BRIEFLY NOTED

Synthetic Insulin and the Bureaucratic Mindset

BY HENRY I. MILLER

This past October marked the 41st anniversary of one of biotechnology's and American medicine's most significant milestones: the U.S. Food and Drug Administration's approval of human insulin synthesized in genetically engineered bacteria to treat diabetes. The first "biopharmaceutical"—a drug made with molecular genetic engineering techniques—to be approved, it launched a revolutionary era in drug development.

Insulin is secreted in the pancreas and is essential to the metabolism of carbohydrates and fats. Insulin deficiency leads to the development of diabetes. Many diabetics require regular injections of insulin to maintain life and health.

As the FDA medical reviewer and head of the evaluation team for "Humulin" (the brand name of the human insulin), I had a front-row seat to this landmark event. The saga is remarkable in several ways, not least of which is that, although both the drugmakers and regulators were exploring unknown territory, the development of the drug and its regulatory review progressed smoothly and rapidly.

Miracle drug / Insulin in crude form was first produced a century ago, in 1922, by Canadian researchers Frederick Banting and Charles Best. Their work lifted the death sentence that had previously been imposed on diabetics. By the end of that year, drug company Eli Lilly had devised a method for much higher purification. But this miracle drug was dependent on extracting insulin from the pancreases of pigs and cows, using waste products from the meat packing industry. More than two tons of pig parts were needed to extract just 8 oz. of purified insulin.

Over the next half century, the pig and cow-derived insulins, which differ slightly in chemical composition from human insulin, were constantly improved in purity and formulated in ways that offered physicians and diabetic patients greater control over blood sugar. The extracted insulin was a miracle drug.

By the early 1970s, however, a crisis emerged. The supply of animal pancreases declined and the prevalence of insulin-requiring diabetes grew, leading to widespread fears of possible future shortages of insulin. Fortunately, around the same time, a new and powerful tool—recombinant DNA technology, also known as "genetic engineering" or "gene-splicing"—became available, offering the promise of unlimited amounts of insulin that, unlike the insulin from animals, was identical to the molecule produced in the human body.

The seminal molecular genetic engineering experiment was reported in a 1973 research article by academic scientists Stanley Cohen, Herbert Boyer, and their collaborators. They isolated a ringlet of DNA called a "plasmid" from a bacterium, used certain enzymes to splice a gene from another bacterium into the plasmid, and introduced the resulting "recombinant," or chimeric, DNA into *E. coli* bacteria. When these now "recombinant" bacteria reproduced, the plasmids containing the foreign DNA were likewise propagated and produced amplified amounts of the functional recombinant DNA. And because DNA contains the genetic code that directs the synthesis of proteins, this new methodology promised the ability to induce genetically modified bacteria (or other cells) to synthesize desired proteins in large amounts.

Scientists at Eli Lilly immediately saw the promise of this technology to produce unlimited quantities of human insulin in bacteria. After obtaining the recombinant *E. coli* bacteria that synthesized human insulin from biotech startup Genentech, they developed processes for the large-scale cultivation of the organism (in huge fermenters like those used to make wine or beer) and for the purification and formulation of the drug.

Insulins had long been Lilly's flagship products, and the company's expertise was evident in the purification, laboratory testing, and clinical trials of human insulin. The company's scientists painstakingly verified that their product was extremely pure and identical to pancreatic human insulin.

Lilly began clinical trials of its human insulin in July 1980. The product performed superbly. There were no systematic problems with treating "naive" patients (who had never received injections of insulin) or those who switched from animal to human insulin. Moreover, a small number of patients who had had adverse reactions to the animal insulins tolerated the human insulin well.

FDA review / The New Drug Application, the dossier that provided evidence of the synthetic insulin's safety and efficacy, was submitted in May 1982 to the FDA, where I was the medical reviewer and head of the evaluation team. Over many years, the FDA had had extensive experience with insulins and with drugs derived from various microorganisms, so it was decided that no fundamentally new regulatory paradigms were needed to evaluate the recombinant human insulin. In other words, recombinant DNA techniques were viewed as an extension, or refinement, of long-used and familiar methods for making drugs. That proved to be a historic, precedent-setting, and *correct* decision.

