Letters

RESEARCH LETTER

Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation

Before US patients can use new prescription drugs, the US Food and Drug Administration (FDA) reviews the clinical trial results to confirm that benefits outweigh harms for the indication. Approval may involve superiority to placebo, not to an active comparator or standard of care (although approval can be based on uncontrolled or historically controlled studies). Numerous pathways expedite drug development and approval for serious or life-threatening conditions. For example, since 2012, the FDA can designate a drug as a "breakthrough therapy" if preliminary clinical evidence—such as an improvement in a pharmacodynamic biomarker—suggests an advantage over existing options.[1] Through April 2015, the FDA designated 76 "breakthrough" drugs,[2] and the term is routinely used in press releases[3] and prescribing resources.[4]

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Although the term *breakthrough* leads consumers to overly optimistic beliefs about drug effectiveness,[5] it is not known how physicians understand this term—or more generally, what FDA approval means.

Methods | We selected a random sample of 300 clinically active internists and 900 specialists (endocrinology, hematology, and infectious diseases) from the American Board of Internal Medicine's diplomate list; 52 lacked updated contact information. Our questions (eAppendix in the Supplement) were part of a larger survey, which was approved by the Brigham and Women's Hospital's institutional review board, about prescription drugs. Consent was implied by participation after reading a description of survey goals. The sample was contacted via email, with nonresponders receiving 2 reminders, then a mailed version, and a final email reminder.

We asked 3 questions about FDA approval and 5 about breakthrough therapies (**Table 1**). Respondents included those who answered at least 1 question.

Physicians then chose between prescribing 2 new, identical hypothetical drugs: both met the statutory definition of breakthrough therapy, but only 1 was named a "breakthrough" drug. Finally, physicians were randomized by computer to read 1 of 4 versions of a mock FDA press release about a hypothetical new drug (Procampa) for lung cancer, approved based on tumor shrinkage: (1) the "facts alone" version described FDA approval data, (2) the "breakthrough" version stated that the FDA "designated it as a breakthrough drug," (3) the "breakthrough/expedited" version added the

Table 1. Physicians' Perceptions of US Food and Drug Administration (FDA) Approval and Breakthrough Therapy Designations

	No. of Responses/ Total Respondents[a]	% (95% CI)[b]
3 Questions on the FDA Approval Process		
1. FDA approval typically means that a drug is as effective as other drugs approved to treat the same condition.		
True	495/682	73 (69-76)
False[c]	187/682	27 (24-31)
2. FDA approval typically means that a drug has benefits that outweigh its harms.		
True[c]	585/686	85 (82-88)
False	101/686	15 (12-18)
3. In order for a drug to get FDA approval, it has to have…		
A statistically significant result	90/687	13 (11-16)
A clinically important result	76/687	11 (9-14)
Both results	480/687	70 (66-73)
Neither of the results[c]	41/687	6 (4-8)
Physicians with number of correct answers		
0	67/675	10 (8-12)
1	423/675	63 (59-66)
2	176/675	26 (23-30)
3	9/675	1 (1-3)
5 Questions About Breakthrough Therapies		
1. The FDA has recently started designating some new prescription drugs it reviews and approves as breakthrough drugs. Before taking this survey, how familiar were you with the "breakthrough" designation?		
Very familiar	24/689	3 (2-5)
Familiar	118/689	17 (14-20)
A little familiar	255/689	37 (33-41)
Not familiar at all	292/689	42 (39-46)
2. In general, I am certain that an FDA-approved breakthrough drug represents a major advance over currently approved treatments for its indication.		
Very certain	39/686	6 (4-8)
Fairly certain	399/686	58 (54-62)
Fairly uncertain	213/686	31 (28-35)
Very uncertain	35/686	5 (4-7)
3. What is the minimum level of evidence that the FDA requires manufacturers to gather for the FDA to label a drug as a breakthrough?		
Strong evidence (eg, randomized trials evaluating clinical outcomes)	352/683	52 (48-55)
Preliminary evidence (eg, uncontrolled studies or studies testing surrogate outcomes)[c]	307/683	45 (41-49)
Very preliminary evidence (eg, in vitro laboratory or animal studies)	24/683	4 (2-5)
4. When the FDA calls a drug a breakthrough, does that mean that there is high-quality evidence that the drug is more effective than currently approved treatments?		
Yes	523/683	77 (73-80)
No[c]	160/683	23 (20-27)

(continued)

drug's review speed, and (4) the "breakthrough/warning" version also warned that the drug's effect on survival was unknown (**Table 2**).

