Testimony of Dr. Diana Zuckerman, President of the National Center for Health Research

House of Representatives Small Business Committee Hearing

Stifling Innovation:

Examining the Impacts of Regulatory Burdens on Small Businesses in Healthcare

May 8, 2024

Chairman Williams, Ranking Member Velazquez, and distinguished members of the Committee on Small Business:

I am Dr. Diana Zuckerman and I am president of the National Center for Health Research, a public health think tank in Washington, D.C. I was trained as a post-doctoral fellow in epidemiology and public health at Yale Medical School, was on the faculty of Vassar and Yale, and a research director at Harvard before coming to Washington as a Congressional Science Fellow. I then spent a decade working as a Congressional investigator on FDA issues at what is now the House Committee on Oversight and Accountability, was in charge of health legislation at the Senate Veterans Affairs Committee, and also served in the White House Office of Science and Technology Policy. While in my current position for the last 25 years, I've served on the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC); been a fellow at the University of Pennsylvania Center for Biomedical Ethics; chaired the Women's Health Promotion Council for the State of Maryland; and trained physicians, patient advocates, and journalists to understand medical research findings as well as FDA and CMS policies.

Thank you for the opportunity to be here today to share my expertise and the views of the National Center for Health Research. Our research center does not accept funding from companies or other entities with a financial interest in our work.

As a scientist, a policy expert, and a cancer survivor, I look for common ground. I respect the very important work of the other panel members and this Committee, and I think we can all agree that we want small businesses to succeed and to provide the best possible products. In medicine and health care, let's agree that we want innovation that is defined as better products and better treatments that have meaningful benefits to patients – living longer, spending less time in hospitals, feeling healthier, and having a better quality of life. It isn't enough for products to be new, they should be better for at least some patients.

The Costs of FDA Flexibility in Drug Approval of a Small Business

The FDA makes it very clear that it does not expect or require absolute certainty when it approves a drug or medical device. Here are examples of evidence that the FDA has considered adequate for approval for two very expensive drugs created by start-up businesses. After that, I will briefly explain FDA regulatory policies and how they differ for drugs and devices.

This March, a company named Amylyx reported that its one and only drug – Relyvrio-- did not work. FDA had granted approval to Relyvrio to treat ALS, also known as Lou Gehrig's disease less than 2 years earlier, despite the company ignoring the FDA's advice to complete their clinical trial before requesting approval, and despite the warnings by FDA scientists and FDA Advisory Committee members that the evidence was not persuasive and therefore it might not work. FDA approved it anyway because ALS is a terrible disease and the agency wanted to be flexible since the drug might possibly work. The drug cost $158,000 per patient per year despite its much less expensive ingredients (one is a dietary supplement sold on Amazon for a few dollars). Since the drug was intended to slow deterioration rather than improve health, it was not immediately obvious to patients that the drug was not working – that required comparing the drug to placebo. The company had promised to continue its research comparing the drug to placebo and found that the patients taking the drug were no better than the placebo group. Meanwhile, the company had $380 million in revenues last year and the two young men who had started the company paid themselves $7.4 million each. When Relyvrio was taken off the market, the stock immediately dropped 80%, and 70% of the staff were let go.

Another example is the small business Sarepta, which also had only one product when it submitted an application for approval for Exondys51 for Duchenne Muscular Dystrophy. The company had only 12 boys in their study and started giving the drug to the placebo group because they were so sure it was working. Despite the extremely small study, unclear evidence, and no placebo group, the FDA granted accelerated approval in 2016 because Duchenne muscular dystrophy is a deadly disease and as a small business Sarepta did not have the capital to continue the research unless they could start selling the drug.[1] The company promised a larger study would be completed in 2020. It is now 2024, the larger study has not yet been submitted, and the price of the drug has increased from about $400,000 per patient per year to over $1 million per patient year. Families went broke even paying the co-pays, so Medicaid has footed most of the bill. And we still don't know if it works.

Are FDA Requirements Too Stringent?

There are many large companies that have also benefited from FDA "flexibility" and therefore had drugs or devices approved that were not proven to be safe and effective and were later proven to not be safe or not be effective. For example, our research on 18 unproven cancer drugs that had been approved based on short-term preliminary data such as tumor shrinkage, found that 4-8 years later there was still no evidence for 17 of the drugs that patients lived longer or had a better quality of life.[2] A study of hundreds of new drugs that FDA approved but required to do post-market studies to confirm that they were safe and effective found that more than two-thirds of those required studies were late, especially those for treatments for children for various treatments.[3] These and similar studies indicate that the problems with confirming that new drugs are safe and effective are not unique to small companies but these problems can't be solved by lowering regulatory standards.

