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The Drug Facts Box: Improving the Communication of Prescription Drug Information

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Communication about prescription drugs ought to be a paragon of public science communication. Unfortunately, it is not. Consumers see $4 billion of direct-to-consumer advertising annually, which typically fails to present data about how well drugs work. The professional label—the Food and Drug Administration's (FDA) mechanism to get physicians information needed for appropriate prescribing—may also fail to present benefit data. FDA labeling guidance, in fact, suggests that industry omit benefit data for new drugs in an existing class and for drugs approved on the basis of unfamiliar outcomes (such as depression rating scales). The medical literature is also problematic: there is selective reporting of favorable trials, favorable outcomes within trials, and "spinning" unfavorable results to maximize benefit and minimize harm. In contrast, publicly available FDA reviews always include the phase 3 trial data on benefit and harm, which are the basis of drug approval. However, these reviews are practically inaccessible: lengthy, poorly organized, and weakly summarized. To improve accessibility, we developed the Drug Facts Box: a one-page summary of benefit and harm data for each indication of a drug. A series of studies—including national randomized trials—demonstrates that most consumers understand the Drug Facts Box and that it improves decision-making. Despite calls from their own Risk Communication Advisory Committee and Congress (in the Affordable Care Act) to consider implementing boxes, the FDA announced it needs at least 3–5 y more to make a decision. Given its potential public health impact, physicians and the public should not have to wait that long for better drug information.

physician–patient communication | evidence summaries | data presentation

Communication about prescription drugs ought to be a paragon of public science communication. Prescription drugs are important: they can literally be a matter of life and death. Americans take a lot of them: nearly half of the US population takes at least one prescription drug every day; two-thirds of those over age 65 y take at least three (1). Poor communication can have serious consequences: people may forgo drugs that can help or take drugs with no benefit or that even cause harm.

In the past, the public was not the intended audience for prescription drug information. According to the 1938 regulations establishing the modern US Food and Drug Adminstration (FDA), for example, it was expected that information in drug labels would "appear only in such medical terms as are not likely to be understood by the ordinary individual." (2) However, much has changed since 1938. With the rise of the consumer movement in society, the shift in medicine from paternalism to respect for patient autonomy, and the expansion of the medical–industrial complex, the public is now the audience for a vast amount of drug information—most obviously in the form of direct-to-consumer (DTC) drug advertising.

Although DTC advertising in the United States began in earnest in the mid-1990s, it remains controversial (in fact, New Zealand is the only other country permitting such advertisements) (3–8). Proponents argue that the advertisements have an educational function, raising consumer awareness about a variety of medical conditions and educating them about treatment options. Opponents, however, worry that the advertisements mostly increase inappropriate demand for marginally effective drugs.

Current investment in DTC advertising is substantial. Pharmaceutical companies spent more than $4 billion in 2011 on DTC advertisements (9), about 10 times FDA's total budget for the evaluation of new drugs (10). In the United States, DTC advertisements are ubiquitous. The average American television watcher views about 15 h of them per year (11). DTC print advertisements appear in nearly every major US newspaper and magazine.

DTC advertising also influences physicians—as do other marketing efforts such as advertisements in medical journals and detailing visits from pharmaceutical representatives. However, physicians mostly learn about prescription drugs from medical journal articles and other professional sources. None is more important than the FDA-approved drug label. Whether they realize or not, physicians get information from the label all of the time. The Physicians Desk Reference is a compendium of labels, and popular electronic medical sources such as UpToDate reprint excerpts of the label.

In this paper, we will look at problems with how prescription drug information is presented to consumers and doctors. To illustrate these problems, we use the example of Abilify (aripiprazole), an antipsychotic drug most recently approved for the treatment of depression that is only partially responsive to another antidepressant (the drug is also approved for a variety of other disorders). Abilify—the fourth most heavily advertised drug in the United States (9)—had sales of more than $5 billion last year (12). The problems we describe below in advertisements, labels, and journal articles are general: they are neither unusual nor unique to Abilify. Moreover, all are "legal"—none violate federal regulations. We end by describing the Drug Facts Box: a standardized one-page summary designed to improve communication of key information about benefits and harms of prescription drugs.