We calculated confidence intervals using the Wilson method (proportions) and the Wald method (differences in proportions), and tested associations using the Pearson χ^2 test (nominal variables) and the Cochran-Mantel-Haenszel row mean scores statistic (ordinal variables). All analyses were done in Stata (StataCorp), version 13.1. A 2-tailed *P* value less than .05 was considered significant.

Table 1. Physicians' Perceptions of US Food and Drug Administration (FDA) Approval and Breakthrough Therapy Designations (continued)

	No. of Responses/ Total Respondents[a]	% (95% CI)[b]
5. When the FDA calls a drug a breakthrough, does that mean that there is high-quality evidence that the drug is safer than currently approved treatments?		
Yes	177/675	26 (23-30)
No[c]	498/675	74 (70-77)
Physicians with number of correct answers out of 3, %		
0	142/670	21 (18-24)
1	215/670	32 (29-36)
2	196/670	29 (26-33)
3	117/670	17 (15-21)
Hypothetical Scenario		
Imagine your patient has a serious medical condition for which there has been no effective treatment. The FDA recently approved 2 new drugs to treat this condition. Both drugs are oral tablets to be taken once a day, have similar adverse effect profiles, and are equally covered by the patient's insurance. Which would you choose first?		
Axabex, an FDA-designated breakthrough drug	640/684	94 (91-95)
Zykanta, a drug with early promising study results but has not been shown to improve survival or disease-related symptoms	44/684	6 (5-9)

[a] Respondents who omitted a particular question (range, 1%-2%) were not counted as incorrect.

[b] Confidence intervals were calculated using the Wilson method.

[c] Correct answer.

Results | Of 1148 physicians contacted, 692 physicians (60%) responded: mean age, 46 years (SD, 10); women, 45%; specialists, 79%. Nonrespondents were similar: mean age, 49 years; women, 43%, and specialists, 80%. Respondents showed limited knowledge of FDA approval: 73% (95% CI, 69%-76%) incorrectly believed FDA approval meant comparable effectiveness to other approved drugs; 70% (95% CI, 66%-73%) incorrectly believed approval required both a statistically significant and clinically important effect. Specialists averaged slightly more correct answers than internists (1.2 vs 1.1, *P* = .02). Among the 3 breakthrough knowledge questions, 52% incorrectly believed that strong evidence (randomized trials) is needed to earn the breakthrough designation. Specialists averaged more correct answers than internists (1.5 vs 1.2, *P* = .01) (Table 1).

In the hypothetical scenario shown in Table 1, physicians preferred the breakthrough drug Axabex (94% [95% CI, 91%-95%]) over the drug Zykanta, which had no breakthrough designation (6% [95% CI, 5%-9%]). In the trial of the mock press release formats, compared with the facts alone version of the press release, the breakthrough/warning version decreased the percentage of physicians agreeing there was strong evidence of benefit (61% vs 48%, *P* = .01; between-group difference, 13% [95% CI, 3%-24%]) or that the hypothetical drug improved survival (64% vs 50%, *P* = .01; between-group difference, 14% [95% CI, 4%-24%]) (Table 2).

Discussion | A national survey of board-certified internists and specialists revealed substantial deficits in knowledge of the

Table 2. Effect of the Different Versions of the Mock US Food and Drug Administration (FDA) Press Release for the Hypothetical Drug Procampa on Physicians' Perceptions