Based on my team's exhaustive review of Lilly's data, which were obtained from pre-clinical testing in animals and later in clinical trials involving thousands of diabetics, the FDA granted marketing approval for

HENRY I. MILLER, a physician and molecular biologist, is the Glenn Swogger Distinguished Fellow at the American Council on Science and Health. He was the founding director of the U.S. Food and Drug Administration's Office of Biotechnology.

CAÍQUE DE ABREU / GETTY IMAGES

human insulin in October 1982. The review and approval took only five months when the agency's average approval time for new drugs was 30.5 months.

In retrospect, that rapid approval was particularly remarkable for a drug that was produced with a revolutionary new technology and that would be available in pharmacies nationwide to millions of American diabetics.

Bureaucratic mindset / The back story, however, is revealing. My team and I were ready to recommend approval after *four* months' review. But when I took the packet to my supervisor, he said: "Four months? No way! If anything goes wrong with this product down the road, people will say we rushed it, and we'll be toast."

That's the bureaucratic mindset. I don't know how long he would have delayed it, but when he went on vacation a month later, I took the packet to his boss, the division director, and he signed off.

That anecdote is an example of Milton Friedman's observation that to understand the motivation of an individual or organization, you need to "follow the self-interest." A large part of regulators' self-interest lies in staying out of trouble. One way to do that, my supervisor understood, is not to approve in record time a product that might experience unanticipated problems.

The Humulin approval had significant effects. An October 30, 1982, *New York Times* front-page article quoted me predicting that the speedy approval was a major step forward in the "scientific and commercial viability" of recombinant DNA technology. "We have now come of age," I said, and potential investors and entrepreneurs agreed. Seeing that biopharmaceuticals would compete with other medicines on a level playing field, the "biotechnology industry" was on the fast track.

Unfortunately, the rapid approval of human insulin proved to be an anomaly. Even with a toolbox of improved technologies available to both the FDA and industry, bringing a new drug to market on average now takes 10–12 years and costs more than $2.5 billion. There hasn't even been much improvement in review times from the pre-electronic era when New Drug Applications were submitted in paper form.

Regulators are highly risk-averse, few new drugs are approved without convening extramural advisory committees, and decisions are sometimes hijacked by political forces outside the FDA. Even so, five of the highest-revenue U.S. drugs in 2022 were produced by biotechnology, either with recombinant DNA or monoclonal antibody technology.

Other FDA-regulated biotech sectors have fared much worse. Regulators have made a colossal mess of the regulation of genetically engineered animals, which the FDA bizarrely chose to regulate as "new animal drugs" based on their interpretation of a 1938 law. That byzantine process led to a grotesquely prolonged, 20-plus-year review of a faster-growing Atlantic salmon. (See "Regulators Kept a Fish Treading Water for Years," Fall 2021.)

More disarray occurred with genetically engineered mosquitoes to control mosquitoes that carry viral diseases. Inexplicably, it took the FDA more than five years to decide that, for regulatory purposes, this "gene drive" technology was a form of pesticide, and that jurisdiction over its approval belonged at the U.S. Environmental Protection Agency. As a result of this bureaucratic bungling, the entire biotech sector of genetically engineered animals is moribund. (See "How the FDA Virtually Destroyed an Entire Sector of Biotechnology," Winter 2017–2018.)

Government regulation has not aged as gracefully as genetic engineering technology itself, which has advanced significantly over the years. Regulators are supposed to abide by the "contract" that society has made with them: civil servants are granted lifetime tenure and are protected from political pressure and retaliation, in return for which they are supposed to make decisions based solely on the public interest. But often they do not. To get FDA-regulated products to those who need them, congressional oversight must emerge from hibernation and create a healthier, more constructive balance. *R*

BRIEFLY NOTED

Was Trump a Deregulator?

BY PIERRE LEMIEUX

Donald Trump ran for president in 2016 promising he would be "cutting regulation at a tremendous clip. I would say 70 percent of regulations can go." When he left office in 2021, he claimed to have "slashed more job-killing regulations than any administration has ever done before." Is Trump's record on regulation an example of, to borrow one of his slogans, "promises made, promises kept"? Or is it just a politician's rhetoric?

