Bad medicine?

Rushing drugs to market was supposed to help people in need, but it may be doing more harm than good. **Jessica Hamzelou** investigates

WEEKS before their due date, some women find themselves stunned, peering through glass at their baby, a tiny body covered in sensors and tubes, striving to stay in the world.

Premature birth can be terrifying. Although survival rates for babies born before 37 weeks of pregnancy have steadily improved, they are still significantly worse than those of babies born later, and the likelihood of longer-term health complications is higher.

So any medication that could reduce that risk would be gratefully received – and has been. In 2011, a drug called Makena was approved by the US Food and Drug Administration (FDA) on the basis of a small trial showing that it helped prevent preterm birth. Later, larger studies found that it didn't. One hospital even reported higher rates of gestational diabetes among women given the drug. Then last month, a large trial found that Makena was no better than placebo; an FDA committee recommended withdrawing it from the market. The FDA has yet to decide.

It isn't just Makena. At drug approvals agencies around the world, more and more medications are being rushed to market after limited testing. Drugs are approved based on preliminary findings, or authorised for a particular use, then widely prescribed for something else. And hanging over the process is a worrying question: are these agencies working to protect the public or to further the interests of drug companies?

We would all like to think that any treatment our doctors offer is the best option available for us, based on credible evidence. But not only do some approved drugs turn out not to work, they may be worse for us than doing nothing.

Decisions made by the FDA or European Medicines Agency (EMA), which agree on approvals more than 91 per cent of the time, have international ramifications. The FDA recently announced an initiative with Canada and Australia for faster, simultaneous approvals of certain cancer medications, for instance. Even when collaboration isn't direct, FDA decisions have ripple effects: the US process is viewed as the "gold standard" worldwide and drugs granted accelerated approval by the FDA or EMA can then be fast-tracked by authorities elsewhere.

Speed wasn't always a priority. In the late 1970s, the FDA was downright sluggish: it took an average of 35 months for a drug to get through the review process. Today, it takes less than a year. Starting in the early 1990s, several measures were introduced to speed up approval, largely in response to public demand from people who faced life-threatening or life-limiting conditions. New pathways were established to give quicker access to medicines that addressed a serious unmet medical need or represented "breakthroughs" in our understanding of how to treat a disease.

Yet despite those virtuous initial goals, these days, many drugs being hurried through are neither of those things. In 2008, the FDA granted accelerated approval for bimatoprost,

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a treatment that encourages eyelash growth.

"Increasingly, these pathways have become the norm rather than the exception," says Caleb Alexander at Johns Hopkins University in Maryland. Today, more than half of all the drugs that the FDA authorises are granted an expedited approval of some kind.

The FDA told *New Scientist* that drugs authorised in this way "are held to the same approval standards as other FDA drug approvals", but some researchers dispute this. "Fewer trials are being relied upon to approve a drug," says Jonathan Darrow at Harvard Medical School. "Those trials are less likely to be randomised than they were 20 years ago, less likely to be blinded, less likely to be [placebo] controlled and likely to be smaller." Barbara Mintzes at the University of Sydney, agrees. "With the expedited approvals, there is a trend toward a lower bar of evidence."

Faster drug approval has become more common in Europe, too. Since 2006, the EMA has been able to grant a "conditional marketing authorisation" to new drugs that treat serious or rare disorders or respond to a public health emergency, but may not meet the standard level of evidence that they work.

Those lower standards of evidence include settling for "surrogate markers". Instead of finding out if a drug can prevent heart attacks, for example, a pharmaceutical company may only need to show that it lowers blood pressure. "These are things that are not necessarily going to tell us that people are going to live longer or have a better quality of life," says Joel Lexchin at the University of Toronto in Canada.

No survival boost

New drugs that are similar to existing ones and treat the same conditions are often approved based on surrogate markers, says Adam Cifu at the University of Chicago Medicine. That includes some of our most widely used drugs, statins, which are taken to lower cholesterol. "If you compare atorvastatin, pravastatin, simvastatin – those drugs are all different," says Cifu. "Because we don't have comparative trials of them, or even individual placebo-controlled trials which we can compare, often it's not entirely clear which is the best of the drugs."

This is also the case with many new cancer drugs, which make up the majority of medicines approved through an expedited pathway. Cancer therapies often have debilitating side effects, so knowing whether they will extend your life or not could be critical in deciding whether to take them at all.

