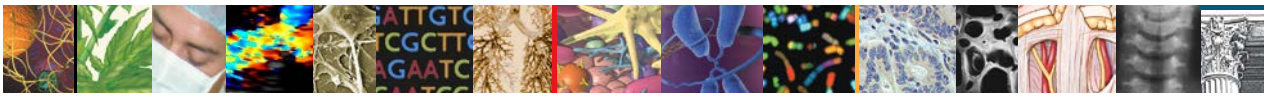

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Perspective

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FDA Approval of Bedaquiline — The Benefit–Risk Balance for Drug-Resistant Tuberculosis

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Bedaquiline was approved by the Food and Drug Administration (FDA) at the end of 2012 for the treatment of adults with multidrug-resistant pulmonary tuberculosis for whom an effective treatment regimen is not otherwise available.[1] One complexity facing the FDA in reviewing the bedaquiline marketing application was that in one of the phase 2 studies, there were more deaths among patients who had bedaquiline added to a background antimycobacterial drug regimen than among those who had placebo added to the same regimen, despite relatively clear evidence of bedaquiline's efficacy in clearing *Mycobacterium tuberculosis* from sputum. Given this imbalance in mortality, the approval of bedaquiline has appeared paradoxical to some.[2] But marketing applications that are reviewed by the FDA often rely on complex risk–benefit evaluations. (The 120-week final results of the aforementioned phase 2 study are reported by Diacon et al. in this issue of the *Journal* [pages 723–732]; the marketing application, however, contained only efficacy data that were available at week 72.)

According to the World Health Organization (WHO), the global burden of tuberculosis remains enormous, with an estimated 8.6 million new cases in 2012.[3] Without effective treatment, tuberculosis is associated with substantial morbidity and mortality. Among sputum-smear–positive cases of pulmonary tuberculosis in HIV-negative patients, the estimated 10-year case fatality rate is 70%.[4] The 27 countries with a high burden of multidrug-resistant pulmonary tuberculosis have been reporting increasing numbers of such cases to the WHO; the estimated incidence reached nearly 450,000 worldwide in 2012.[3]

Bedaquiline is an antimycobacterial drug that operates by a new mechanism of action: it inhibits mycobacterial ATP synthetase and depletes cellular energy stores. Since its mechanism differs from those of other available antimycobacterial drugs, it has the capacity to retain activity against some *M. tuberculosis* isolates that are resistant to other drugs and hence may provide an important treatment option for patients with multidrug-resistant pulmonary tuberculosis when an effective multidrug treatment regimen cannot otherwise be constructed. Bedaquiline was approved under the FDA's accelerated-approval regulations, which allow for the approval of drugs for serious or life-threatening conditions that provide

meaningful therapeutic benefit over existing therapies. Accelerated approval can be based on surrogate markers that are reasonably likely to predict clinical benefit (e.g., conversion of sputum culture from positive to negative).

In the two-stage phase 2 trial that provided evidence of bedaquiline's safety and efficacy, the investigators enrolled patients with positive sputum smears and sensitivity to at least three of the five classes of drugs used in the background antimycobacterial drug regimen for multidrug-resistant pulmonary tuberculosis. Because of that sensitivity, an active regimen could be constructed using currently available drugs for the patients in the trial. The preferred background regimen was generally kanamycin, ofloxacin, ethambutol, pyrazinamide, and cycloserine or terizidone (with criteria allowing for substitutions).[5] In the first stage, 47 patients were randomly assigned, in double-blind fashion, to receive 8 weeks of placebo or bedaquiline in addition to the background antimycobacterial drug regimen. At completion of the 8-week trial period, the rate of sputum-culture conversion among bedaquiline-treated patients (48%) was markedly higher than that among patients who received placebo (9%).

In the second stage, patients were randomly assigned, also in double-blind fashion, to receive placebo or bedaquiline for 24 weeks, both in combination with their background antimycobacterial drug regimen, for a total of approximately 18 to 24 months. There were 79 patients in the bedaquiline group and 81 in the placebo group. In the second stage, the median time to sputum-culture conversion was significantly shorter in the bedaquiline group than in the placebo group (83 days vs. 125 days; $P<0.001$). These two trials thus demonstrated bedaquiline's effectiveness on the basis of sputum-culture conversion.

In an open-label, single-group trial involving 233 patients, some of whom had pulmonary tuberculosis that had proved resistant to multiple antimycobacterial drugs as well as to isoniazid and rifampin, the median time to sputum-culture conversion was 57 days, a time frame generally consistent with that found by Diacon et al. in stage 2 of their study.

