To: Secretary of HHS, Alex Azar
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Subject: Policy Memo – Drug Facts Box

The Drug Facts Box

Reconsidering a Solution to FDA's Failure to Communicate Drug Risks and Benefits

Executive Summary

American patients do not understand the risks of prescription drugs they take, and the FDA does nothing to help them. In 2010, Congress directed the then Secretary of HHS, Kathleen Sebelius to investigate the effectiveness of the Drug Facts Box (DFB), a tool for communicating drug risks and benefits to patients. The FDA was directed to begin creating DFBs if they were found to improve patient and physician decision-making (Strokoff et. al., 2010, 453).

The Secretary's final report to Congress concluded there was not enough evidence that the drug facts box would improve decision making (FDA, n.d., 3-7). However, the report fails to fully investigate the impact on decision making. Instead, it presents alternative efforts as though they are on track to provide much-needed risk communication to patients. None of these efforts are even directed to patients. The report further attempts to justify its premature rejection of DFB by presenting difficulties in its implementation.

This difficult task of communicating drug risks to patients is precisely the FDA's responsibility. No other entity is in position to provide this service to patients. The relevant risk information is already available in FDA drug reviews. Scientists have created a handbook for FDA reviewers to use while populating the DFB. After a decade of pursuing approaches that have failed to improve drug risk communication, it is time for the FDA to empower patients to make informed decisions on their prescription drugs by implementing the Drug Facts Box.

No Drug Risk Communication from the FDA

The FDA currently leaves to pharmaceutical companies all responsibility for communicating drug risk and benefit information to patients. While America's pharmaceutical companies have produced lifesaving and life-improving drugs for years, the status quo rewards companies that mislead consumers on their drug's effectiveness and risks. The FDA should assume the responsibility for that communication. Doing so will free pharmaceutical companies to compete on what matters most – value to consumers.

FDA reviewers already spend up to one year reviewing new and updated drugs for approval. They consider several factors including the current state of available drugs and the evidence of effectiveness from clinical trials. They may approve a high-risk drug because patients desperate for its effects may be willing to take its risks when no alternative drugs are available on the market (FDA, 2018, 3-4). But without the FDA attempting to summarize the relevant information in patient-friendly language, how can the patient make an informed decision on choosing whether to take this prescription drug?

Evidence for the Drug Facts Box

The Drug Facts Box (DFB) provides necessary drug risk and benefit communication to patients. It uses the evidence from clinical trials included in FDA reviews of the drug. Fig. 1 displays an excerpt of an example DFB for Abilify, the fourth most advertised drug in the country (Schwartz and Woloshin, 2013, 14069). Here are two important observations this DFB enables:

1. Abilify's positive effect is very small: +3 points on a 60-point depression scale when compared to the control group.
2. The drug has a relatively high risk of akathisia (severe restlessness): 25% of the group taking Abilify developed akathisia while only 4% of the control group did.

The medical journal publication on Abilify exaggerates its positive effect so that even physicians may be misled on its effectiveness. Abilify's risk communication to patients downplays the risk of akathisia by including it in a long list of less severe side effects, including headaches, dizziness, and nausea (Schwartz and Woloshin, 2013, 14070-14071).

Studies show most patients understand and remember risks better after reading the DFB than without it; additionally, many patients report they would change their behavior to choose the better drug if given this information (Schwartz and Woloshin, 2013, 14073). The HHS Secretary's report to Congress discounted this evidence because the respondents were not actually purchasing a drug – the context was hypothetical (FDA, n.d., 20).

STUDY FINDINGS (combined results of 2 identical trials)

741 people – ages 19 to 67 years – with major depression that persisted after 8 weeks of an anti-depressant were randomized to have either ABILIFY or PLACEBO **added for 6 weeks**. Here's what happened:

What difference did ABILIFY make?	Anti-depressant + ABILIFY (10 mg each day)	vs.	Anti-depressant + PLACEBO (No drug)
How did ABILIFY help?			
Depression scores improved by 3 points more than placebo (on a scale from 0 to 60).	9 points better	vs.	6 points better
11% more people had an important response and were no longer considered to have major depression	26%	vs.	15%
Functioning scores improved by 0.5 points more than placebo (on a scale from 0 to 10).	1.2 points better	vs.	0.7 points better
What were ABILIFY'S side effects?			
Serious side effects			
21% more people developed akathisia - severe restlessness that makes it hard to keep still	25%	vs.	4%
3% more people developed movement disorders –like Parkinson's disease	8%	vs.	5%
Symptom side effects			
6% more people had insomnia	8%	vs.	2%
5% more had blurred vision	6%	vs.	1%
4% more had substantial weight gain	5%	vs.	1%
4% more had fatigue	8%	vs.	4%
3% more had constipation	5%	vs.	2%