Between 2009 and 2013, via both expedited and routine pathways, the EMA approved 48 cancer drugs for 68 different uses. At the time of approval, the drugs had been shown to improve survival for only a third of those uses; in just 10 per cent they seemed to benefit quality of life. Even after these drugs had been on the market for between three and eight years, they still hadn't been shown to improve survival or quality of life for half of the approved uses.

Many cancer drugs authorised by the FDA ›

"The drugs that receive the fastest reviews are the ones that tend to have the most serious risks"

have similarly unclear benefits. Between 1992 and 2017, says Mintzes, "only 19 of 93 new cancer drugs showed a survival advantage".

Consider Afinitor, a drug used in the treatment of metastatic breast cancer. It was approved by the FDA in 2012 based on a surrogate marker – that it limited tumour growth – but has since been shown not to extend survival. "It's very costly, it has real side effects and it doesn't let you live longer," says Vinay Prasad, an oncologist at Oregon Health and Science University. "And yet it remains on the market in both the US and European Union."

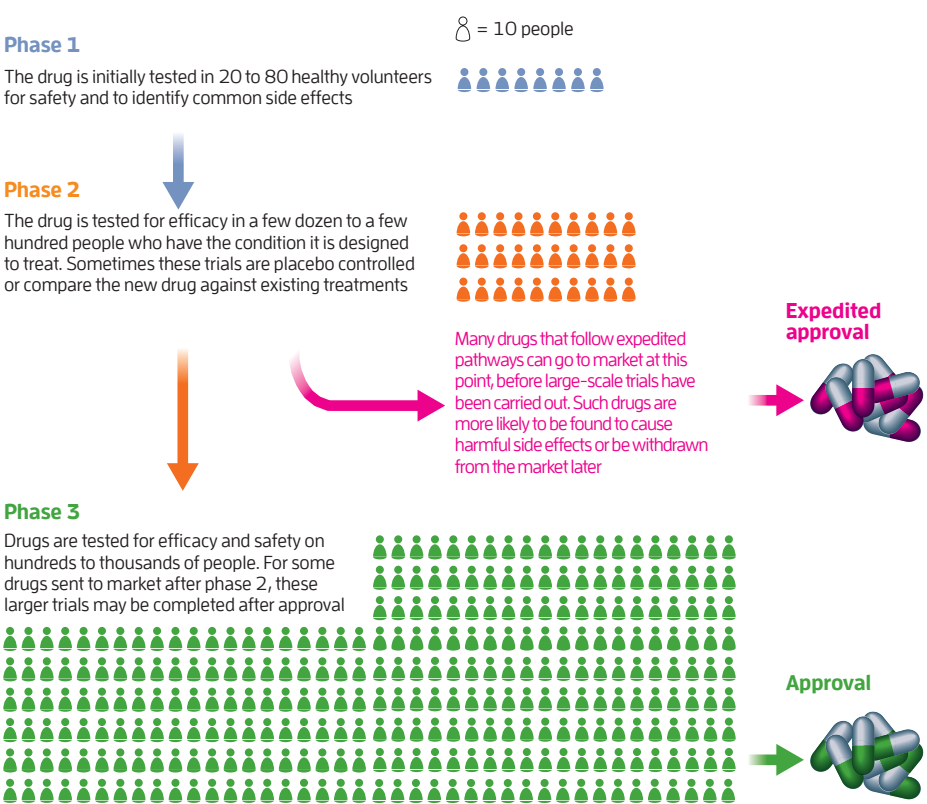
When drugs are approved on the basis of slim evidence, it is sometimes on the understanding that testing will be carried out after they get the green light – as was the case with Makena. Yet these trials can take years to complete and are often poor quality. In some cases, they just don't happen. Nearly half of post-marketing studies requested by the FDA haven't been completed five years later.

It is also more likely that drugs approved this way will later be found to have serious side effects, says Mary Olson at Tulane University in New Orleans. "The drugs that receive the fastest reviews are also the ones that tend to have the most serious risks, and even serious risk resulting in death," she says. "There is a trade-off between speed and safety, and the FDA has been struggling to find the right balance."

Having to attach serious warnings and even ultimately withdraw certain medicines are clear indications that some of these drugs "should not have been approved in the first place", says Christopher Robertson at the University of Arizona.

Lowering the bar

Getting drugs to market faster often means relying on lower standards of evidence



SOURCE: GAO, FDA

Dangerous alternatives?

Once medicines make their way to market, it can be hard to wrest them back. When the latest data on Makena was released, the American College of Obstetricians and Gynecologists, which has more than 58,000 members, said it would still recommend prescribing the drug.