Problems with Drug Information for Consumers

DTC Advertising. The multimedia "Me and my depression" Abilify advertising campaign exemplifies how the drug is being intensely promoted to consumers. One ad features a cartoon image of a woman being dragged down by a ball and chain who says "After 6 weeks on an antidepressant, I was still struggling with my depression"; the ad then suggests that people ask their doctor about adding Abilify to their drug regimen. However, the ad never says

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DRUG FACTS

ABILIFY (aripiprazole) **for adults with major depression that persists on antidepressants**

What is this drug for?	To reduce symptoms of major depression– nearly everyday feelings of extreme sadness, or hopelessness.
Who might consider taking it?	Adults with major depression that persists after one or more 8-week courses of an anti-depressant.
How long has the drug been used?	First approved in **2002 for schizophrenia**; in **2007 for persistent depression** (based on studies of about 1,000 people). As with all drugs, rare but serious side effects may emerge when more people use it for a new purpose.
What precautions should I take?	Use caution driving or operating machinery because ABILIFY may impair judgment, thinking or motor skills. Do not drink alcohol or breastfeed. Check blood tests if you've' had low white blood cell count or high sugar levels.
What other choices are there?	Cognitive behavioral psychotherapy, exercise, switch to a different anti-depressant, add another anti-depressant, or electroconvulsive therapy.

Bottom line

Adding ABILIFY to an antidepressant for persistent depression is a tradeoff: some people's depression will improve but more will experience a serious side effect – akathisia. And some will gain a substantial amount of weight.

The 2 FDA-approval studies combined below had nearly identical findings about how much the drug helped over 6 weeks. This makes the numbers in the table more believable. Benefits and side effects over a longer time are more uncertain.

Like all anti-psychotic drugs, Abilify can cause a number of uncommon serious or life-threatening side effects including Tardive Dyskinesia, a potentially irreversible movement disorder with uncontrollable, jerky movements of the face or body.

The FDA reviewer was concerned that side effects like weight gain, sedation and serious movement disorders may be worse or more common when Abilify is combined with antidepressants.

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.

how well the drug works. That information is not available on either the front page (glossy visual page) or on the required second text page called the "brief summary" (Table 1).

Unfortunately, this is the rule rather than the exception; few print DTC advertisements provide data on drug benefit (4, 13). In a content analysis of DTC advertisements in popular magazines, we found that only 13% of advertisements provided any data on drug benefit (13). Instead, advertisements typically asserted drug benefits with vague qualitative statements (e.g., a celebrity saying "It works for me"). This situation may seem surprising given the FDA regulation that states that "all advertisements for any prescription drug shall present a true statement of information in brief summary relating to side effects, contraindications, and effectiveness." Although in ordinary use the word "effectiveness" means how well a drug works, FDA interprets the word to mean indication—what the drug is used for. Under this interpretation, advertisements without benefit data satisfy the regulation as long as they include the drug's indication.

The minority of advertisements that do present data typically use formats that tend to exaggerate the magnitude of the benefit (13). For example, a recent Lipitor advertisement claimed "Lipitor cuts the risk of stroke by nearly half" but never says half of what (the chance of stroke without Lipitor). The "nearly half" statistic (the relative risk reduction) reported in the ad corresponds to a change in the risk of stroke over 4 y from 2.8% with Lipitor to 1.5% without Lipitor—an absolute difference of 1.3 percentage points. Numerous studies have demonstrated that relative risk reductions without the "of what" lead patients and physicians to overestimate a drug's benefit (14–16).