On first glance, the answer is unclear. Clyde Wayne Crews, a regulation expert at the Competitive Enterprise Institute, writes:

> During Trump's four years, there had been some unique reversals, such as a slowdown in the issuing of new rules and some rollbacks of existing ones. ... At the same time, many of Trump's actions imposed rather than decreased burdens, including trade interventions like tariffs, anti-dumping and "Buy American" agendas, and domestic regulatory interventions.

So, what was the net effect of Trump's administration on federal regulation? His supporters claim that he deregulated, even if most of his administration's actions were administrative and were rapidly canceled by his successor, Joe Biden. The question is difficult to answer because there is no objective way of measuring total regulation. Still, there are data that can give us a decent picture of Trump's regulatory record.

Regulatory burden / The Trump administration famously introduced a "one-in two-out" goal of abolishing two existing regulations (technically called "rules") for every new one implemented. That seemingly would guarantee the federal regulatory burden would decrease. Yet, a major new regulation may be more consequential and burdensome than two minor ones that have been abrogated. So, what were the results of the Trump administration?

There are some indirect indicators of the level of federal regulation. One is the total number of pages of the *Code of Federal Regulations* (*CFR*), the existing stock of all federal regulations. A reasonable conjecture is that if the regulatory burden increases on net, the number of pages of the *CFR* would increase—and mutatis mutandis if the number of pages decreases. Admittedly, it is a rough indicator.

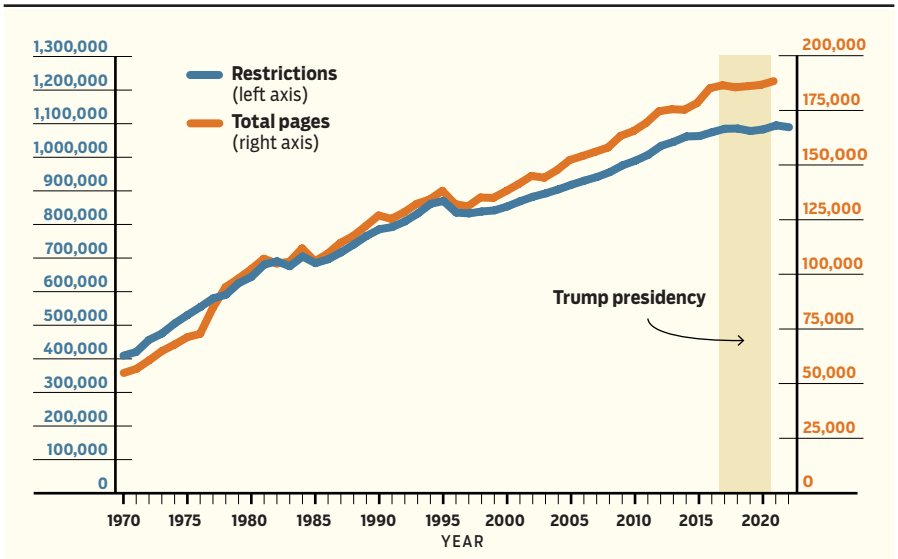
A new and more sophisticated measure of federal regulation, devised by economists at George Mason University's Mercatus Center, consists in counting the number of *CFR* "restrictions" indicated by the keywords "shall," "must," "may not," "required," and "prohibited." Interestingly, both the *CFR* page count and restriction count show a strikingly similar evolution of federal regulation, bolstering our confidence that they provide a reliable indicator of the phenomenon.

Figure 1 compares the two series since 1970. The total number of *CFR* pages, measured on the right vertical axis, was 54,834 at the end of 1970, and 188,346 at the end of 2021 (the last year available). The number of restrictions, measured on the left axis, stood at 409,520 in 1970 and increased to 1,089,462 by 2022. Both measures show a nearly non-stop rise in federal regulation, with only very short periods of deregulation. The two series don't exactly match but show similar bumps in the trend.

Trump's record / These data help us evaluate Trump's claim to be a deregulator. Both indicators show a rough plateauing of the upward trend, with a very small increase between the last year of Barack Obama's administration (2016) and the last year of Trump's (2020). Between these landmark years, the number of pages in the *CFR* increased 0.8 percent (to 186,645), as did the number of restrictions (to 1,083,001). According to both series, then,

Figure 1

Code of Federal Regulations Pages and Restrictions over Time



Sources: (*CFR* pages) Clyde Wayne Crews, Jr., *Ten Thousand Commandments: An Annual Snapshot of the Regulatory State*, 2023 ed., Competitive Enterprise Institute; (*CFR* restrictions) Patrick McLaughlin, Jonathan Nelson, Thurston Powers, Micheal Gilbert, and Stephen Strosko, RegData US 4.0 Annual (dataset), QuantGov, Mercatus Center at George Mason University, 2021.

