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FEATURE

Quality of evidence behind FDA approvals varies widely

The approval processes of the US Food and Drug Administration have been scrutinized by several studies. **Michael McCarthy** explains

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Three studies appearing in *JAMA*, the journal of the American Medical Association, take a peek under the hood of the often recondite approval processes of the US Food and Drug Administration (FDA).

Study 1: FDA approval of new drugs

The first of these studies looked at recent FDA drug approvals and found that the quality of the clinical trial evidence used by the agency to approve new drugs varies considerably depending on the proposed drug's indications.[1]

In this study, Nicholas S Downing of Yale University School of Medicine, New Haven, Connecticut, and colleagues reviewed pivotal efficacy trials used to support FDA approval decisions for novel therapeutic agents between 2005 and 2012, looking at such factors as trial size, design, duration, and endpoints.

Gathering records through Drugs@FDA, a publicly accessible database, Downing and his coworkers found that during this period the FDA approved 188 novel therapeutic drugs.

Of these, 31 (16.5%) had been granted orphan status because they targeted a rare disease for which effective treatments are lacking and 22 (11.7%) were approved by the agency's accelerated approval pathway, which is reserved for drugs for serious conditions that fill an unmet medical need.

All told, these 188 drugs were approved for 206 indications. "Three therapeutic areas accounted for nearly half of indications: 41 agents (19.9%) were used to treat cancer, 29 (14.1%) to treat infectious disease, and 23 (11.2%) to treat cardiovascular disease, diabetes mellitus, or hyperlipidemia," the researchers write.

The approvals were based on 448 clinical trials. The median number of pivotal trials per indication was two (interquartile range, 1 to 2.5). But 74 indications (36.8%) were approved on the basis of a single pivotal trial.

"Nearly all trials were randomized ([proportion of trials] 89.3%, 95% confidence interval, 86.4% to 92.2%), double blinded (79.5%, 75.7% to 83.2%), and used either an active or placebo comparator (87.1%, 83.9% to 90.2%)," the researchers report.

A surrogate outcome was used as a primary endpoint in 219 (48.9%) trials, a clinical outcome for 130 (29.0%) trials, and a clinical scale for 99 (22.1%) trials.

"Median trial duration was 14.0 weeks (interquartile range, 6.0 to 26.0 weeks); 113 trials (25.2%, 21.2% to 29.3%) lasted six months or longer," the researchers said.

The features of the trials varied by the agent being evaluated and the new drug's indication, the researchers found.

Trials of drugs used for cancer, for example, were least likely to be randomized (47.3% *v* 95.2%; P<0.001) and double blinded (27.3% *v* 86.8%; P<0.001).

Surrogate endpoints were used in nearly all trials of agents approved through the accelerated approval pathway (38 (95.0%)) compared with fewer than half (181 (44.4%)) of trials for agents receiving non-accelerated approval.

"Most therapeutic agents approved for cancer indications were approved on the basis of a single trial, whereas the approval of therapeutic agents for cardiovascular disease, diabetes mellitus, or hyperlipidemia and for psychiatric indications often relied on at least three trials," according to the researchers.

Altogether, only about one third of indications were approved on the basis of a single pivotal efficacy trial.

The findings, the researchers write, "highlights" the FDA's "flexible standards for approval" that allow the rapid introduction of therapies for life threatening or orphan diseases.

They add, however, that the varying quality of the trials leaves many clinical questions unanswered for providers: few trials include comparative effectiveness data, making it difficult for doctors to decide whether the new drug is safer or more effective than existing treatments; many rely on surrogate outcomes, raising the question of actual clinical benefit; and most trials for chronic diseases lasted less than one year, raising concerns about the treatments' long term efficacy and safety.

To deal with these and other concerns, the paper's authors recommend that the FDA adopt a "life cycle" approach, in which the agency would monitor and evaluate the benefits and risk of drug therapies throughout their market life, summarizing its findings in a continually updated benefit-risk profile document.

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"Alternatively, or as part of this effort, the FDA could provide a summative statement, or even a grade, for each approval to signal the quality of clinical trial evidence used to determine safety and efficacy, allowing therapeutic agents approved on the basis of more robust evidence to be distinguished from those approved on the basis of less robust evidence," they write.

