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COVID-19 Teaches Us the Real Definition of a 'Novel' Drug

Peter Kolchinsky

Peter Kolchinsky, managing partner, RA Capital

Will the world care how we beat COVID-19 – whether with a drug we make from scratch or an older one that turns out to get the job done? As people concerned for our families, we all know the answer. Just get it done!

But as drug developers, let's be honest that it doesn't feel quite as heroic unless it's really novel.

I think we may have developed an unhealthy, facile relationship with the word "novel," looking to it for security against the attacks on our industry that, while deserved by some companies, seem indiscriminate at this point. As if experiencing Stockholm Syndrome, we are on the brink of accepting the public's notion of novelty at the expense of the novelty that really matters.

After years of being ridiculed by Congress, the media, and the public as highly profitable, greedy, and not innovative — merely retweaking old drugs — it's no surprise that the drug industry would want to emphasize all of the incontrovertibly novel breakthroughs of late. Gene therapy is hardly a modest tweak. Neither are RNAi, antibody-drug conjugates, and protein folding correctors. Those who are working with technologies like these can rightfully claim the term "novel" in the most straightforward way most people mean it, which is to say "never before seen" or "had to be developed from scratch."

Many of our industry leaders believe that pursuing such novelty should be the industry's sole purpose. Recall **the letter signed by over 200 biotech CEOs** in January that promised:

> **"We will invest only in novel therapies that address unmet patient needs."**

If indeed we did that, presumably the public would have a harder time claiming that high drug prices are unjustified because the drugs weren't innovative-looking enough, so I can understand the merits of this imperative.

The reality is that the public doesn't actually care about novelty. The public only claims to care, or maybe only *thinks* that it cares. Consider the urgency with which the public has looked to innovators to come up with treatments for

COVID-19. Companies are running new discovery programs and screening for novel inhibitors of various viral components. I have no doubt some of these programs could eventually succeed, but they are far from the market and each faces long odds.

Meanwhile there are already dozens of older drugs, including many generics, being tested individually or in combination for the treatment of COVID-19. Dozens more older but unapproved compounds, like Gilead's remdesivir, that failed in their original indications, are being reheated. If we're lucky enough that any of those programs really can reduce the severity of the disease, keep patients out of hospital, and/or save lives, then the world will have been saved by… **drug repurposing.**

Yes, we could end up saving lives with an old drug that most people wouldn't consider "novel."

Does that mean developing those drugs for COVID-19 will have been easy? No. Without risk? No. Inexpensive? No.

Will it matter to the people whose lives are saved and to everyone who will be able to come back to work once the pandemic is resolved that their salvation wasn't "novel"? It absolutely shouldn't, though some of the harshest critics will never be satisfied, but the vast majority of people would be grateful. And certainly all of us in the drug industry should know better than to denigrate a COVID-19 treatment simply because it didn't require inventing a new drug from scratch. We should be so lucky.

COVID-19 might just leave us with a novel definition of the word "novel" that we've long needed. Specifically, all anyone should care about is whether we've addressed an unmet need. That's what society should reward, and that's what our industry should commit to doing.

Whatever therapy or intervention solves a previously unmet need is inherently novel. Any treatments for COVID-19, that turn out to work will be "novel" in every way that matters.

For many in our industry, swearing by novelty is a means of, let's say, #socialdistancing themselves from notorious drug companies that the public reviled for charging high prices without engaging in almost any actual drug development. Here I'm thinking of the Marathons and Belchers of the world, which, seeing no competition from altruists, stepped up to earn high rewards for doing low-risk paperwork the FDA needed someone to do.

Though they make for bad press, we mustn't overreact to these fringe cases. If we feel that the few outliers like this are a stain on our names, we should push for reforms that empower the FDA to contract with a nonprofit to, for example, get a foreign generic drug licensed, labeled, and marketed in the US at a low price so patients don't have to illegally import it. Turning our noses up at Marathon and Belcher just because their work didn't seem novel enough to merit a high price is not only unproductive, the unintended consequences could be counter-productive.

Here's the harm of committing to "novelty" at all costs. Imagine if a company suspected it could repurpose a low dose of an old generic HIV drug combined

with an old generic epilepsy drug to treat a different neurological disorder. They know the combination would likely be safe because the drugs, as single agents, have already been in millions of patients. Yet studies would still need to demonstrate efficacy in the new indication and determine proper dosing limits. But the company would worry that payers, enjoying the support of a jeering public conditioned to denigrate anything that isn't clearly novel, will refuse to pay for this combination drug. The company might fear that insurers would tacitly nudge physicians to prescribe the old generic drug components together, failing to reward the company that invested significant time and money in teaching the world about the medical value of this new drug combination. Would it risk the ridicule and financial uncertainty of repurposing these generics?

Or would it instead develop an entirely new molecule that does the same thing? That would take longer and be riskier. The final product would have a high price, and payers might resent having to pay, but at least no one could say that the product wasn't "novel" in the conventional sense.