WARNINGS ABOUT UNCOMMON LIFE-THREATENING AND VERY SERIOUS SIDE EFFECTS

Young adults using anti-depressants for major depression have a higher risk of suicidal thinking and behavior.
Elderly patients with dementia-related psychosis should not use antipsychotic drugs – **like ABILIFY**–because they increase death.
Antipsychotic drugs cause: Neuroleptic Malignant Syndrome (very high fever and blood pressure, delirium), Tardive Dyskinesia (uncontrollable facial / body movements), Dangerous Heart Rhythms, Seizures, Low White Blood Cells, Trouble Swallowing, Aspiration Pneumonia, Diabetes, Low Blood Pressure, Trouble Regulating Body Temperature

Fig. 1. Drug Facts Box for Abilify for adults with major depression that persists on antidepressants.

HHS Report to Congress (2010)

Secretary Sebelius reported to Congress that the current scientific literature showed that the Drug Facts Box (DFB) improved patient understanding of risk but did not show that the DFB would improve patient decision-making. While technically accurate, this conclusion is functionally dishonest. In effect the authors state that *although the evidence suggests patients who read a DFB understand the risks of different drugs better, we do not know if they would use that information to choose the better drug.*

The authors even directed studies to evaluate the DFB, but they omitted the very behavioral-analysis methodology they criticize the scientific community for not including in its studies. Either the authors failed to fulfill the investigation they promised, or they must admit that some results of the regulation (i.e. the effect on consumer choice) can only be known after the regulation is implemented.

If the authors had put forth concerns that a DFB could further mislead patients, more discussion would be warranted before implementing this regulation. But their concerns were primarily over the complexity of the task: it is not always clear which clinical trial should be used as the basis for the DFB, and it is not obvious how to communicate that patients should not take a drug if they have certain conditions (contraindications). While these issues do present a challenge, they do not preclude action. The FDA can populate the DFB for the simplest drugs first while deliberating how to standardize more complicated drug reviews.

Failed Communication Efforts

In this same report, the Secretary pointed Congress to several alternative efforts the FDA was undertaking to improve risk communication. In only one of these efforts does the FDA take responsibility for risk communication. That effort – the Benefit Risk Framework – is not crafted for patient use. The other efforts are unenforced documents to guide drug companies in their communication.

The Benefit Risk Framework provides a summary of the reviewer's key considerations for approval, but it is hardly written in language appropriate for a patient-audience (FDA, 2018). Perhaps even more problematic is how difficult it is to find. The author of this memo was unable to find a single example of the Benefit Risk Framework on the FDA's website. An FDA employee ultimately provided instructions to find an example[1].

The other efforts were guidelines to pharmaceutical companies discouraging techniques that mislead consumers in TV advertisements[2], print advertisements[3][4], and the CLINICAL STUDIES section of drug labeling[5]. **None of these guidelines are enforced**. This rewards companies who disregard the guidelines. It is time for the FDA to accept the responsibility for communicating to patients the risks and benefits of drugs *they have already reviewed for approval*.

[1] Instructions to find the Benefit-Risk Framework example:
1. Navigate to this website: https://www.fda.gov/vaccines-blood-biologics/jynneos
2. Click "Approval History, Letters, Review, and Related Documents" to download zip file
3. Extract files and open "Clinical Review Memo, September 19, 2019 – JYNNEOS"
4. The Benefit-Risk Framework is on page 198

[2] https://www.fda.gov/media/82590/download
[3] https://www.fda.gov/media/70768/download
[4] https://www.fda.gov/media/76269/download
[5] https://www.fda.gov/media/72140/download

Recommended Actions

This memo recommends taking the following actions. To guide each, FDA reviewers can use the handbook Drs. Schwartz and Woloshin (2013) crafted (14073).

Direct the FDA to

1. Create a list of drugs for which choice of clinical trial to include in DFB is clear
2. Assign the original reviewers of these drugs to populate DFBs
3. Draft a team to discuss how to display contraindications on DFBs and which clinical trial to represent when that choice is unclear
4. Survey patients and physicians for opinions on DFB
5. Study impact DFB has on decision making

Conclusion

This memo re-introduces the Drug Facts Box as a solution for the FDA's failure to communicate drug risks and benefits precisely to patients. The FDA previously rejected the tool due to inherent complications in standardizing the risk communication, but no alternative has materialized since Congress first requested the Drug Facts Box in 2010.

The FDA's own investigation of the Drug Facts Box suggests it would improve patient understanding of risk. It is time for the FDA to take responsibility for communicating risks to patients by providing Drug Facts Boxes with their prescription drugs.

References

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Strokoff, S. L., & Grossman, E. G. (2010). *OFFICE OF THE LEGISLATIVE COUNSEL*. 974.