PIERRE LEMIEUX is an economist affiliated with the Department of Management Sciences of the Université du Québec en Outaouais.

the net effect (new regulations, including deregulatory rules, minus abrogated or simplified ones) of the Trump administration has not been deregulation but, at best, a plateau in the upward historical trend. At best, 0 percent of federal regulation did "go," to use Trump's expression

These data don't include what Crews calls "regulatory dark matter"—that is, instead of formal rules, administrative documents such as executive orders and memoranda and, from different government agencies, guidance documents, bulletins, circulars, etc. The Trump administration had started a process of publicizing guidance documents and recognizing their non-legal character, but the Biden administration stopped that. The conclusion remains that the Trump administration presided over a plateau in the growth of formal federal regulation, not deregulation.

Interestingly, Figure 1 is ambiguous as to the regulatory trend of the Biden administration. So far, the volume of new regulations has been relatively low, but it should soon jump given the administration's ambitious interventionism. Everything points to a decisive return to galloping regulation with less oversight from the Office of Management and Budget. One suspects that a second Trump administration would have followed a similar trajectory, although perhaps not with the same ferocity. R

Examining the SEC's Proposed Order Competition Rule

BY ROBERT BATTALIO AND ROBERT JENNINGS

The market for trading stock in the United States is remarkably complex. As of July 2023, there were 16 registered public exchanges like the New York Stock Exchange, 70 alternative trading systems (ATS) that act like private exchanges, and numerous other entities where equities securities can be bought and sold. Large institutional investors use their own trading desks and the trading desks of investment banks to source liquidity—that is, to exchange stock for money or vice-versa—across this array of choices. Individual investors (i.e., retail traders) typically rely on their brokers to route their orders, matching buyers and sellers with nearly similar bid and ask prices (with the trading platform getting a small payment for its services).

There are economies of scale in the technology associated with this order routing and execution, meaning that the larger a trading entity is, the more cheaply and readily it can match buyers and sellers. Retail brokers have come to rely on a set of electronic marketplaces known as "wholesalers" to execute their customers' liquidity-demanding orders promptly at, or better than, the quoted price. The largest of these wholesalers are Citadel, G1X Susquehanna, Jane Street, Two Sigma Securities, UBS, and Virtu Financial. The Securities and Exchange Commission estimates that over 90 percent of retail orders were routed through those six wholesalers in the first quarter of 2022.

In both historical and absolute terms, retail traders currently enjoy excellent execution quality both in terms of transaction speed and the price at which orders fill. Five retail brokers in the United States stopped charging commissions for equity trades in October 2019. Most other discount brokers did likewise, largely because many of them now charge the wholesalers for the opportunity to facilitate all those trades.

There is abundant empirical evidence that wholesalers offer high-quality executions. SEC Rule 605 requires that execution venues report the execution quality of orders that are routed to them. In 2022, the largest wholesalers' Rule 605 reports showed a $3 billion savings for retail customers from quick execution.

However, because the reports cover only a portion of the orders handled by wholesalers and ignore some important additional services offered by wholesalers, we have estimated that the actual retail customer savings might be five times the officially reported number. The fact that wholesalers offer customer savings that are not officially recognized suggests that the wholesaler market is quite competitive. A 2022 paper by Anne Dyhrberg, Andriy Shkilko, and Ingrid Werner also provides evidence consistent with strong competition among wholesalers.

SEC's proposed rule / Nevertheless, the SEC has expressed concern about concentration in the wholesaler market. In late 2022 it proposed the Order Competition Rule. This rule would all but prohibit wholesalers from immediately filling most orders "internally," meaning from their own inventory rather than submitting the orders to a qualified auction operated by an "open competition" trading center such as a registered exchange. The SEC posits that retail traders will receive better prices if the order is exposed to competition from additional liquidity providers and estimates a current market structure annual "competitive shortfall" of between $1.12 billion and $2.3 billion, yielding a 0.15¢–0.47¢ per-share benefit to the proposed rule.