What would patients want? A safe and effective treatment they can afford. In other words, for insurance to pay for whatever works. So what should society want? The same.

To the extent that the public, the media, and Congress are concerned about novelty, it's because it's a litmus test for whether they think an innovation deserves to be rewarded with a high drug price. The corollary is if it's not novel, then calls for price controls are fair.

The public, the media, and Congress are outraged over drug prices because many patients can't afford the treatments they need. Unfortunately, society has collectively misdiagnosed the reasons drugs are unaffordable. It isn't systematic price gouging by drug companies (the industry's profit margins are too modest to tolerate even a 20% cut in US drug prices); it is, has always been, and continues to be America's terrible insurance coverage. While many Americans do have good insurance and can afford their copays, some are crushed by their out-of-pocket costs, and ~15% of Americans have no insurance at all. Nothing about healthcare is affordable without insurance.

If there were ever an illustration of how stupidly counter-productive America's health insurance designs are, recall the people who dutifully reported for COVID-19 testing and were sent home with massive bills, deterring others from seeking testing at all. They went home, or back to work, and unwittingly started spreading the new coronavirus. And even when ordered to cover COVID-19 testing, some payers interpreted that narrowly, sticking patients with bills for necessary but ancillary tests, such as those for flu, that doctors would order to help them interpret COVID-19 testing results. We all see the absurdity of that because we know that testing is essential for our collective public health. We're outraged that payers, as our chosen agents for making appropriately-prescribed care affordable, are deterring healthcare that is essential for the public health.

But what's true for COVID-19 and for testing is also true for all diseases and all treatments. And while it's not as obvious as with COVID-19 coverage, affordable healthcare for all diseases for any individual is also a public health

issue for all. When payers don't cover insulin well enough for patients to afford it, then some will ration it and suffer. Later, when they go blind because they couldn't afford to manage their diabetes, the added cost of that care is unavoidable. Yet so much individual suffering and societal cost could have been avoided had the insulin been covered properly by the insurer in the first place. It's an example of being penny wise, pound foolish.

So let's recognize that the pressure that we as drug developers feel to only develop and charge for what society agrees is "novel" is really an outcry over two things.

First, we need proper insurance to make all appropriately-prescribed drugs affordable for everyone. Second, the pharmaceutical industry should only develop and charge America high prices for products that solve problems that are still unmet by all the known uses of our existing armamentarium of generic drugs (which, with few exceptions, it already does – just consider how impossible it would be to even run a trial for a new drug that aspired to be no better than a statin).

Society doesn't want anyone playing games with REMS programs to price-jack an old, off-patent drug for the same old use, as Turing notoriously did with Daraprim. But the public does want biosimilars. By design, those aren't novel, but they will bring down drug prices. The public doesn't want companies exploiting ASP+ loopholes in Medicare Part B reimbursement to enjoy high revenues from branded drugs that are undifferentiated from generics. But it does want fast-followers (aka me-too drugs) in new classes that offer a greater variety of treatment options and drive price competition, as has happened with PCSK9s, SGLT2s, GLP-1s, CGRPs, and and many of the other acronyms we've ever drugged. Consider that America would have enjoyed greater negotiating power and discounts from Humira had there been a comparable me-too; developing competitors to branded drugs should be encouraged, not shunned by a commitment to "only invest in novel therapies."

So what should we as an industry commit to so that it shows that we are aligned with what society really wants and deserves from us?

I propose this:

> **We will invest in drug development to address healthcare needs that are not yet met by the known uses of generic drugs.**

Some might not find this satisfying because it doesn't include the word "novel," which the public likes to hear. Yet this statement captures everything we are doing to solve COVID-19 as quickly as possible, including new drug discovery and old drug repurposing.

And this statement applies to all of drug development for all our remaining unmet needs. Whether that means we will repurpose an old drug for a new use, reformulate an old drug to make it safer or more effective, invent an entirely new drug, or launch a similar competitor to another branded drug, it's all in the public's interest.

As long as all Americans are properly insured with affordable (or no) out of pocket costs, they will all be able to get the care they need. And as long as all

those drugs go generic without undue delay — which means patents expire when they should, and aren't extended through patent gamesmanship — then America and the world will be getting value for its money. I've written elsewhere, including a book, proposing specific reforms to shore up genericization for all drugs that would spur innovation.

So let's either retire the word "novel" or at least resist the urge to cave to the public's old notions of what it means. The COVID-19 crisis has primed the public to appreciate both the value of having an armamentarium of approved drugs and the benefits of searching for new uses for them. Let's therefore learn together to see all solutions of important unsolved problems as "novel, in every way that matters."

Peter Kolchinsky, a biotechnology investor and virologist, is Managing Partner of RA Capital Management, L.P., and author of **The Great American Drug Deal**.

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