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Methods. A list of new active substances (NASs) (the equivalent of new molecular entity) approved between January 1, 1995, and December 31, 2010, was compiled from the annual reports of the Therapeutic Products Directorate and the Biologic and Genetic Therapies Directorate (available from publications@hc-sc.gc.ca). All serious safety warnings (those using boldface black print or boxed warnings) and drug withdrawals for the period January 1, 1995, to October 31, 2011, were identified from the MedEffect Canada website (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php). Kaplan-Meier survival curves were calculated to estimate the probability that any NAS would have a serious safety issue during the study period and separately for an NAS with a priority and a standard review.

The characteristics of drugs with a priority approval might account for differences in the percentage with safety issues compared with drugs with standard reviews. Drugs that received a priority approval but were not considered to be major therapeutic advances were compared with drugs that received a standard review.

Drugs are usually assigned a priority review on the basis of anticipated clinical benefits and may be licensed with a lower benefit to harm threshold, leading to a higher rate of safety warnings. Drugs with priority reviews for 5 serious diseases—cancer, human immunodeficiency virus/AIDS, inborn errors of metabolism, multiple sclerosis, and the prevention of transplant rejection—were compared with drugs with standard reviews for the same diseases. Kaplan-Meier survival curves were calculated using XLSTAT add-in for Excel (Addinsoft).

Results. A total of 434 NASs were approved from January 1, 1995, to December 31, 2010; 84 (19.4%) had a serious safety issue. The probability of an NAS acquiring a serious safety issue was 23.7% (95% CI, 19.1-28.3) (Figure).

Three hundred twenty-one NASs (74.4%) had a standard review, and 112 (25.6%) had a priority review. (The approval status of 1 product could not be determined.) For products with a standard review, there was a 19.8% (95% CI, 14.8-24.8) estimate of acquiring a serious safety
issue compared with a 34.2% (95% CI, 24.3-44.2) estimate for an NAS with a priority review (P=.005, log-rank test). Eighty-one NASs with a priority review that were not major therapeutic advances were compared with the 321 NASs with a standard review. The estimate of this group of priority review NASs having a serious safety issue was 36.0% (95% CI, 24.3-47.7) compared with 19.8% (95% CI, 14.8-24.8) for standard review NASs (P=.004, log-rank test).

Priority reviews and standard reviews were assigned to 42 and 45 NASs, respectively, for 5 serious diseases. The estimate of the first group having a serious safety issue was 31.1% (95% CI, 14.3-46.0) vs 34.9% (95% CI, 16.8-52.9) for the second group (P=.96, log-rank test).

Comment. Just fewer than one-fourth (23.7%) of all NASs introduced between 1995 and 2010 had serious safety issues. This result is similar to that reported by Lasser et al. The difference between drugs with a standard approval and those with a priority approval in terms of their safety record may be attributable to the shorter period that the latter spends in the approval process and may reflect deficiencies in Health Canada’s priority review process.

Alternative explanations for the difference between standard and review NASs are less likely. Priority review drugs that were not major therapeutic advances were still more likely to acquire serious safety issues than standard review NASs. If priority review drugs for serious diseases were approved with a lower benefit to harm ratio, they should be more likely to develop serious safety issues than standard review drugs for the same diseases. However, there was no difference between the 2 groups. New products that offer major therapeutic advantages should be embraced even with the significant lacunae that exist about their safety, but because most NASs do not fall into this category, clinicians and patients should use these drugs very cautiously.

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INVITED COMMENTARY

New Drug: Caution Indicated

In assessing a new therapeutic drug, regulators at Health Canada and the US Food and Drug Administration (FDA) are entrusted with making critical and difficult scientific judgments that can affect the health of hundreds of thousands of patients in a matter of months after product launch. In drug evaluation, the cost of error may be high. Casualties in pharmaceutical disasters are measured in tens of thousands, and the population exposed to unsafe drugs often numbers in the millions.1 In a new research letter, Lexchin2 provides a valuable but basic report card for the drug approval decisions at Health Canada over a 16-year period.

The first lesson from Lexchin’s study is that serious safety issues were not detected or fully understood at approval for 1 out of 5 drugs, and 17 of the 434 drugs approved were later withdrawn for safety reasons. The results were worse for the subset of priority review drugs—those evaluated under deadline pressure because they were intended to treat a life-threatening disease or were thought to provide an important therapeutic advance. Of those drugs, 1 out of 3 was approved without a warning about a serious safety issue. A recent report from the Institute of Medicine for the United States suggests a future vision under which preapproval testing is only the first installment in a life cycle research program extending over many years.3 In a recent article in the Archives,4 my colleagues and I reported on a single year’s major postmarket safety actions by the FDA and noted that 25 drugs received new boxed warnings and that the 181 safety actions that were approved in 2009 occurred a median of 11 years after initial approval.