Study 2: FDA approval of cardiac implantable electronic devices

In the second study, Benjamin N Rome and his colleagues at Harvard Medical School, Boston, Massachusetts, looked the FDA's approval processes of cardiac implantable electronic devices, such as pacemakers, implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy devices.[2]

To obtain approval of such "high risk" medical devices, the FDA requires manufacturers to "collect preclinical and clinical data as necessary to provide 'reasonable assurance' of the device's safety and effectiveness," the researchers note.

However, the FDA also approves changes to devices on the basis of "supplements" to applications that might include both major and minor design changes to an approved device as well as routine changes to such things as labeling, materials, and packaging.

"Supplements allow patients to benefit from incremental innovation in device technology by providing efficient and inexpensive FDA review pathways for smaller device changes," the authors write. However, recent product recalls because of problems such as defects in ICD leads, have raised concerns about the approval process, they add.

Rome and his coworkers reviewed records for all the cardiac implantable electronic devices approved by the FDA via either the standard premarket approval process (PMA) or via subsequent PMA supplements from 1979, the year the first cardiac implantable electronic device was approved, to 2012.

The FDA approved 77 PMA applications for such devices during this period and 5829 supplements to PMA applications; the median number of supplements for each original PMA was 50 (interquartile range 23 to 87). They also found that the number of supplements approved each year increased nearly 10-fold, from 77 to 704, in the past decade.

"More than one-third (37%; 2163) of supplements represented at least minor alterations to the device's design or materials. In the vast majority of these cases, the FDA deemed that new clinical data were not necessary for approval," they write.

In their discussion the researchers note that preclinical testing may be better than clinical testing in many cases: "For example, mechanical testing of ICD leads can simulate years of clinical conditions relatively quickly, and animal studies may allow for repeated induction of arrhythmias that would be impossible in a human model."

The study's results should not be interpreted as an indication the FDA is failing to adequately review PMA supplements, the researchers write, but do underscore the importance of post-approval surveillance of these devices.

"In making decisions about use of these high-risk devices, clinicians and patients should consider the strengths and limitations of the PMA supplement approval processes," they conclude.

Study 3: delay and denial of FDA approval of initial applications for new drugs

In the third paper, Leonard V Sacks from the FDA's Center for Drug Evaluation and Research and his FDA and colleagues looked at reasons why drug applications were denied or delayed by the agency.[3]

For their study, the researchers looked at 301 new molecular entity applications submitted to the FDA between 2000 and 2012. Of these, 222 (73.5%) were ultimately approved, 151 (50%) were approved when first submitted, and the remaining 71 (47%) required one or more resubmissions before approval. The median delay to approval after the first unsuccessful submission was 435 days.

"Failures late in drug development are costly," the researchers note, "often involving the commitment of many study participants and personnel. It is advantageous to identify products that fail as early as possible in the development process to avoid these issues. For those drugs that require resubmission before approval is obtained, delays are taxing on the industry and regulators, and patients might have to wait for access to promising, and sometimes lifesaving, new treatments."

Among the reasons why first time applications failed, included choice of study endpoints that failed to adequately reflect a clinically meaningful effect, inconsistent results when different endpoints were tested, inconsistent results when different trials or study sites were compared, and poor efficacy when compared with the standard of care.

Of the applications that failed to prove efficacy, the researchers write, "the choice of study endpoints was often inadequate to demonstrate a clinically meaningful benefit to patients (for example, pain relief, survival, or durable cure).

And while surrogate endpoints can be meaningful for some diseases, in others, such as Alzheimer disease, "satisfactory endpoints for long term outcomes remain elusive and early responses may not translate into durable responses," they note.

They conclude: "For drug developers and clinical investigators, our findings suggest areas of deficiencies in new drug applications in which strategies for drug development could be improved. Early and frequent dialog between the FDA and drug sponsors addressing critical aspects of study design (including the selection of study populations, study endpoints, and drug doses) has the potential to reduce delays in the approval of new drugs."

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See also Analysis: Presumed safe no more: lessons from the Wingspan saga on regulation of devices, doi:10.1136/bmj.g93.

News: Cardiologists criticize US regulator for keeping intracranial stent on market, doi:10.1136/bmj.g357.

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2 Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012. *JAMA* . doi:10.1001/jama.2013.284986.

3 Sacks LV, Shamsuddin HH, YasinskayanYI, Bouri K, Lanthier ML, Sherman RE. Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000-2012. *JAMA* 2014. doi:10.1001/jama.2013.282542.

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