for lung cancer screening should be reexamined and efforts should be refocused on smoking cessation and smoking prevention to prevent lung cancer and improve health.

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Disclaimer: Dr Redberg was Chairperson of the MEDCAC for the meeting on lung cancer screening on April 30, 2014, but as Chairperson, she did not vote.


Editor's Note page 721

Communication of Nonefficacy Benefits of New Drugs Approved on the Basis of Noninferiority Trials Alone: Cohort Study of FDA and Sponsor Communication, 2011-2017

About one-third of new therapeutics are tested in head-to-head, active-controlled trials prior to licensure.1 Some of these trials test noninferiority hypotheses, which by design allow for some potential loss of efficacy in exchange for potential nonefficacy benefits.

The literature specifies several hypothetical nonefficacy benefits that new interventions approved based on noninferiority trials may offer, including decreased adverse events, less invasiveness, more convenient formulation, and reduced cost.2-5 However, empirical evidence of actual benefits is lacking. We sought to characterize the nonefficacy benefits of new molecular entities (NMEs) approved based on noninferiority trials.

Methods | We identified NMEs approved by the US Food and Drug Administration (FDA) between January 2011 and September 2017 using the FDA’s yearly Novel Drug Approvals website (Novel Drug Approvals, 2017). We identified all indications approved based solely on noninferiority pivotal trials (ie, trials that included active control groups with stated noninferiority margins or stated objectives evaluating noninferiority hypotheses) using FDA and sponsor communications (press releases at market entry and FDA Drug Trials Snapshots), and statistical and medical officer reports. New indications for previously approved NMEs were excluded.

For each indication, FDA and sponsor communications were read by 2 investigators. All statements that expressed a nonefficacy benefit were extracted. Extracted statements were classified into categories (I) derived from the literature2-5 regarding the nonefficacy purposes of noninferiority trials and (2) categories we developed through inductive reasoning. Categorizations were independently reviewed; disagreements were resolved through consensus.

Direct drug cost comparisons were made using average unit prices obtained from IBM Micromedex Red Book.

Results | Between January 2011 and September 2017, the FDA approved 262 indications for 238 NMEs. We excluded 242 indications (220 NMEs) not approved exclusively on noninferiority pivotal trials, leaving 20 indications (18 NMEs) for analysis.

Overall, 15 (75%) of FDA or sponsor communications mentioned a nonefficacy benefit. Sponsors mentioned nonefficacy benefits more often (n = 15; 75%) than the FDA (n = 6; 30%). The most common nonefficacy benefit mentioned by FDA were decreased adverse events (n = 3; 15%) and simpler dosing/administration (n = 3; 15%). Sponsors most often mentioned simpler dosing/administration (n = 10; 50%), reduced non-drug health care cost (n = 6; 30%), and decreased adverse events (n = 6; 30%). Noncomparative benefits were reported for all NMEs by sponsors or the FDA with “new treatment option” being the most common expression, appearing in 19 (95%) sponsor and 14 (70%) FDA communications (Table 1).

A treatment course with the NME was less expensive in 8 (35%) and more expensive than the active control in 13 (57%) comparisons (Table 2).

Table 1. Sponsor and FDA Statements Regarding Nonefficacy Benefits of 20 NME Indications Approved Exclusively on the Basis of Noninferiority Trials

<table>
<thead>
<tr>
<th>Statement</th>
<th>FDA (n = 20)</th>
<th>Sponsor (n = 20)</th>
<th>FDA or Sponsor (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonefficacy benefits over already approved treatments</td>
<td>6 (30)</td>
<td>15 (75)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Formulation benefit*</td>
<td>0</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Simpler dosing/ administration benefitb</td>
<td>3 (15)</td>
<td>10 (50)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Lower direct drug cost</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased nondrug health care costs</td>
<td>0</td>
<td>6 (30)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Decreased need for hospitalization</td>
<td>0</td>
<td>3 (15)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Improved efficacy on nonprimary end point</td>
<td>1 (5)</td>
<td>3 (15)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Decreased adverse events</td>
<td>3 (15)</td>
<td>6 (30)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Explicit statement</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Implicit statement</td>
<td>1 (5)</td>
<td>4 (20)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Noncomparative benefits</td>
<td>17 (85)</td>
<td>19 (95)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Safe</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Effective</td>
<td>11 (55)</td>
<td>8 (40)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>“New treatment option*</td>
<td>14 (70)</td>
<td>19 (95)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Fills unmet medical need</td>
<td>1 (5)</td>
<td>6 (30)</td>
<td>7 (35)</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; NME, new molecular entity.