In contrast to how they treat benefits, DTC advertisements always include information about side effects. In fact, side effect information is often overwhelming: some present laundry lists on the front page of the ad (occasionally quantified) and some in tables (often quantified) in the brief summary. In the Abilify "Me and My depression" print ad, the side effects are neither organized into any hierarchy of importance, nor are they quantified. As a result, it is hard for readers to know which side effects matter or how often they occur. For example, a potentially serious side effect called akathisia (a severe inability to keep still) is downplayed by its inclusion in a list that surrounds

Table 1. Prescription drug information for consumers

Statements	Problem
Direct to consumer ad	
Benefit (complete text)	
"After 6 weeks on an antidepressant, I was still struggling with my depression." If you have been on an antidepressant for at least 6 wk and are still struggling with depression, having ABILIFY added to your antidepressant may help with unresolved symptoms in as early as 1–2 wk. ABILIFY is a prescription drug used to treat depression in adults as add-on treatment to an antidepressant when an antidepressant alone is not enough.	Neither the ad nor brief summary provide any data on benefit
Side effects (excerpt)	
Antidepressant symptoms can increase suicidal thoughts and behavior in children, teens, and young adults. ...high fever, rigid muscles, shaking, confusing, sweating or increased heart rate and blood pressure, these may be signs of a rare by potentially fatal condition, called neuroleptic malignant syndrome.	No explicit organization of side effects and no data on frequency due to the drug.
Commons side effects in adults in clinical trials (>10%) include nausea, vomiting, constipation, headache, dizziness, an inner sense of restlessness or need to move (akathisia), anxiety and insomnia).	Akathisia—a severe restlessness that makes it hard to keep still—is downplayed by inclusion in a list with common symptom side effects like headache.
Medication guide	
Benefit (complete text)	
None (other than mention of indication)	No discussion of benefit
Side effects (excerpt)	No explicit organization of side effects and no data on frequency due to the drug.
Common side effects with ABILIFY in adults include:	
nausea	
vomiting	
constipation	
headache	
dizziness	
inner sense of restlessness/need to move (akathisia)	Akathisia is downplayed by inclusion in a list with common symptom side effects like headache.
anxiety	
insomnia	
restlessness	

Quoted text is shown in bold.

it with mild symptom side effects such as headache, dizziness, and nausea.

Medication Guides. Medication guides are informational sheets required for drugs that the FDA deems to have serious side effects (17). The guides are given to patients at the pharmacy when prescriptions are filled in an effort to promote the safe use of drugs. Like all medication guides, the Abilify Guide does not discuss the drug's benefit (18). It only mentions the drug's indication, and like the DTC ad, the medication guide fails to prioritize or quantify side effects.

Problems with Drug Information for Physicians

FDA-Approved Drug Label. The prescription drug label (also known as the package insert) summarizes the safe and effective use of the drug. The primary purpose of the label "is to give healthcare professionals the information they need to prescribe drugs appropriately" (19). Although many doctors and patients assume that the FDA writes drug labels, they are actually written by the pharmaceutical companies who produce the drugs. The FDA's role is reviewing and approving the labels (FDA approval must be obtained before a drug can be marketed). Unfortunately, despite FDA approval, important information about how well drugs work may be missing from the label (20, 21). For example, a 4-mg dose of Zometa (zoledronic acid) was approved for treating hypercalcemia of malignancy. The FDA label warns that the unapproved 8-mg dose causes renal toxicity—but does not mention the doubling of mortality observed with this dose in the phase III trials from 19% to 33% (20). The label for Rozerem (ramelteon), a "sleeping pill" approved to reduce time to fall asleep, fails to acknowledge important uncertainties about the drug's benefit. The FDA review team leader (22) was concerned that