	Mock FDA Press Release Version			
	Facts Alone (n = 180)	Breakthrough (n = 147)	Breakthrough/ Expedited (n = 179)	Breakthrough/ Warning (n = 181)
I Believe Procampa Improves Survival of Patients, No. of Respondents (%)[a]				
Strongly agree	24 (13)	15 (10)	27 (15)	10 (6)[b]
Somewhat agree	92 (51)	78 (53)	81 (45)	80 (45)
Somewhat disagree	52 (29)	45 (31)	53 (30)	62 (35)
Strongly disagree	12 (7)	9 (6)	18 (10)	27 (15)
I Believe That There Is Strong Evidence of Procampa's Benefit to Patients, No. of Respondents (%)[a]				
Strongly agree	22 (12)	20 (14)	26 (15)	13 (7)[c]
Somewhat agree	88 (49)	66 (45)	72 (40)	73 (41)
Somewhat disagree	56 (31)	48 (33)	68 (38)	72 (40)
Strongly disagree	14 (8)	13 (9)	13 (7)	22 (12)
If I Had Patients With Late-Stage Lung Cancer, I Would Suggest They Try Procampa, No. of Respondents (%)[a]				
Strongly agree	65 (36)	58 (39)	69 (39)	57 (31)
Somewhat agree	102 (57)	78 (53)	90 (50)	104 (57)
Somewhat disagree	11 (6)	7 (5)	17 (10)	18 (10)
Strongly disagree	2 (1)	4 (3)	3 (2)	2 (1)

[a] The full version of each mock FDA press release is in the Supplement.

[b] Two additional respondents did not answer this question.

[c] One additional respondent did not answer this question.

meaning of FDA approval. Physicians tended to overestimate the minimum evidence of efficacy required of new drugs. Similarly, many misinterpreted the term *breakthrough*—believing these drugs were supported by stronger evidence than required by the statute.

Our results are limited by social desirability and other inherent survey response biases and may not be generalizable beyond internists and medical specialists. The misconceptions identified may lead physicians to overprescribe newly approved drugs—particularly breakthrough therapies—and inadequately communicate how well these drugs work to the patients who will use them.

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1. Pub L. No. 112-144, § 902, 126 Stat 993 (2012).

2. US Food and Drug Administration. Breakthrough therapy approvals. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373418.htm. Accessed December 3, 2015.

3. Pfizer. TRUMENBA (Meningococcal Group B Vaccine) is now available. http://www.pfizer.com/news/press-release/press-release-detail/trumenba_meningococcal_group_b_vaccine_is_now_available. Accessed December 3, 2015.

4. Medscape. Idelalisib (Zydelig) approved for CLL and lymphoma. http://www.medscape.com/viewarticle/828751. Accessed December 3, 2015.

5. Krishnamurti T, Woloshin S, Schwartz LM, Fischhoff B. A randomized trial testing US Food and Drug Administration "breakthrough" language. *JAMA Intern Med*. 2015;175(11):1856-1858.

COMMENT & RESPONSE

Acute Kidney Injury With Buffered Crystalloids vs Saline Among ICU Patients

To the Editor In the study by Dr Young and colleagues[1] comparing kidney toxicity of a buffered crystalloid solution vs saline in patients admitted to the intensive care unit (ICU), acute kidney injury (AKI) was defined based solely on the serum creatinine criteria of the risk, injury, failure, loss, and end-stage renal failure (RIFLE) classification. The mean volumes of intravenous study and nonstudy fluids administered in 24 hours prior to enrollment and during the observation period were not significantly different between groups, but the ranges were variable. We would like to know whether the serum creatinine levels used for diagnosis of AKI in this study were adjusted for the fluid balance of patients. It has been shown that not adjusting serum creatinine levels for fluid balance in patients who are critically ill may underestimate the severity of AKI, whereas adjusting serum creatinine levels for fluid balance can improve recognition and staging of AKI.[2,3]

Furthermore, the RIFLE classification includes urine output criteria, and use of serum creatinine alone has been shown to underestimate the incidence and grade of AKI and delay the diagnosis in adult patients who are critically ill admitted to the ICU.[4]

In addition, most of the included patients underwent cardiothoracic and vascular surgeries, and a long, 90-day observation period after ICU admission was used. However, adverse events and postoperative complications that occurred during the observation period were not provided. In patients who are critically ill and admitted to the ICU, anemia, hypotension, use of vasopressors or nephrotoxic drugs, hypoalbuminemia, pulmonary complications, sepsis/systemic inflammatory response syndrome, and severe surgical complications have been associated with an increased risk of AKI.[5] Thus, the possibility that intergroup imbalances in these factors would have contributed to their results cannot be excluded.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. *JAMA*. 2015;314(16):1701-1710.

2. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39(12):2665-2671.

3. Macedo E, Bouchard J, Soroko SH, et al. Fluid accumulation, recognition, and staging of acute kidney injury in critically-ill patients. *Crit Care*. 2010;14(3):R82.