would more likely counteract rather than mimic fentanyl's effects.

Such preliminary findings merit further study, and they underscore the broader issue that the structural scope of FRS scheduling is wide enough to encompass compounds that belie the assumptions embedded in the proposed uniform sentencing enhancements.

III. The Commission Should Consider Potency Data Where Available

From both a scientific and sentencing-policy standpoint, it would be appropriate for the Guidelines to acknowledge a range of potencies of both fentanyl analogues and FRS rather than assuming a uniform enhancement category.

The Guidelines should permit proportionality where credible potency evidence exists

Given this scientific variability, the Commission could consider approaches such as:

- permitting downward adjustments or departures where credible evidence demonstrates lower potency than fentanyl;
- creating potency-sensitive tiers or equivalency ranges rather than a single category;
- encouraging courts to consider pharmacological and toxicological evidence when available, rather than assuming enhanced severity in all cases.

Such flexibility would better align sentencing outcomes with the Commission's statutory responsibility to "provide certainty and fairness" in sentencing, to avoid unwarranted disparities, and to maintain sufficient flexibility for individualized sentences when warranted.⁶

5. The Overdose Crisis: Interagency Proposal to Combat Illicit Fentanyl-Related Substances: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce, 117th Cong. 4 (2021) at <https://www.c-span.org/clip/house-committee/user-clip-fda/4994371>

6. See 28 U.S.C. § 991(b)(1)(B) at <https://www.govinfo.gov/app/details/USCODE-2023-title28/USCODE-2023-title28-partIII-chap58-sec991>

IV. Isomer Inclusion Further Reinforces the Need for Potency-Based Adjustments

A related consideration is the treatment of isomers⁷ within the Guidelines' existing approach to fentanyl analogues and proposed approach to fentanyl-related substances.

Isomers are different chemical compounds that share the same molecular formula but differ in structure or configuration. As a result of their structural differences, isomers can vary substantially in form and function, including in potency or overall pharmacological effect.

When enhanced penalties apply broadly to fentanyl analogues and/or fentanyl-related substances *and their isomers*, the covered category technically becomes even more expansive. A substance may technically qualify as an isomer of a fentanyl analogue or FRS while having little meaningful similarity to fentanyl in potency or functional effect. For example, the molecular formula of *meta*-fluorofentanyl (C₂₂H₂₇FN₂O) is shared by over 1000 known isomeric substances,⁸ including substances with no known or expected potency relationship to fentanyl.

The existence of many structurally distinct isomers illustrates that categorical treatment based solely on formal chemical relationship can capture substances with a wide range of pharmacological profiles. The breadth of these categories reinforces the importance of allowing sentencing outcomes to reflect scientific reality where data are available. If the Guidelines treat all substances within these broad structural groupings, *including their isomers and salts of isomers*, as uniformly more serious than fentanyl, without the possibility of potency-based mitigation, sentencing enhancements may apply even when the underlying substance is less potent or functionally distinct.

Accordingly, to the extent fentanyl-related substances are incorporated into the Guidelines, the Commission may wish to ensure that courts have appropriate flexibility to consider potency and pharmacological evidence, rather than presuming uniform severity across an exceptionally broad structural category.

V. Conclusion

The fentanyl overdose epidemic is serious, and illicit trafficking in highly potent opioids is dangerous. Such dangers can be reflected appropriately in the guidelines by allowing for consideration of the actual dangers whenever possible. From a chemistry perspective, broad structural categories do not map cleanly onto relative functions, potencies, or harm.

7. The Guidelines already include "isomers" within controlled substance definitions, and I recognize that this is not the primary focus of the Commission's current proposal. I raise the point here only because it underscores the broader scientific concern with relying on structural classification alone.

8. A search of the Chemical Abstracts Service (CAS) database using SciFinder (<https://scifinder-n.cas.org/>) on 02 June 2023 for substances having the molecular formula C₂₂H₂₇FN₂O produced 1,265 results.

FRS (and fentanyl analogues) can be more potent, less potent, or even functionally distinct from fentanyl. A proportional and evidence-based framework that allows for consideration of potency and potential harm would be consistent with the Commission's duty to promote fairness, reduce unwarranted disparities, and preserve appropriate sentencing flexibility and would serve public safety and rational sentencing policy.

I respectfully suggest that the Commission incorporate fentanyl-related substances in a manner that permits potency-based proportionality and avoids unwarranted categorical enhancements. Thank you for considering these comments.

Respectfully submitted,
Gregory B. Dudley, Ph.D.
February 6, 2026