In part, the rationale may be that having something to offer is better than nothing. On the 16-person FDA advisory committee that recommended withdrawing Makena, seven members voted against this move. Jonathan Davis, a paediatrician at Tufts Medical Center in Massachusetts, was among them. He wants Makena to stay on the market while more trials are conducted because he worries that doctors will seek out potentially dangerous alternatives if it is no longer available.

The reality is that sometimes the drugs that doctors prescribe may simply be best guesses. Once approved for one purpose, drugs can be prescribed "off label" for other uses. Officially, Makena is intended for pregnant women who have already experienced a spontaneous premature birth. "But doctors prescribe it for all sorts of other risk factors," says Amy Romano, a midwife and maternity care researcher based in Milford, Connecticut. "Even if the trials haven't been done to show it does anything, they'll still prescribe it because they want to do something rather than nothing."

Sometimes off-label prescribing can be useful, says Cifu, as in the case where only one birth control pill has specifically been approved to treat adolescent acne, but there are several with similar chemical structures and doctors know from clinical use that they have similar effects. "To prescribe one of those for acne makes perfect sense," he says.

But 80 per cent of off-label uses for drugs aren't supported by evidence because companies aren't required to run clinical trials for such unofficial uses. "We can proceed for

years and years using a drug off-label without ever really knowing if it's safe and effective for those uses," says Robertson.

Off-label prescribing can also benefit pharmaceutical firms that develop what are known as "orphan drugs". These are medications intended to treat rare diseases, defined in the US as those that affect fewer than 200,000 people. There and in places such as Europe and Australia, orphan drugs are granted fast-tracked approval and either reduced fees or tax breaks. In 2018, 34 of the 59 new drugs authorised by the FDA were orphans. After approval, drug developers are usually granted exclusive rights to market new medicines for several years. With orphan drugs, this period may be extended, allowing firms to set higher prices for longer. Makena was granted orphan drug status. It was first marketed at $1500 per shot, or $30,000 over an entire pregnancy.

Once these drugs are on the market, they can be prescribed for much more common disorders. "There are products that have made tens of billions of dollars that are anything but orphans," says Alexander.

A lidocaine patch marketed as Lidoderm, for example, was approved as an orphan drug by the FDA in 1999 to treat nerve pain caused by shingles – which affected about 191,000 Americans at the time. Since then, it has become widely prescribed for other types of pain. By 2005, 82 per cent of Lidoderm prescriptions were for uses not approved by the FDA. "Once you let a product on the market, it's very difficult to control how it's going to be used," says Lexchin. "The drugs get around – people use them for other conditions where they're not found to be beneficial."

"We're in this odd situation where the off-label use is largely unregulated, but the reimbursements for it can be extremely profitable for the companies," says Robertson.

It is illegal for drug companies to deliberately market drugs for disorders that they haven't been officially approved for. But whether the FDA can intervene if salespeople do this is now "a little bit hazy" thanks to a 2012 court case, says Robertson.

The story starts with Alfred Caronia, a sales rep for the company that made Xyrem, a drug officially approved to treat narcolepsy. In 2005, Caronia was recorded telling a doctor that the drug could also benefit people with insomnia and fibromyalgia, that it was being investigated in Parkinson's disease and multiple sclerosis and that it was safe to use in children.

The US government argued that Caronia was "marketing a dangerous drug for use not approved by the FDA". In 2009, he was found guilty of misbranding and sentenced to a year of probation and 100 hours of community service. But Caronia appealed on the grounds that he was merely exercising his right to free speech. In 2012, a court of appeals overturned his conviction, deciding that, "as long as everything he was saying was true, he had a constitutional right to say it", says Robertson. To the court, it didn't matter that there wasn't robust evidence to support his claims.

Robertson thinks the FDA may now be unwilling to pursue similar cases because, if one made it to the US Supreme Court and the agency lost, it would lose the ability to effectively regulate drugs and medical devices. Since the Caronia case, the number of warning letters sent by the FDA to pharmaceutical companies appears to have dropped. Yet it remains the case that off-label prescriptions can be dangerous. They are more likely to cause adverse or allergic reactions, for instance.

For many, when these issues are taken together they become a major source of worry: is the FDA prioritising the interests of drug companies over those of the public?

It is certainly the case that an increasing amount of the agency's funding comes from industry. Under the Prescription Drug User Fee Act introduced in 1992, pharmaceutical companies agreed to pay fees to help fund additional FDA salaries and, in return, the agency agreed to speed up approval times. Back then, the FDA received around $36 million a year from drug companies, says Darrow.