In the study by Diacon et al., more patients in the bedaquiline group than in the placebo group died: whereas 2 deaths were reported among the 81 patients in the placebo group, 10 deaths occurred among the 79 bedaquiline-treated patients. One of the deaths in the bedaquiline group was due to a motor vehicle accident that occurred at 130 weeks of follow-up, and this patient was not included in further analyses. In the FDA assessment, both deaths in the placebo group appeared to be related to progression of disease, as did 5 of the 9 deaths in the bedaquiline group. Among the 4 other patients in the bedaquiline group who died, there was no apparent common cause of death. One of the deaths among bedaquiline-treated patients occurred during the 24-week trial period; the median time to death in the remaining 8 patients in the bedaquiline group was 329 days after the patient last received bedaquiline. The unexpected finding of a mortality imbalance is an important concern; however, the length of time between the last receipt of bedaquiline and death makes it difficult to discern a mechanism by which bedaquiline could be directly related to the deaths, even if we take bedaquiline's long half-life into consideration.

Nonetheless, the product label prominently conveys the seriousness of the mortality finding. The mortality data appear in the product label in multiple locations, including a boxed warning, the "Warnings and Precautions" section, and the "Adverse Reactions" section. In addition, the indication for bedaquiline's use is limited to patients with multidrug-resistant pulmonary tuberculosis for whom an effective treatment regimen cannot be constructed without including bedaquiline (e.g., because of resistance to other drugs). For this population, the FDA assessment is that the benefits of bedaquiline outweigh the risks. The previously cited historical data show that outcomes are very poor in patients who do not receive adequate treatment.[4]

The confirmatory trial that is required as part of the accelerated approval of bedaquiline should bring further clarity to the observed mortality finding for bedaquiline. Nonsurrogate end points such as patient survival, clinical resolution of tuberculosis, and rate of relapse will be included in the confirmatory trial. Although these clinical end points may be regarded as more rigorous and "traditional" than a microbiologic end point of sputum-culture conversion, their use will prolong the study, since they will be assessed 12 to 24 months after patients have completed a multiple-month study-treatment regimen.

In considering the approval of bedaquiline, the FDA weighed the benefits of treatment with bedaquiline for patients with smear-positive, multidrug-resistant pulmonary tuberculosis, for whom

there were insufficient treatment options, against the risks, including the observed mortality imbalance. The risk associated with inadequate treatment of tuberculosis includes the likely progression of disease, which would be fatal in some cases, and the development of increased antimycobacterial resistance not only for the patient, but also for broader populations at risk for acquiring tuberculosis. The limited indication of use for bedaquiline identifies a patient population for which there is considerable unmet need and a positive benefit–risk balance.[1] It is crucial that physicians and patients with multidrug-resistant tuberculosis carefully consider this information as well as the potential ramifications of inadequate treatment and increasing resistance.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Did Hospital Engagement Networks Actually Improve Care?

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Everyone with a role in health care wants to improve the quality and safety of our delivery system. Recently, the Centers for Medicare and Medicaid Services (CMS) released results of its Partnership for Patients Program (PPP) and celebrated large improvements in patient outcomes.[1] But the PPP's weak study design and methods, combined with a lack of transparency and rigor in evaluation, make it difficult to determine whether the program improved care. Such deficiencies result in a failure to learn from improvement efforts and stifle progress toward a safer, more effective health care system.

CMS launched the PPP in December 2011 as a collaborative comprising 26 "hospital engagement networks" (HENs) representing more than 3700 hospitals, in an effort to reduce the rates of 10 types of harms and readmissions. The HENs work to identify and disseminate effective quality-improvement and patient-safety initiatives by developing learning collaboratives for their member facilities, and they direct training programs to teach hospitals how to improve patient safety. In a February 2013 webcast, CMS announced that the rates of early elective deliveries had dropped 48% among 681 hospitals in 20 HENs and that the national rate of all-cause readmissions had decreased from 19% to 17.8%, though it is unclear which HENs were included for each measure and what time periods were the pre- and post-intervention periods.[1]

These numbers appear impressive, but given the publicly available data and the approach CMS used, it's nearly impossible to tell whether the PPP actually led to better care. Three problems with the agency's evaluation and reporting of results raise concerns about the validity of its inferences: a weak design, a lack of valid metrics, and a lack of external peer review for its evaluation. Though the evaluation of many other CMS programs also lacks this basic level of rigor, given the large public investment in the PPP, estimated at $1 billion, and the strong public inferences about its impact, the lack of valid information about its effects is particularly troubling.

The design of a quality-improvement program influences our ability to make reasonable inferences about its benefits to patients. Although individual HENs may have used more rigorous methods, the overall PPP evaluation had three important weaknesses: it used a pre–post design with only single points in the pre and post periods, did not have concurrent controls, and did not specify the pre and post periods a priori. Such an approach is highly subject to bias.[2] Several recent examples suggest that some patient-safety interventions appear to lead