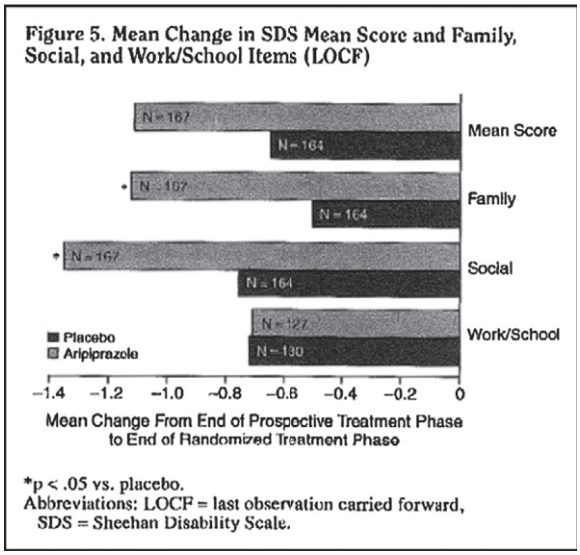
> "The applicant has conducted a significant number of studies in the course of the development of ramelteon.... However, after approximately 3,500 patients being exposed to ramelteon in various studies, the final assessment is that ramelteon has a statistically significant treatment effect that is of marginal clinical significance. . . .. . .patients who are currently being targeted by the proposed indication do not seem to recognize any benefit from treatment with ramelteon."

Nor did the label for the recently approved 23-mg dose of Aricept (donepezil) to treat dementia alert physicians that the FDA's medical and its statistical reviewers recommended against approval because the drug did not meet prespecified criteria defining a clinically meaningful benefit (21).

The Abilify label typifies another problem: it presents no benefit data at all (23). Instead, it merely states that the drug "was superior to placebo in reducing mean MADRS total scores" (Table 2). We documented a similar absence of benefit data in the FDA-approved labels for Lunesta (eszicIopine) and Rozerem (20). This problem is not surprising because the FDA's own Guidance for Industry recommends omitting benefit data from the label under certain circumstances (24). Specifically, the FDA guidance recommends "less detail" when

> "The new drug appears to have effects that are typical of its class"; or when "the magnitude of the effect on clinical endpoints measured in the study is not readily translatable into effects in clinical practice.

Table 2. Prescription drug information for physicians

Statements	Problem
FDA-approved drug label	
Benefit (complete text)	
In the two trials (n = 381 and n = 362), ABILIFY was superior to placebo in reducing mean MADRS total scores. In one study, ABILIFY was also superior to placebo in reducing the mean SDS score.	No data on efficacy
Side effects (excerpt)	
ADVERSE REACTIONS **Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.2):** **Adult patients with schizophrenia: akathisia** **Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision**	While the highlights section (first page of newer labels) includes a summary of serious and symptom side effects, the frequency of individual effects is not provided.
Medical journal article	
Benefit [excerpt (36)]	
	The magnitude of the modest effect of the drug on the primary and FDA-designated key secondary outcome is presented in an exaggerated way: the change scores for both these outcomes are graphed on an extremely truncated scale. For example in one trial, the effect of the drug on the secondary outcome (which measures how much depression impairs patient's lives) was modest (0.5-point improvement over placebo on a 10-point scale), yet the graph axis only goes from 0 to −1.4. This key secondary outcome (SDS score) is not reported in the abstract of either published phase III studies.
Side effects (complete text of abstract conclusion)	
Trial 1: In patients with MDD (major depressive disorder) who showed an incomplete response to ADT (antidepressant therapy), adjunctive aripiprazole was efficacious and well tolerated (36). **Trial 2: Aripiprazole is an effective and safe adjunctive therapy as demonstrated in this short-term study for patients who are nonresponsive to standard ADT (37).**	Conclusion of abstract minimizes the substantial side effects of these drugs in 6-wk trials.

Quoted text is shown in bold.

