Table 4: Examples of problems in drug approval and regulation

Problem	Examples
Safety compromised by pressure to accelerate drug review and approve	Drugs approved shortly before PDUFA*-imposed deadlines for re-viewing new drug applications have higher odds of being withdrawn for safety reasons, getting a new black-box safety warning, or having a dosage-form discontinued after they are marketed, suggesting that regulators compromise safety standards when a deadline is looming.[29]
	Compared to drugs approved before the implementation of PDUFA in 1992, drugs approved after 1992 had a 1.35 higher odds of withdrawal for a safety reason or getting a new black box warning.[30]
Trade-off between review time and drug safety	Each standard deviation reduction in the time the FDA spent reviewing drugs was associated with an approximately 20% increase in serious adverse drug reactions, including those associated with hospitalization and death.[31]
Drugs approved with dubious risk-benefit ratio	In March 2017, the FDA approved a minor variant of desmopressin for the treatment of idiopathic nocturia in adults, despite the fact that the drug only trivially reduced the number of episodes of nocturia per night (2.1 episodes per night for desmopressin vs. 1.9 for placebo), and received a black box warning for hyponatremia.[32]
	Duloxetine was approved in the European Union for stress urinary incontinence. A reanalysis using patient-level data showed that the drug's harms outweighed its benefits for this indication.[33]
"Priority review" pathways and compromised safety	Among drugs approved by Health Canada between 1995 and 2010, those assigned "priority" review as compared to "standard" review were more likely to develop serious safety issues in the post-approval period, even in the case of me-too drugs.[34]
	Among drugs approved by Health Canada between 1998 and 2013, those approved under the "Notice of Compliance with conditions"—a pathway for drugs for serious conditions that are approved based on limited data (equivalent to the US fast-track review)—had a higher rate of having serious safety issues than those approved under the standard pathway. Few drugs approved under this accelerated pathway represent major therapeutic advances.[35]
	Among new drugs approved between 1999 and 2014 by the FDA, those approved through one of three expedited programs (fast track, accelerated approval, and priority review) had a 48% higher rate of receiving a black box warning or a new contradiction added to their labelling than those that went through the standard pathway.[36]

**PDUFA = The Prescription Drug Users Fee Act.*