* Formulation benefit refers to change in the chemical composition of what is administered to patients that may result in nonefficacy benefit (eg, removal of preservatives).

b Simpler dosing/administration benefit refers to change in the way the intervention is administered to patients (eg, less frequently, fewer pills, or lower volume of administration).
Discussion | Our analysis of NMEs approved on the basis of non-inferiority trials found that sponsors generally named nonefficacy benefits (n = 15; 75%), while the FDA did so in a minority of cases (n = 6; 30%). This is concerning because potential nonefficacy benefits form the ethical and scientific justification for choosing noninferiority hypotheses, which allow potential loss of efficacy relative to older effective, often less expensive therapies.

The FDA’s most frequently cited benefit was “new treatment option.” However, all NMEs are by definition new treatment options. Novelty alone carries no intrinsic therapeutic value, is known before initiation of studies, and neither explains added benefits for patients of new interventions nor justifies harms to participants enrolled in trials. We found that some nonefficacy benefits were based on assumptions not evaluated in trials themselves (eg, reduced nondrug costs).

The study had several limitations. The FDA Snapshots, which always include a section on drug benefits, existed for only 7 of 20 indications. Also, we did not evaluate whether named nonefficacy benefits were worth the trade-off for potential reduced efficacy, which requires evaluating the efficacy results.

Future noninferiority trials should present potential nonefficacy benefits in protocols and consent forms.6 Potential nonefficacy benefits that can be formally studied, such as decreased adverse effects, should be required by regulators to be evaluated in trials and clearly communicated in study results.

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Communicating, and Justifying, Nonefficacy Benefits for New Drugs Approved on the Basis of Noninferiority Trials

Noninferiority clinical trials are designed to determine whether an intervention is not "unacceptably worse” than a comparator by more than a prespecified difference, known as the noninferiority margin. The US Food and Drug Administration (FDA) has established guidance for industry to clarify when a superiority study design does not need to be used to establish new drug effectiveness, usually because it would not be ethical to use a placebo or "no-treatment" control. Other justifications for noninferiority-designed trials include testing interventions with more favorable safety profiles or more convenient dosing, less patient burden, reduced cost, or other benefits for which patients and clinicians might accept diminished effectiveness as a trade-off.

In this issue of JAMA Internal Medicine, Doshi and colleagues bring attention to the FDA's approval of new drugs on the basis of noninferiority-designed trials, which occurred among nearly 10% of approvals since 2011. The authors examined how these nonefficacy benefits were communicated at the time of first approval through product sponsors (ie, pharmaceutical companies) and the FDA's press releases and through the FDA's Drug Trials Snapshots. Examining these communications for 18 new drugs approved for 20 distinct indications, they found that sponsors communicated nonefficacy benefits for 75% of approvals, while the FDA did so only for 30%, with the most common nonefficacy benefits being simpler dosing or administration, reduced nondrug health care costs, and decreased adverse events.

The FDA's lower rate of communicating nonefficacy benefits than sponsors is not surprising because the evidence underlying these benefits may not be conclusively demonstrated, such as for safety, or may be considered promotional, such as for associated health care costs. The study did not address whether prespecified noninferiority margins and their justifications were adequately communicated. This is important because null results from noninferiority designed trials are often incorrectly interpreted as demonstrating equivalence in effectiveness between 2 therapies, when in fact the new therapy may be worse than the prespecified noninferiority margin. Nevertheless, these findings highlight the importance of improving communication of nonefficacy benefits to the public and being clear when new drug approvals are based on noninferiority-designed trials, ensuring that trade-offs made in exchange for diminished effectiveness are clear and justified.