The fees have been repeatedly renewed and expanded since. "Now it's around $1.5 billion per year coming from user fees," he says. At the EMA, 89 per cent of the €330 million annual budget comes from similar fees. For the FDA, it's 45 per cent. "There is some concern about the quality of evidence and the willingness of the FDA to consider the industry as its primary client, rather than the public," says Darrow.

New Scientist contacted both agencies to ask whether that financial dependency conflicts with their missions to serve the public. The EMA didn't respond by the time this went to press. An FDA representative replied in a ›

Most drugs given fast-tracked approval are to treat cancer

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"We can proceed for years using a drug off-label without ever knowing if it's safe and effective"

"We're losing out on our ability to treat patients because medicines aren't being properly evaluated"

written statement that user fees are "to hire additional staff and upgrade its information technology systems", and that the user fee act "committed the Agency to speed the application review process for new drugs without compromising its high standards for new drug safety, efficacy, and quality".

Upfront payments aren't the only way the industry can influence the FDA. Drug companies may offer payment for work on advisory boards or cover accommodation or travel expenses for members of an FDA panel after a drug has been approved, avoiding the need to report a conflict of interest beforehand.

Once approved, the way drugs are promoted or prescribed might also be influenced by drug company funds – even at a surprisingly small scale. A 2018 study found that physicians who receive financial benefits from companies that make opioid drugs are more likely to prescribe them, even when the compensation is as small as a $13 meal.

With the enactment of the Physician Payments Sunshine Act in 2010, it became a legal requirement in the US for drug and device manufacturers to report any financial ties with doctors greater than $10. According to publicly available data, two of the doctors who voted to keep Makena on the market received financial compensation from the manufacturer at some point. The amount one reportedly received was just $17. That may seem like peanuts, but that money represents an opportunity for the sales rep to give a pitch directly to the doctor – "an intimate education session" as Romano puts it. "They wouldn't do them if they weren't so effective," she says.

As intended, these kinds of disclosures are enabling the public to subject financial ties to much closer scrutiny. Last September, an investigation by *The New York Times* and ProPublica revealed that José Baselga, then chief medical officer at the highly regarded Memorial Sloan Kettering Cancer Center in New York, "put a positive spin on the results of two Roche-sponsored clinical trials that many others considered disappointments", without disclosing that he had received more than $3 million from Roche in the preceding three years. When the story broke, Baselga issued an apology and resigned, but within months was given a senior role at AstraZeneca. "It really isn't much of a punishment when you get a very lucrative job," says Prasad.

Getting better

The first step towards addressing these issues is to shine a light on them, and an increasingly vocal group of physicians, researchers, lawyers and policy-makers are attempting to do just that. Prasad is writing a book exposing flaws in the way cancer drugs get approved and prescribed, for instance. Darrow has published paper after paper examining the nuances of how drugs make it to market in the US and abroad. Aaron Kesselheim of Harvard Medical School, a co-author with Darrow on several papers, has testified before the US Congress multiple times to draw attention to problems in drug development, approvals and pricing.

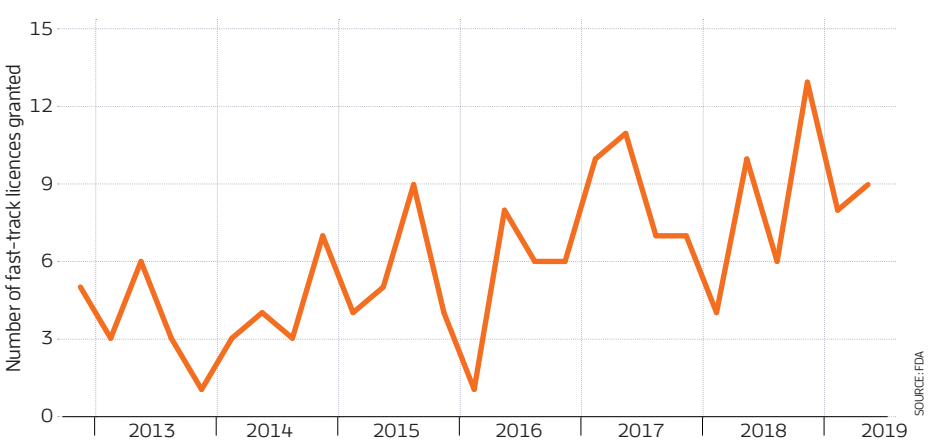
But change is slow in coming. What's more, most doctors and scientists contacted by *New Scientist* don't necessarily blame regulatory bodies for the lack of evidence in support of many new drugs. They point out that organisations like the FDA are balancing the need for scientific evidence with pressure from doctors and patient groups – even if some of these groups are funded by drug companies.

