Testimony Before the FDA's Drug Safety and Risk Management & Anesthetic and Analgesic Drug Products Advisory Committees

regarding intravenous tramadol

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I have no financial conflicts of interest.

Background for today's meeting

- In March 2016, then-FDA Commissioner Robert Califf asked the National Academies to convene an ad hoc committee of experts to, among other things, provide input on "How to **formally** incorporate the broader public health impact of opioid abuse in future FDA approval decisions regarding opioids."
- This resulted in a report issued four and one-half years ago (July 2017) by the National Academies, with the major finding explicitly being that the FDA had failed to adequately "incorporate public health considerations into opioid-related regulatory decisions."
- In addition, the report recommended many specific changes, compatible with the agency's existing statutory authority, to be incorporated into a new FDA framework for opioid regulation that would address the agency's long-standing deficiencies in this process.

Background for today's meeting (cont'd)

National Academies Recommendations included:

"The investigational drug evaluation process also has important limitations, particularly with respect to the approval of opioids."

The major controlled study that the FDA relied on for [Dsuvia-sufentanil] approval involved patients who had just undergone abdominal surgery. In the Dsuvia-treated subjects, the median time before they reported clinically meaningful pain relief was 54 minutes. Because no active comparator drug was used in the study, 54 minutes was not statistically significantly sooner than the median time to onset of clinically meaningful pain relief in subjects given a placebo, clearly falling short of adequate management of severe pain. Multiple alternative opioid treatments would not have required patients to wait almost an hour for meaningful relief of acute postoperative pain. All of the controlled studies upon which the FDA's approval of Dsuvia was based were placebo-controlled; none used a comparator opioid or non-opioid analgesic that could establish whether Dsuvia was even as good as alternative treatments.

Table 1. Rate of prescribing hydrocodone and tramadol products per 100 people before and after the rescheduling of hydrocodone combination products. (Source, Harrison and Walsh, 2019[37])

State/Opioid	Prescribing Rate 2 Years Before	Prescribing Rate 1 Year Before	Prescribing Rate 1 Year After	Prescribing Rate 2 Years After
California				
Hydrocodone	44.3	43.2	35.0	31.7
Tramadol	0.0	0.2	9.9	9.7
Michigan				
Hydrocodone	69.1	66.8	55.6	52.7
Tramadol	0.0	0.1	17.3	17.4
New York				
Hydrocodone	-	20.8	15.1	14.3
Tramadol	-	0.0	7.6	7.5

High Rate of Tramadol Misuse Compared to Schedule II Opioids

…..for the interval of 2016 through 2018, the proportion of people using tramadol who misused the drug exceeded the corresponding proportions of people who misused Demerol and morphine and was approximately two-thirds as high as the corresponding proportions of people who misused fentanyl, hydrocodone, and oxycodone. (The year-to-year decrease in tramadol misuse in 2018 paralleled decreases in the misuse of all other opioids. NSDUH data)

Table 2. Estimated misuse of pain reliever subtypes in past year among past year any users of pain relievers, aged 12 or older: numbers in thousands of people misusing each drug (percentages of all users of the drug who were misusing the drug), 2016 to 2018. (Source: Detailed tables from the 2017 and 2018 National Survey on Drug Use and Health[41,42])

Opioid Product	2016	2017	2018
Hydrocodone	6,924 (12.6)	6,262 (12.0)	5,502 (11.5)
Oxycodone	3,905 (14.1)	3,735 (14.0)	3,374 (12.8)
Tramadol	1,591 (8.4)	1,753 (9.5)	1,455 (8.1)
Codeine	2,767 (10.4)	2,832 (10.5)	2,393 (9.4)
Morphine	536 (7.9)	501 (8.0)	486 (7.9)
Fentanyl	228 (12.4)	245 (12.0)	269 (12.7)
Buprenorphine	712 (31.6)	766 (31.7)	718 (28.3)
Oxymorphone	302 (27.6)	332 (36.2)	237 (28.4)
Demerol	95 (6.9)	116 (9.6)	54 (4.5)
Hydromorphone	239 (11.3)	244 (12.6)	229 (13.0)
Methadone	346 (25.5)	261 (19.5)	256 (23.5)

Table 4. Adjusted risk ratios* (95% confidence intervals) and p values† for persistent opioid use (three definitions) in patients who received tramadol only, tramadol and another short-acting opioid, or any long-acting opioids (reference group: short-acting opioids excluding tramadol). Reproduced from Thiels et al., 2019.[48]

