Has compassionate use ever sunk a drug?

NEW TREATMENTS FOR A SERIOUS disease generate understandable excitement among patients with life-threatening conditions. As pharmaceutical companies consider compassionate use of experimental drugs, one factor is commonly cited as a barrier to such use: fear that adverse events incurred by patients during Compassionate Use/Expanded Access (CU/EA) will impede regulatory approval of the drug. Such concerns stem from the obligation to report adverse events—that are serious, unexpected, and suspected to be related to the investigational drug—experienced by patients during treatment under CU/EA programs. Such reports, if feared, will damage the future of the drug, particularly since adverse events may not be related to the experimental drug and patients taking such drugs are typically sicker than the average patient.

Existing evidence, however, does not support the notion that such events jeopardize regulatory approval. An observed potential safety signal may result in a hold on use of an investigational new drug (IND), allowing examination of additional data or changes in trial or access protocols. However, between 2005 and 2014, 1033 unique, commercial, active EA INDs were approved by the US Food and Drug Administration (FDA); in only two instances (0.19%) did a serious adverse event lead to a hold on use of the drug. Both holds were lifted within a matter of months, and both drug development programs continued. These data contradict the industry claim that CU/EA impacts approval decisions. An FDA spokesperson described this assertion as ‘something of an urban legend, and [the FDA is] not aware that this has ever occurred’.

It is noteworthy that medications in CU/EA programs have already demonstrated efficacy in trials even though they have not yet been approved for market use, and patients receiving them have no other approved treatment options. Granting permission for CU/EA of medications for the treatment of the human immunodeficiency virus proved key in stemming the AIDS (acquired immune-deficiency syndrome) crisis, but such widespread implementation has not been made available for tuberculosis (TB) patients. Each year nearly 600 000 new cases of TB that cannot be cured by first-line regimens (i.e., multidrug-resistant or MDR-TB) occur, resulting in a substantial unmet need for such programs. One report suggests that 125 000–250 000 patients each year would have benefited from access to either bedaquiline or delamanid.

As no evidence supports the claim that adverse events occurring in patients undergoing CU/EA therapy result in denial of approval, mechanisms should be developed to encourage the establishment of (or discourage delays to) early, routine CU and EA for drugs being developed for indications such as MDR-TB. These could include adjustments to the US FDA Neglected Tropical Disease Priority Review Voucher System or the EMA Orphan Designation incentives, and increased sharing of financial and legal burden for providing access; in France, Italy, and some Nordic countries, the costs associated with treatment are borne by the health care system, not by industry or the patient. Such changes are essential to assure access to new potentially life-saving products by patients suffering from tuberculosis. Without such changes, disproportionately poor populations, largely outside the US and Europe, will continue to be denied access to effective treatment options.

Sarah McAnaw*†
Carly A. Rodriguez ‡
Abbe Muller§
Carole MITNICK*¶
C. Robert Horsburgh, Jr*†#
RESIST-TB
†Partners In Health
Boston, MA
‡Department of Epidemiology
Boston University School of Public Health
Boston, MA
§Department of Epidemiology
Yale University
New Haven, CT
¶Department of Global Health & Social Medicine
Harvard University
Boston, MA
#Department of Medicine
Boston University School of Medicine
Boston, MA
USA
e-mail: rhorsbu@bu.edu

Conflicts of interest: none declared.

References
5 Vale J. Expanding expanded access: how the Food and Drug Administration can achieve better access to experimental drugs for seriously ill patients. Georgetown Law J 2008; 96: 2143–2175.
10 Bedell E. Global access to medicinal products: compassionate use procedures. Regulatory Focus 2010; January: 9–12.