> For example, exercise testing in a study of heart failure can demonstrate effectiveness, but does not translate into a quantifiable clinical outcome. Similarly, changes in HAM-D [Hamilton depression rating scale] scores can be used to demonstrate effectiveness of an antidepressant, but the results for a given study are population- and probably site-specific, and thus, do not necessarily translate to a numerically similar outcome in clinical practice. In these cases, it could be useful to describe the study in general terms (e.g. population, duration, endpoints measured and qualitative outcome) without providing detailed results."

Without benefit data, doctors cannot possibly judge how well a drug works. Not reporting benefit data for new drugs in an established class or drugs approved based on outcomes with uncertain clinical meaning or using unfamiliar scales does not solve the problem but makes it worse. Instead, the FDA should be clear about the magnitude (and meaning) of the effect that merited approval, to whom it applies, and translate the benefit into clinically meaningful terms or explicitly acknowledge that the drug may not have a clinically important effect.

Medical Journal Article. Published reports of clinical trials in medical journals are another important source of drug information for physicians. Unfortunately, a growing body of literature has documented disturbing problems with the quality of published research reports, particularly when they are industry sponsored, including selective publication of trials with favorable results (25–29),

selective reporting of favorable outcomes (26, 30, 31), and "spinning" results and conclusions to overstate the benefit of an intervention (32–34) or to minimize the side effects (35).

There is evidence of "spin" in the journal articles (Table 2) reporting on the two Abilify studies that were the basis of its approval by the FDA for depression that persists despite an antidepressant (36, 37). In both articles (36, 37), the benefit of the drug was magnified visually by presenting graphs with extremely truncated axes (e.g., only 10 points of a 60-point scale, only 1.4 points of a 10-point scale). Side effects were also downplayed in both articles: the conclusions of each abstract referred to the drug as being "well tolerated," despite a sixfold increase in akathisia among patients randomized to the drug compared with placebo: 25% vs. 4%.

Medical journals have a responsibility to avoid publishing biased trials or allowing misleading reports of trial results. Ongoing efforts initiated by medical journal editors are mitigating these problems to some extent. For example, clinical trial registration in a public registry (such as clinicaltrials.gov) before patient enrollment is now a condition for publication (38); journals are encouraged to review the trial protocol along with the manuscript (39), and journals are trying to implement reporting guidelines such as CONSORT (Consolidated Standards of Reporting Trials) (40). Unfortunately, even these efforts may not be sufficient to control spin, which will require substantial ongoing editorial attention.

How to Do Better

To make informed decisions, doctors and consumers need to weigh drug benefits and side effects. Unfortunately, consumers and even physicians may have difficulty finding the relevant information. In contrast to DTC advertisements, medical guides, FDA labels, and medical journal articles, benefit and side effect data are always available in FDA review documents. FDA reviewers with clinical, statistical, chemical, pharmacologic, and epidemiologic expertise write these documents after spending up to 1 y reviewing the evidence submitted in the pharmaceutical company's drug approval application. Usually this evidence consists of at least two phase 3 randomized clinical trials in patients with a specific condition (the indication sought for approval). The FDA review documents (publicly available at www.accessdata.fda.gov/scripts/cder/drugsatfda/) provide a detailed description of all of the phase 3 clinical trial data considered. They also provide important insight into how reviewers decided whether the drug offered a meaningful benefit and whether the benefit exceeded harms. Unfortunately, the review documents are practically inaccessible: they are lengthy (typically hundreds of pages long), poorly organized, and weakly summarized.

To make such information accessible, we developed the Drug Facts Box: a simple one-page summary of drug benefit and side effect data for a given indication of a drug. The central feature of the box is a data table with the absolute risks of various outcomes with and without the drug. The data are from the FDA review documents, supplemented by high quality systematic reviews.

Creating boxes requires many decisions, including which data to present (which trials, which outcomes) and how to present it (means or percentages, how to communicate statistical significance, etc.). To make these decisions transparent and reproducible, we developed a handbook with both general principles and specific guidance on drafting boxes. We pilot tested the handbook in October 2007 with seven FDA medical reviewers who drafted boxes (in the hope that, in the future, FDA reviewers would routinely write boxes for all newly approved drugs). We revised the handbook based on feedback from the FDA reviewers and from independent drug experts outside the FDA.