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Frequency of Sale and Reasons for Purchase of Over-the-Counter Insulin in the United States

Insulin, such as insulin isophane suspension and 70% human isophane suspension/30% human insulin injection, is available over the counter in 49 US states and the District of Columbia. Over-the-counter insulin is banned in Indiana.\(^3\) Reports suggest that some patients with diabetes who are uninsured or underinsured purchase Walmart-brand ReliOn (Novo Nordisk) insulin over the counter because it is considerably less expensive ($24.88 per 10-mL vial) than the Novolin (Novo Nordisk) and Humulin (Lilly) insulins sold over the counter at other pharmacies ($152-$163 per 10-mL vial).\(^1\) Information, however, is lacking to support these reports, and Walmart does not make public its sales data.\(^1\) We sought to obtain such information.

**Methods** | In 2018, we conducted a national telephone-based survey of Walmart and chain pharmacies in the 49 states where over-the-counter insulin is sold. In each state, we surveyed 6 Walmart pharmacies (1 in each geographic quadrant of each state and 2 in a central location) and the closest chain pharmacy (CVS, Walgreens, Rite Aid), identified using Google Maps. One of the authors (K.B.) administered a 5-item questionnaire with questions about the frequency of over-the-counter insulin sales and the perceived reasons why patients purchased insulin over the counter. We categorized frequency of sales as daily, weekly, monthly, a few times a year, and never. We asked pharmacies that reported daily over-the-counter insulin sales to estimate the number of vials sold per day. Survey responses were collected in REDCap. Stata software (version 14, StataCorp) was used to generate descriptive and bivariate statistics. The Christiana Care Health System institutional review board approved the study, and participant written informed consent was not required.

**Results** | Of the 582 pharmacies that were contacted, 561 (96.4%) completed the questionnaire; all 49 states were represented. Among the respondents, 557 (99.3%) self-identified as pharmacists or pharmacy technicians and 4 (0.7%) identified as pharmacy managers or interns. When participants were asked whether the pharmacy sold insulin over the counter/without a prescription, 500 (89.1%) responded “yes” (284 of 292 Walmart pharmacies and 216 of 269 other chain pharmacies).

Among the 284 Walmart pharmacies with over-the-counter sales of insulin, 247 (87.0%) respondents stated that they sold it daily, 31 (10.9%) sold it weekly, 3 (1.1%) sold it monthly, and 3 (1.1%) sold it a few times a year (Figure). Among the other chain pharmacies, 0 sold over-the-counter insulin daily, 3 (1.4%) sold it weekly, 19 (8.8%) sold it monthly, 100 (46.3%) sold it a few times a year, and 94 (34.5%) never sold it ($P < .001$ for the overall comparison of Walmart and chain pharmacies). When participants were asked whether they were aware of patients who purchased insulin over the counter because they could not afford the copay for their prescription insulin, 223 (54.9%) of the respondents answered yes; 199 (70.1%) positive responses were from Walmart pharmacies and 24 (19.7%) were from chain pharmacies ($P < .001$).

Walmart pharmacies reported selling a median of 4 vials of insulin over the counter daily (mean, 6 vials; range, 1-50 vials). Based on a total of 4700 Walmart pharmacies in the United States (Walmart spokesperson; written communication; October 25, 2018) and median daily sales of 4 vials, an estimated 18 800 vials of insulin may be sold over the counter daily.

**Discussion** | Our national survey provides information about the sale and reasons for purchase of over-the-counter insulin. Although our data represent perceptions of pharmacy employees rather than actual sales data, they support an estimate of daily sales of more than 18 000 vials of over-the-counter insulin at Walmart pharmacies. Our finding that over-the-counter insulin is sold more commonly at Walmart than at other chain pharmacies likely reflects the fact that the Walmart brand is considerably less expensive than other brands of insulin sold at chain pharmacies.\(^1\)\(^3\) Inability to afford copays for prescription insulin was noted as a common reason for purchase, particularly at Walmart pharmacies. Further studies should explore clinical and safety outcomes related to the use of over-the-counter insulin.

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**Author Contributions:** Dr Goldstein and Ms Bland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goldstein, Hicks. Acquisition, analysis, or interpretation of data: Goldstein, Patel, Bland.