Opioid type	Additional opioid use after surgery‡	Persistent opioid use after surgery§	CONSORT definition of opioid dependence¶
Other short-acting	Reference	Reference	Reference
Tramadol only	1.06 (1.00-1.13); p=0.049	1.47 (1.25-1.69); p<0.001	1.41 (1.08-1.75); p=0.013
Tramadol + short-acting	1.05 (0.96-1.14); p=0.261	1.04 (0.86-1.21); p=0.685	1.40 (1.05-1.74); p=0.022
Any long-acting	0.95 (0.87-1.03); p=0.218	1.18 (1.02-1.35); p=0.029	1.69 (1.36-2.02); p<0.001

*Risk ratios calculated as ratio of predictive margins after logistic regression including covariates of year, surgery, female sex, beneficiary type, race/ethnicity, census division, age category, categorical measurement of morphine milligram equivalents at discharge, and flags for each of Elixhauser comorbidities; see appendix F for full regression output.

†P values from hypothesis test that risk ratio does not equal 1.

‡At least one opioid fill 90-180 days after surgery.

§Any span of opioid use starting in the 180 days after surgery and lasting ≥90 days.

¶Opioid use episode starting in the 180 days after surgery that spans ≥90 days and includes either ≥10 opioid fills or ≥120 days' supply of opioids.

U.K. Mortality Study*

Zeng et al. conducted a sequential, propensity score-matched cohort study using an electronic medical records database for general practitioners in the U.K. that contains health information on approximately 11 million patients.44 They assessed the all-cause mortality risk in osteoarthritis patients aged 50 years or older within one year after an initial tramadol prescription (n=44,451), compared with five other analgesic medications: naproxen (n=12,397), diclofenac (n=6,512), celecoxib (n=5674), etoricoxib (n=2,946), or codeine (n=16, 992).

Zeng et al. found that after 12 months of follow-up, the mortality rate was higher for tramadol users than for users of naproxen (hazard ratio [HR] 1.71; 95% CI 1.41-2.07), diclofenac (HR 1.88; 95% CI 1.51-2.25), celecoxib (HR 1.70; 95% CI 1.33-2.17) and etoricoxib (HR, 2.04; 95% CI 1.37-3.03). No statistically significant difference in all-cause mortality was observed between users of tramadol and codeine. (HR 0.94; 95% CI 0.83-1.05).

* Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA*. 2019;321(10):969-982

Concern about rapid tramadol metabolizers

There is now clear recognition that a substantial proportion of the population has the cytochrome P450 2D6 (CYP2D6) genotype, which makes them ultra-rapid metabolizers of tramadol into a form that greatly increases the risk of fatal respiratory depression. This is the case across many racial subgroups.* The FDA-approved product labeling now warns that individuals who are ultra-rapid metabolizers should not use tramadol. However, few people know whether they are ultra-rapid metabolizers of tramadol because CYP2D6 genotyping generally is not performed prior to prescribing tramadol to patients.

* 3-4% of African Americans, 1-2% of East Asians, and greater than 10% of certain other racial/ethnic groups (Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, and Puerto Rican).

The FDA Discussion Questions and Vote

DISCUSSION: Discuss the importance of time to onset of action and risks related to delayed onset of action for intravenous tramadol proposed for the management of moderate to severe acute pain in the inpatient setting, such as post-operative or acute severe injury setting.

Since "approximately 50% of patients administered tramadol IV 50 mg did not report meaningful pain relief in 6 hours," I agree with FDA's concern that patients will need additional opioids, thereby severely reducing the efficacy of the IV tramadol and increasing risk such as respiratory depression.

DISCUSSION: Discuss the benefits and risks of intravenous tramadol for acute pain management in the inpatient setting considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.

As with the above question, and the additional risk of increased opioid dependence with tramadol, the risks further outweigh the benefits of the drug.

DISCUSSION: Discuss the relevance of tramadol's Schedule IV status in the context of the proposed use for the management of acute pain in an inpatient setting with consideration on the following issues:

a. Any impact on risk of abuse, misuse, or addiction in the outpatient setting

The 2019 Thiels study of transitioning from acute to prolonged opioid use in opioid-naïve patients treated with tramadol for postoperative pain clearly showed tramadol with higher long-term dependence than other short-acting opioids.

b. Any comparative advantage over currently available Schedule II opioids approved for the
management of acute pain in an inpatient setting

The company's study failed to show superiority over morphine and failed to use non-opioid alternatives in any randomized study.

VOTE: Has the Applicant submitted adequate information to support the position that the benefits of their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient setting?

The FDA "questions whether the minimal benefit from using tramadol IV, given its delayed onset of analgesia, outweighs the potential risk of sedation and respiratory depression from opioid stacking."

Based on the evidence from the agency as well as increased long-term opioid dependence following post-operative tramadol use, the risk benefit balance argues unequivocally for rejecting its approval.