Rachel Sachs
The pace of genuine scientific progress is remarkable. We've talked about GLP-1s, gene therapies. These are incredible scientific advances to be able to have one-time treatments for conditions that used to mean a lifetime of chronic disease management and that's really giving me hope for thinking about addressing some of these health needs that patients have.

Ellen Kelsay
That's Rachel Sachs, Professor of Law at Washington University in St. Louis, and one of the nation's leading experts on drug pricing, policy, and innovation. Her research examines how these factors shape the medicines that are developed and the prices that patients and purchasers ultimately pay.

I'm Ellen Kelsay, and this is the Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers.

In today's episode, we step back to look at the full life cycle of a drug, from the earliest stages of research to FDA approval, market launch, generic competition, and the policy decisions that influence innovation and access along the way.

Rachel, welcome to the podcast. So happy to have you with us.

Rachel Sachs
Thank you so much for having me.

Ellen Kelsay
Well, we are here today to talk about an important topic. Many of us know that healthcare costs and affordability concerns are well known and seemingly growing more acute by the day and pharmacy costs are a key driver of overall healthcare spending. While prescription drug affordability and access are certainly top of mind for employers, many of the issues driving those conversations begin years before a drug even reaches a patient. Let's help set the stage and start at the beginning. Essentially, when a drug does get its patent, can you share with our listeners what does a drug patent cover?

Rachel Sachs
Of course. We generally talk about patents as temporary government-granted monopolies. If a patentee meets the relevant statutory requirements, and they publicly disclose their invention, then the U.S. Patent and Trademark Office, the PTO, gives the inventor the exclusive right to make, use, or sell that invention for a period of time. Today, that's 20 years from the date of filing. At the end of that time, the information disclosed in the patent becomes usable by others. Now, as applied to the drug context, maybe a couple of key points to note here. One is that a single drug is usually covered by more than one patent. So for small molecule drugs, which you might think of as the pills that you pick up at the pharmacy counter, they might be covered by a handful of patents. But for biological products, some of these complex molecules that are injected or infused for the treatment of autoimmune diseases, cancer, etc., the recent evidence that we have suggests that they're covered by many more patents, on average over 20, but a small number of them are covered by more than 100 patents. So when people talk about the patent on a drug, they're often really talking about this portfolio of patents that can expire on different timelines. Then one related note here is that patents are not the only form of exclusivity a pharmaceutical company might benefit from for any particular product. The Food and Drug Administration, FDA itself, awards exclusivity periods that start on approval of a particular drug, and they're tied to the

drug itself rather than some element of the drug, and they can run concurrently with any patents that exist.

Ellen Kelsay
There's a lot of technical nuance to this and I want to start with maybe an aspect of research and development. We know that that often is a lengthy part of the patent process and many drugs don't even make it through that. Please explain what a typical R&D process looks like.

Rachel Sachs
Sure. As you said, this is very technical. It can be very detailed. This question about a typical R&D process is so important for understanding some of these downstream questions about pricing and access. Drug development is expensive. It has a high failure rate. Now development timelines and costs, they can vary depending on the types of products. But in general, we typically say that we start with drug discovery and preclinical research. So a scientist, sometimes in academia, sometimes in a small pharmaceutical company, sometimes in a big one, will identify a candidate drug compound, and they'll test it, often in the lab, maybe in animals for years before it can enter human trials. But if that looks promising enough and safe enough, then we move into human clinical trials in which the typical process might have three phases. We say phase one is usually a small trial and healthy volunteers and we're focused on safety and dosing. Phase two, we expand to more patients. We're looking at effectiveness and side effects. Then phase three trials for some diseases can include thousands of patients to generate the evidence FDA wants to decide whether or not this drug is safe and effective in the relevant population. This whole process can take a decade and sometimes more. Now the failure rate, as I noted, is also high. So most drug candidates that enter clinical trials do not make it all the way to approval. Then for funding, we have this combination of public and private investment. So public funding plays a particular role in this basic research, in this early-stage research. One recent study found that funding from the National Institutes of Health, or NIH, contributed to over 99% of drugs that were later approved by FDA. So even though later phases are largely supported by private industry, private companies, this mixed public-private funding structure matters a lot to current debates about things like the stability of the NIH, given recent grant cancellations and decreases in funding of new products.

Ellen Kelsay
You mentioned the high failure rate. Assuming a drug actually does make it through and it is time for them to apply for FDA approval, what are some of the key things that a drug needs to demonstrate in order to be approved?