The examples of Amylyx and Sarepta are important for this Committee because they show that the FDA is sometimes very helpful to small businesses, ignoring their own written policies. I will briefly describe what those written policies are.

For drugs, the FDA usually requires at least one clinical trial that shows that the drug has benefits that outweigh the risks compared to placebo. FDA does not require the new product to be better than older products that are already on the market, even if those older products are much less expensive. And for numerous products, FDA doesn't even require that the new product has meaningful health benefits, and instead only asks that there is evidence that the new drug probably will have health benefits. In other words, FDA doesn't require absolute certainty or even a high level of certainty, but rather a subjective judgment that there is a reasonable probability of benefit.

For medical devices, the standards are even less rigorous: the FDA standard is a "reasonable assurance of safety" and a "reasonable assurance of effectiveness." Approximately 98% of new devices are cleared for market without any clinical trials and without any clear evidence of safety or effectiveness, as long as the FDA considers the new device to be "substantially equivalent" to a device legally on the market. And the agency's definition of substantial equivalence does not require the new device – even an implanted life-saving device – to be made of the same materials, be the same shape, or have the same mechanism of action. For example, the robotic surgery systems that are widely used today were allowed on the market as substantially equivalent to traditional scalpels and other surgical tools, even though the robotic systems are in other ways very different from those tools.

What about the other 2% of medical devices – the highest risk devices that require clinical trials? High risk devices that can either save a life or cause a death -- such as an artificial heart -- are only required to submit one clinical trial (rather than 2 that are traditionally required for drugs) and these studies are very rarely randomized double-blind clinical trials, even though that is considered the gold standard for testing the benefits of medical products. And yet, a recent study of a national random sample of physicians found that most believed that FDA approval decisions should be based on 2 randomized double blind clinical trials and many did not realize that the FDA often did not require that evidence.[4]

FDA Has Reduced Regulatory Burdens on Small Businesses

Given the implications for the health of all of us when we are patients, and for the health of our friends and loved ones, I am comfortable with the FDA being careful not to unduly burden small businesses, but I want to be able to trust that the medical products – drugs and devices – made by small businesses are just as safe and effective as those made by the largest companies. If they aren't, any benefits to a small business will be short-lived, as they were with Relyvrio.

There are some specific FDA policies that help reduce regulatory burdens on small businesses. User fee legislation is negotiated by FDA and industry every 5 years and then passed by

Congress. The negotiations are behind closed doors but reportedly focus on the fees that companies must pay the FDA when they submit applications to the FDA average timeline for FDA reviews. In addition, user fee legislation has an important benefit for small businesses – it requires the FDA to regularly meet with industry staff throughout the application process to answer the applicants' questions and help ensure that the applicant has the information necessary for a successful application. Such meetings are required regardless of the size of the company, and that helps to level the playing field for smaller companies and start-ups that otherwise would not have access to that level of specific advice about their application materials.

User fees also provide lower fees and waivers for small businesses. Device companies must pay a registration fee of $7,653, but the FDA waives all user fees for small businesses with revenues below $30 million when they submit their first medical device application. Equally important, the user fee for most device applications submitted by businesses with revenues below $100 million only cost $5,800 this year, since that is the price that medical device companies negotiated with the FDA and Congress passed in MDUFA, the medical device user fee legislation. Here are FDA's device user fees for different types of applications in FY 2024 taken directly from www.FDA.gov:

Application Type	**Standard Fee**	**Small Business Fee†**
510(k)‡	$21,760	$5,440
513(g)	$6,528	$3,264
PMA, PDP, PMR, BLA	$483,560	$120,890
De Novo Classification Request	$145,068	$36,267
Panel-track Supplement	$386,848	$96,712
180-Day Supplement	$72,534	$18,134
Real-Time Supplement	$33,849	$8,462
BLA Efficacy Supplement	$483,560	$120,890
30-Day Notice	$7,737	$3,869
Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs, and PMRs)	$16,925	$4,231

Drug user fees are much higher because applications are much more complex and require more staff resources. However, FDA allows waivers for small businesses, defined as "an entity that

has fewer than 500 employees, including employees of affiliates, and that does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce." Similarly, FDA may grant a fee waiver for applications meeting small business applications for biologics.

Conclusions

Good evidence for medical products requires resources. Small businesses will have the resources to meet the FDA's evidence standards for many types of medical products, but if we want these products to be safe and effective enough to help patients, some small businesses will not be able to raise the capital to provide the kind of evidence that patients and health professionals need to make informed decisions. That is the reason why small businesses often partner with larger companies on novel medical products. However, when the FDA reduces the burden on companies to provide clear evidence that a product is safe and effective, that increases the burden on patients and physicians to make life-changing and life-saving medical decisions without the facts they need to make the decisions that are best for them.

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