The SEC has received many comment letters claiming those benefit estimates are heavily overstated. We have a different concern about the SEC analysis: we think it significantly understates the proposed rule's cost.

The SEC used real-world data to infer (with a considerable degree of uncertainty) which public-reported trades result from a retail investor. After identifying alleged

ROBERT BATTALIO is a professor of finance in the University of Notre Dame's Mendoza College of Business. ROBERT JENNINGS is professor emeritus of finance at Indiana University's Kelley School of Business.

retail trades using this algorithm, the SEC estimated how frequently the quoted price would move against the trader during the auction period—that is, the final transaction price would shift (usually just slightly, what is known as "quote fade") from the initial buy or sell orders. In these cases, customers are harmed should the auction fail because they now trade at worse prices than they would have if the auction had not been imposed. The SEC then assumed the cost to the customer is 1¢ per share when an auction fails instead of actually measuring the cost. The expected cost of auction failure is the *frequency* with which quotes move against the trader multiplied by the *cost* when the quotes move against the trader—assumed to be a penny. The SEC concludes that the expected potential cost of failed auctions is 0.046¢ per share, an order of magnitude smaller than the upper bound of their benefit estimate.

Testing the SEC's analysis / We tested the SEC's analysis by using a sample of actual retail orders in May 2022. We found that the potential expected cost per share of failed auctions is considerably greater than the commission's estimate of 0.046¢ per share. It was frequently as large as the commission's lower bound estimate of the proposed rule's benefit of 0.15¢ per share, and potentially greater than the commission's upper bound on benefit of 0.47¢ per share. We estimated the annual cost of the proposed rule to be $1.12–$1.97 billion under the range of proposed auction lengths.

Why did we and the SEC reach such different conclusions regarding the potential cost of failed auctions? The possible reasons are numerous but begin with the fact that we assessed auction failure costs relative to the order-receipt-time quote and not (as the SEC did) the trade-time quote. Although wholesaler trades generally happen quickly after order arrival, quotes also move quickly, which means delaying the measurement of quote fade to trade time diminishes the cost estimate. At the longest proposed auction period (three-tenths of a second), we found that adverse quote changes affect over 20 percent of our actual retail shares compared to less than 5 percent of the SEC's inferred retail trades.

We also measured the actual amount of quote fade (per share) and found that it frequently exceeded the 1¢ assumed by the SEC. Using the Commission's preferred mid-quote benchmark price, the average per-share cost of failed auctions was 31 percent higher than the Commission assumed. If we consider the actual price the retail trader received in the current trading environment, the average per-share cost of the auction is 1.98¢, nearly double the SEC's assumed cost.

Taking the likelihood of an auction failure and multiplying by the associated average cost per share produced an expected cost per share of 0.35¢. In comparison, the SEC's estimated expected cost was 0.046¢ per share, 7.6 times larger. If all the order flow that wholesalers currently execute is forced into the proposed auctions, that would impose a $1.968 billion annual cost on retail investors.

Conclusion / Given our estimates, we are concerned the SEC's proposed rule would fail a cost–benefit test, *even if* the Commission's benefit estimates are accurate. If the SEC is concerned about order quality in wholesalers, we suggest instead that it proceed with another proposal, the Disclosure of Order Execution Information Rule, which would expand execution quality statistics reporting. That would allow market participants to better judge these venues' quality themselves. *R*

READINGS

- "On the Potential Cost of Mandating Qualified Auctions for Marketable Retail Orders," by Robert Battalio and Robert Jennings. *Journal of Investing*, forthcoming.
- "Retail Order Execution Quality under Zero Commission," by Samuel Adams and Connor Kasten. SSRN Working Paper no. 3779474, 2021.
- "The Retail Execution Quality Landscape," by Anne Dyhrberg, Andriy Shkilko, and Ingrid Werner. Working paper, 2022.

Is It Pro-Competition to Make Amazon and Google Less Consumer-Friendly?

BY THOMAS LENARD

The Biden administration's antitrust cases against Google and Amazon both involve remedies that would help competitors by making Google's and Amazon's services less convenient for consumers to use. The antitrust agencies seem to believe that is the only way competitors can develop sufficient scale to succeed.