Rachel Sachs
Yeah, basically the FDA approval standard asks a company to show that its drug is both safe and effective for its intended use. They're looking for substantial evidence of effectiveness from adequate and well-controlled clinical trials. A couple of points to flag here. So first, safe doesn't mean that there are no risks or no side effects. What it means is that the benefits outweigh the risks for the intended patient population. So a cancer drug might have significant toxicity, but it could be approved if it is also effective in treating the cancer it's intended to work against. There are some common misconceptions or some questions people sometimes have about FDA. For example, FDA isn't always evaluating whether a drug is better than existing treatments. They're not necessarily looking at comparative effectiveness and they're not looking at whether a drug represents good value for our healthcare system. They're not looking at the cost-effectiveness of the product. We also have a number of accelerated pathways that companies can use for certain types of drugs that are intended to treat serious conditions or unmet medical needs. These have names like accelerated approval, breakthrough therapy, priority review, and they can help manufacturers reach the market faster for some of these products.

Ellen Kelsay
You mentioned a couple things there that I do want to double click on because I think a lot of people would probably be surprised to hear the point you just made about FDA not looking at things like comparative effectiveness relative to other existing drugs or the value a new drug may or may not bring to the ecosystem overall. Elaborate there, why is that a role that the FDA does not play?

Rachel Sachs
Focusing maybe on your second question about cost and cost-effectiveness, FDA's statutory mandate is to figure out whether these drugs are safe and effective. They're not asked to look at whether they represent good value for money. Internationally, that's not a role that we see pharmaceutical regulators play. That question is typically one that health technology assessment bodies, that insurers or insurance regulators or pricing regulators play once a drug is approved. We sometimes talk about FDA caring about things that are adjacent to cost. For example, FDA is instructed by Congress to care about competition. They're interested in this question of generic approval, biosimilar approval, but they're not specifically instructed to care or worry about cost. And we typically don't know what the price of a drug is before it's approved.

Ellen Kelsay
We're going to get to that in a minute, don't worry. Question on the comparative effectiveness. There are many drugs out there that treat very similar types of conditions. Why is that not a part of the calculus? I guess it probably goes back to what you've said a little bit, but anything more that a consumer might want to know about that?

Rachel Sachs
Yeah, some of it is again about FDA's statutory authority. They're instructed to look at a drug's safety and effectiveness. Congress has not told them to conduct head-to-head trials for approval. Sometimes it's a timing issue. So if you mandated comparative effectiveness trials for new drugs, it might increase the time, the complexity of new development. Some of it is about the historical development. So these products are sometimes moving through the clinical trial process at the same time. There's a new scientific breakthrough that leads to a new pathway, and multiple candidates are moving through the process at once. From a timing perspective, it's not clear that they could be tested against each other in the same way. There's a number of reasons why FDA doesn't look at these questions, but they're very important ones that clinicians and patients and insurers want information about in order to be able to determine things like, what's the place and therapy of this product? Which product should we try first? How do we know if this drug has more or fewer side effects than this other drug where the clinical trial was designed very slightly differently? It's something that a lot of people are trying to figure out how do we encourage the development of more of this comparative effectiveness information?

Ellen Kelsay
Well, and clearly as you've already illuminated, there are many hurdles in order for a drug to come to market. You've talked about the patent, the R&D process, FDA approval. And often, once a drug does receive approval by the FDA, there's still many times a gap between when that drug is available in the market. What's happening during that time, that gap period between FDA approval and a drug actually launching and being available?

Rachel Sachs
Yeah, there's a number of things happening, some more on the business side, some more on the legal regulatory side. As you noted, FDA approval is necessary, but it's not always sufficient to get

the drug to the patient who needs it. Some of what's happening is logistical. The manufacturer is making sure they've scaled up their manufacturing to commercial volume. But the company is also figuring out how to price the drug, how to negotiate with insurance companies, with pharmacy benefit managers, or PBMs regarding coverage. They will have negotiations about price, but also non-price coverage terms, formulary placement, etc. On pricing, we sometimes say that manufacturers charge what the market will bear. The U.S. does not regulate manufacturers' launch prices. The companies set those prices based on a whole range of factors, but including things like therapeutic context and expected reception from payers. You might think that insurers would push back hard if launch prices appear to them to be too high by refusing to cover the drugs, but they often have fairly weak bargaining leverage, at least for our public payers, because FDA approval is often directly linked to coverage obligations.

