# FDA Meeting on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products

November 9, 2016

Testimony by Sidney M. Wolfe, MD

Public Citizen's Health Research Group

I have no conflict of interest

# The Public Health Topic: Question One

What are the benefits for clinical decision-making of communicating preliminary or inconclusive information about unapproved uses of approved/cleared medical products to physicians and patients?

What are the drawbacks and risks?

Are there safeguards or requirements that would effectively mitigate any drawbacks or risks?

# U.S. Off-label prescriptions (‘05–mid ‘07)
# Scope and inadequacy of evidence for efficacy

| Drug | All Off-Label uses | All On-Label uses | % uses Off-label | Off-label uses: Inadequate efficacy evidence | % of Off Label uses with inadequate evidence |
|---|---|---|---|---|---|
| All top 25 drugs* | 74,105,000 | 181,254,000 | 29% | 60,844,000 | 82% |
| 1st,4th,5th and 7th top drugs | | | | | |
| quetiapine Seroquel | 6,507,000 | 2,120,000 | 75% | 6,507,000 | 100% |
| escitalopram Lexapro | 3,580,000 | 21,376,000 | 14% | 3,580,000 | 100% |
| gabapentin Neurontin | 6,334,000 | 446,000 | 93% | 3,423,000 | 54% |
| risperdone Risperdol | 4,034,000 | 2,366,000 | 63% | 1,465,000 | 36% |

*Top 25 drugs with greatest # of off-label uses with inadequate efficacy evidence

Walton SM, et al. *Pharmacotherapy*. 2008;28(12):1443-1452.

## Summary of findings from Walton, et al:

For only the 25 drugs with the largest number of off-label uses with inadequate evidence of efficacy---

- Total off-label uses were 74,105,000 out of a total of 255,359,000 uses or 29% of all uses for the 2 ½ years represented by the data.

- There were 60,844,000 off-label uses with inadequate evidence of efficacy, or 82% of all off-label uses.

*Thus, more than four fifths of off-label uses of these 25 drugs occurred for uses in which there was inadequate evidence of their efficacy.*

*The absence of evidence adequate to demonstrate efficacy for those uses may also suggest a lack of evidence of safety for the same uses. A recent study examined adverse drug reactions occurring with off-label compared to on-label use to test this.*

# Criteria used for the Canadian (Eguale, et al) study to determine if there is strong efficacy evidence for off-label use

- the drug *is* effective or favors efficacy for the off-label treatment indication and
- the drug is recommended for at least most patients with the off-label treatment indication and
- the studies used to evaluate efficacy and the strength of evidence include at least one randomized controlled trial

# Off-label prescriptions, (Quebec, 2005-2009) Scope and adequacy of evidence for efficacy

| | # Off-Label Prescriptions (Rxs) '05-'09 | Off label Rxs as % of *all* Rxs | # Off-label Rxs lacking strong efficacy evidence | % Off Label Rxs lacking strong efficacy evidence |
|---|---|---|---|---|
| All drugs | 17,847 | 11.8% | 14,431 | 81% |

# Increased adverse drug reactions (ADRs) for off-label compared to labeled use of drugs

| | Total # of ADRs with all drugs | Adjusted Hazard Ratio (AHR) for all off-label uses compared to labeled uses | AHR for uses lacking strong efficacy evidence | AHR for uses with strong efficacy evidence |
|---|---|---|---|---|
| All drugs | 3484 | 1.44 (44% higher ADRs off-label | 1.54 | 1.10 |

Eguale, et al. *JAMA Intern Med*. 2016;176(1):55-63.

# Evidence of increased risks to patients along with absence of strong evidence of benefits for most off-label use

- Closely agreeing with the earlier (2008) finding that 82% of off-label uses lacked adequate evidence of efficacy, the newer study published last year found that 81% of off-label uses of drugs lacked strong evidence of efficacy. Importantly, using electronic health records, these investigators additionally measured adverse drug reactions (ADRs) sufficiently severe to discontinue the drug in patients---for both off-label and on-label uses.
- 46,000 adult patients received 151,000 new prescriptions during the study,11.8% of which were for off-label use. There was a 54% adjusted excess of ADRs (hazard ratio) for off-label use of those drugs lacking strong evidence of efficacy, compared with that for on-label use. For the small fraction of off label uses (19%) for which there was strong evidence of efficacy, there was a non-significant increase in ADRs compared with the rate for on-label use.

# The Public Health Topic: Question One

What are the benefits for clinical decision-making of communicating preliminary or inconclusive information about unapproved uses of approved/cleared medical products to physicians and patients?

The high prevalence of such inconclusive information for off-label use leads to prescriptions for uses, 80% of which lack strong evidence of effectiveness. This is hardly a “benefit for clinical decision-making”.

What are the drawbacks and risks?

Beyond lacking strong evidence of effectiveness, the more than 50% increase in adverse drug reactions, compared to on-label uses, presents a clear health hazard to patients receiving drugs for such uses: these increased risks, combined with the lack of strong benefit evidence heighten the need for strong restrictions against promotion for unapproved uses.

.

# The Public Health Topic: Question One (continued)

Are there safeguards or requirements that would effectively mitigate any drawbacks or risks?

FDA requirements for substantial evidence of effectiveness with adequate evaluation of safety, the standards for adding an on-label use for a drug, would clearly be a safer alternative to off-label promotion, reaping additional benefits for the public.

The well-documented fact that strong efficacy evidence is lacking for most off-label use is at the core of this deficit of benefits and excess of risks. There is no feasible way to mitigate these problems by FDA encouraging the provision of more communications that reinforce, probably worsen this status quo.

# Conflict between recommendations by *JAMA Internal Medicine* study authors (Eguale, et al) and FDA's proposed Guidance about Manufacturer Communications Regarding off-label promotion

Eguale, et al: "Off-label drug use, and particularly off-label use without strong scientific evidence, is a risk factor for ADEs. Hence, physicians and physician organizations should recognize the enormity of the problem and **be active participants in the promotion of cautious prescribing of drugs for off-label uses lacking strong scientific evidence."** (emphasis added)

Instead of any industry proposals that will predictably increase the amount of off-label use, the FDA should be working to decrease off-label use. Otherwise, the FDA will be complicit in allowing the promotion of more reckless prescribing instead of the "**promotion of cautious prescribing."**