A Drug Facts Box for Abilify for major depression that persists on antidepressants (Fig. 1) summarizes the combined data from the two identical 6-wk randomized trials that were the basis for FDA drug approval for this indication (41). The box shows that Abilify has only a modest benefit: on average, patients on Abilify improved by 3 points more (on a scale of 60) than patients on placebo, and only an additional 11% of patients had a clinically important response as defined in the trial: a 50% or greater reduction in their depression score and no longer meeting the criterion for major depression [i.e., a 6-wk follow-up depression score less than 10 on the Montgomery–Åsberg depression rating scale (MADRS)]. The box also highlights Abilify's most important side effects: an additional 21% of patients experienced akathisia (severe restlessness), and an additional 4% gained a substantial amount of weight. The box alerts readers to the fact that Abilify—like all antidepressants—can cause a small increase in suicidal thoughts and behavior among young adults, and that Abilify, like all antipsychotics, can also cause a variety of uncommon but life-threatening side effects.

We envision two versions of boxes: one for consumers and another for physicians. The consumer version (such as the Abilify Box; Fig. 1) would be based on the longest, largest phase 3 trial measuring patient as opposed to surrogate outcomes (data from identical replication trials would be combined if the results were similar). The physician version would present more details, for example, specific outcome scales used (e.g., "depression score was measured with MADRS") and the cutoffs selected for diagnostic thresholds. The physician version would also include data tables for all phase 3 trials submitted to the FDA.

The Drug Facts Box can improve prescription drug communication in multiple ways. It can educate physicians and provide them with an unbiased summary of drug benefit and side effects using the same data the FDA used in the drug approval process. It can educate consumers by filling in important gaps that exist in current informational sources such as drug advertisements and medication guides. Also, it can foster better physician–patient communication by facilitating evidence-based discussions about drugs.

When we first proposed the Drug Facts Box, the FDA expressed concern about whether consumers could understand the data. Based on a series of studies, we are confident that most can (42–46). The first study ($n = 203$) tested consumer comprehension of the benefit portion of the box: for example, 97% were able to correctly read percentages from the data table (45). The second study ($n = 274$) tested a full box for the drug Tamoxifen for preventing first breast cancers (42). This more complex table included nine rows and two columns of data. On average, participants correctly answered four out of five data comprehension questions. In a nationally representative randomized trial ($n = 231$), 68% of people randomized to see DTC advertisements with drug boxes chose the objectively better of two heartburn drugs compared with 31% of people seeing standard advertisements (44).

Most recently, we conducted two national randomized trials (both $n = 2,944$) to test features of the box. One trial tested simplified numeric formats: percentages alone were as good and sometimes better than the original combination format of percentages plus frequencies (46). Based on this finding, we now use percentages alone. The other trial found that brief explanations about surrogate outcomes and the safety of new prescription drugs improved drug choices: 71% (explanation group) vs. 59% (control) chose the cholesterol drug that reduced heart attacks over the one that only reduced cholesterol levels; 53% (explanation group) vs. 34% (control) chose the equally effective older drug over a newly approved drug (43).

Based in part on the foregoing studies, the FDA's Risk Communication Advisory Committee (47) and Congress (48) called on the FDA to consider implementing Drug Facts Boxes. Unfortunately, the FDA has said it needs an additional 3–5 y to study the evidence. Given its potential public health impact, physicians and the public should not have to wait that long for better drug information. They should have access now. In fact, the FDA's own evidence-based user's communication guide says, "It is imperative to provide patients with numerical estimates of the risks and benefits associated with treatment options." (49) If

the FDA is unable to clearly and succinctly communicate what it knows—and does not know—about the drugs it approves, then it is time for another independent entity to do it for them.

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