Frustratingly, too, direct efforts to change things have fallen short. In 2005, a UK parliamentary select committee recommended that the government's Medicines and Healthcare products Regulatory Agency work with industry to design trials that test whether each drug is likely to improve a person's life. It also suggested a limit on how much promotional material doctors receive about new drugs. But the government decided to maintain the status quo, stating that "there is no indication that the measures currently in place are not effective".

There is a lot at stake. "We're losing out on our ability to treat patients because medications are not being properly evaluated and not being properly prescribed," says

Racing to market

The use of expedited pathways for drug approval has steadily increased at the US Food and Drug Administration



Links to relevant research papers are included in the online version of this article at **newscientist.com**

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Fact boxes on packaging could be a way to inform the public about the evidence for new medications

Lexchin. Robertson echoes the point. "If we end up in a situation where we know less and less about the chemicals that we are putting in our bodies in situations where we are the most vulnerable and the most desperate for health solutions, that's really worrisome," he says.

That is why they and other outspoken critics won't stop trying to raise the alarm. Meanwhile, their wish list for how to do things better grows longer by the day. Lexchin thinks we need to make organisations like the FDA and EMA financially independent. "Regulation should be funded out of public money, not out of user fees that the industry pays," he says.

Huseyin Naci at the London School of Economics says that "drugs should be evaluated on the basis of their overall survival benefit wherever possible". Mintzes agrees. The use of expedited approval pathways shaves an average 11 months off the time it takes for a drug to get to market. "That's not that long," she says. If data collection ahead of approval were to take longer, people who wanted to try the drug in the meantime can be granted access by taking part in clinical trials or through compassionate access schemes, says Mintzes.

When drugs are approved without clear evidence that they work, this should be made apparent on their packaging, says Darrow. "Patients overestimate the value of new medications, in some cases by a factor of 10 or more," he says. "What's really needed is a drug fact box, just like we have nutrition fact boxes, where we use terms that patients can understand."

One idea that is gaining some traction is for approved drugs to automatically be withdrawn from the market if they aren't shown to improve survival within a set number of years. Most of those contacted by *New Scientist* had heard this suggestion brought up at conferences, but it has yet to develop into a coherent campaign.

While advocates for reform carry on with the long slog towards meaningful change, there are things we can all do to ensure we get the best possible medicines (see "Taking your health into your hands", left). That starts with taking an active role in our healthcare and weighing up the risks and benefits of any new treatment. If a doctor recommends a drug, ask questions about it, says Robertson. Ask if that drug is approved for your specific condition, and for the evidence supporting its use.

Your doctor should also be able to tell you how new the treatment is, how much is known about its safety and if a new treatment outperforms older ones. It may seem like a lot to ask of doctors who are pressed for time or who may struggle to keep up with the constantly evolving research. But when your health is on the line, this may be your best chance of getting the medicine that is genuinely best for you.

"Gone are the days when a doctor should tell you, 'You need drug A'," says Prasad. "Here are the days when a doctor should tell you, 'Let's sit down, let's talk about drug A, let's talk about drug B, let's talk about what if we do nothing.'" ▮

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Taking your health into your hands

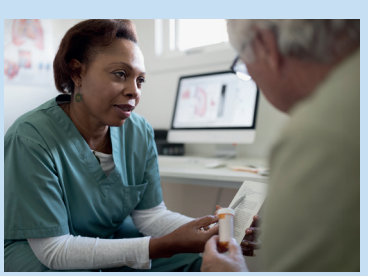
Ask your doctor how new the drug is
Newer drugs may have less safety information. We don't find out about the side effects of some drugs until they have been on the market for years, and given to hundreds of thousands of people.

Ask if the medicine was approved for your condition or symptoms
Drugs are often prescribed "off label" for uses unapproved by regulatory bodies, and for which there is little or no evidence to support their use. "If it is, you're covered, if not, it's worth asking, 'Why are we using it?'" says Adam Cifu at the University of Chicago Medicine.

Ask how likely the medicine is to work
The "number needed to treat" reveals how many people would have to try a drug before one person benefits. A high number suggests the drug is less likely to help you.

Ask how the drug compares with other drugs
Newer drugs may not have been compared with existing drugs. Ask where the evidence lies.

Look for studies on the drug
You can find out how a drug was approved by searching the website of the regulatory body, such as the FDA or EMA. Cochrane reviews provide easy-to-understand summaries on how the drug has fared in clinical trials.



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