Amazon's MFN provision / The Federal Trade Commission's Amazon complaint at least recognizes that low prices are good for consumers. In contrast, FTC chair Lina Khan's famed 2017 *Yale Law Journal* article focuses on the effect of Amazon's low prices on its competitors and seems almost unaware that they benefit consumers. The complaint's recognition of the benefits of low prices is a step forward.

THOMAS LENARD is a senior fellow and president emeritus of the Technology Policy Institute.

But consumers aren't just concerned about the list price of an item; they are concerned about the all-in price, which includes transactions costs. The FTC's case against Amazon is essentially about transactions costs. Amazon has adopted a business model that reduces transactions costs to consumers. This model also benefits Amazon, which presumably is why Amazon adopted it. But the FTC alleges that these practices are anticompetitive and would like to do away with them.

LAWRENCE GLASS / ALAMY STOCK PHOTO

The FTC notes:

> By providing sellers access to significant shopper traffic, Amazon is able to attract more sellers onto its platform. Those sellers' selection and variety of products, in turn, attract additional shoppers. More shoppers yield more customer-generated product ratings, reviews, and valuable consumer data for Amazon to use. All of this enables Amazon to benefit from the accelerated growth and momentum that network effects and scale economies can fuel.

If this weren't in the FTC's complaint, one would think it was part of Amazon's defense because it sounds pretty good for consumers—but the FTC doesn't think so.

The FTC believes that "Amazon uses a set of anti-discounting tactics to prevent rivals from growing by offering lower prices, and it uses coercive tactics involving its order fulfillment service to prevent rivals from gaining the scale they need to meaningfully compete." This at least sounds like a complaint rather than a defense. But let's take a look at how consumers would fare in the absence of those practices.

The anti-discounting tactic refers to Amazon's policy that sellers not charge a higher price on Amazon than they do on other platforms. The antitrust concern is that such "most favored nation" (MFN) provisions could facilitate collusion and higher prices. Whether they do so in this case is a proposition the FTC needs to prove and, if so, that the costs outweigh the benefits—notably, lower search costs for consumers. Amazon's MFN provision assures shoppers that the same product is not available at a lower price elsewhere. In the alternative, shopping online for even simple products could be a time-consuming process. Moreover, some consumers might use Amazon to gather product information and then go elsewhere to complete the purchase, which would diminish Amazon's incentive to invest in improving the platform.

With respect to the second allegation, Amazon requires sellers to use Amazon's fulfillment service—which includes inventory storage, packing, delivery, and processing of returns—to be eligible for the popular Amazon Prime service, which comes with fast, mostly free, shipping. The FTC thinks the fulfillment requirement is also anticompetitive, but consider the alternative: Customers would likely confront multiple fulfillment operations with varying reliability, delivery times, and return policies. Amazon would incur costs policing those operations to assure they satisfy Amazon's service commitments—costs that would be passed onto consumers.

By the way, none of Amazon's policies prevent retailers from selling on their own or other platforms or using their own fulfillment services, and many do. But those alternatives are too costly for many retailers.

Google's pre-install contracts / The Department of Justice's case against Google also hinges largely on transactions costs. The government claims that Google's 90 percent share of general search is due to its contract with Apple to be the default pre-installed search engine on Apple devices and similar arrangements with other distribution channels. Because of these arrangements, competitors—most prominently, Microsoft's Bing, which has only a 3 percent share—can't achieve sufficient scale to succeed.

These arrangements are the central issue in the Google case, and their importance depends on switching costs. Google claims it is easy to switch to a different search engine like Bing, and the reason most users don't use it is because Google is the superior product. But if switching is easy, why does Google pay Apple so much money to be the default?

On the other hand, if switching is as difficult as the Justice Department claims, the argument for preinstalling the search engine that most consumers prefer—generally agreed to be Google—is strong. Otherwise, consumers would incur substantial costs switching to their preferred product. Even if installing a search engine is relatively simple, most consumers would probably prefer a phone with the search engine they want right out of the box.

The antitrust agencies should take care their policies do not discourage more user-friendly business models that might make it more difficult for competitors to attract customers and achieve scale. That is not the way to promote competition or benefit consumers. *R*