Ellen Kelsay
Okay, this is probably where our audience has a lot of reaction, a lot of questions that they're thinking about as they're hearing us speak. You mentioned manufacturers can charge what the market will bear and I started our conversation about healthcare costs and affordability concerns looming large, and that pharmacy costs are a growing driver of overall healthcare spending. Anything more you would share about how drug prices are set and key influencers in that process? I think many people would say that the market can no longer bear what is being charged. So anything else that you would like to bring to light?

Rachel Sachs
Yeah, one core challenge for academics, but also for policymakers, is that a lot of the information we would want to really make policy much more evidence-based is not transparent. We talk about prices, but which price are we talking about? The manufacturer might set the list price, but that's not always the price that's paid. Sometimes there's a really big gap between the list price and the net price that ends up being paid for the product, and that net price results from, exactly as you suggested, this series of transactions, sometimes involving intermediaries. So you have manufacturers, you have PBMs, you have insurers, but you may also have wholesalers or GPOs or other types of organizations, sometimes clinicians, right, involved as intermediaries. Those negotiations, those transactions are taking place against a backdrop of legal rules, but also against certain types of market realities.

Ellen Kelsay
That's very helpful. Probably still not fully satisfying to a lot of our listeners, but helps explain a bit of the conundrum. Okay, so let's talk about now, once a drug has been on the market for a while, and fast forward, the patent has expired, typically we see that generic competition enters in. But we also see that in some cases, manufacturers can pursue further exclusivity. What does that look like?

Rachel Sachs
Yeah, this is one of the key policy issues that's been debated for quite some time and is still definitely a subject of live contestation. As we've talked about, the core patent, usually on a drug's molecule, expires around 20 years from filing. But companies have developed a range of strategies to extend their effective market exclusivity. One is, they can file these secondary or follow-on patents on things like new formulations, new uses, new dosing regimens, etc. And individually, these may be legitimate incremental innovations, but collectively, if a company files dozens or hundreds of these applications around a single product, we sometimes refer to what results as a patent thicket. It's this cluster of patents that any generic or a biosimilar competitor has to navigate or challenge before they can enter the market. Humira is the canonical example a lot of scholars point to. It was protected by well over 100 patents and biosimilars didn't reach the

market in the U.S. until several years after they had already launched in Europe. But there's real debate here about what is the line between important follow-on innovation. If you have a genuinely better formulation that's valuable to patients, to clinical care, and more strategic evergreening that's designed to delay competition. There's a number of bills in Congress and other policymaking efforts that are attempting to address this question.

Ellen Kelsay
I definitely wanted to ask you about this, about where is that line, and a lot of some of the more recent lawsuits that we've been seeing, you've mentioned some related to patent thickets. We've also seen some related to skinny labeling. Could you describe first what is skinny labeling and then what are you also seeing as some of these actions are being brought forward in the courts?

Rachel Sachs
Sure. I think one underlying theme of your question is there's a lot of different strategies that both branded pharmaceutical companies and generic pharmaceutical companies try to use to protect their exclusivity and also to come to market. One of the recent areas of contestation in the courts is this approach called skinny labeling. Sometimes a brand name drug can have multiple FDA approved uses and if the manufacturer has applied for patents in this serial way, where some of the uses may be protected by patents that expire earlier and others may be protected by patents that expire later. The Hatch-Waxman Act, the federal statute relating to generic drug approvals, it allows a generic company to seek approval using what we sometimes refer to as a skinny label. They can omit the patent protected uses from the labels for their generic product and enter the market earlier. I will not go into the details about why the statutory provision is necessary, but it means that there is a pathway that Congress created to enable generic manufacturers to market their drugs for only these unpatented conditions and carve out the patented ones from their label. Recently there has been a number of challenges brought by branded manufacturers who attempted to claim that generic manufacturers were liable for patent infringement on a theory relating to physicians prescribing the generic for the patented or carved out uses anyway. There was very recently a Supreme Court case which, I'll say, limited the potential liability of generic manufacturers in this case. Not to say that they can never be liable, but the brand has to prove certain things about what the generic company did or encouraged through their own statements. It has to be something more than the requirements in the label. But this is certainly an ongoing area.

Ellen Kelsay
Yeah, for sure. Well, thank you. That was helpful for you to break it down the way that you did. You are highly prolific. You write, you speak, you've testified before Congress on all of these issues and you talk about the path forward being one of, you know, a myriad array of potential avenues that all need to happen and it's not just one thing and there is no quick fix. One of the things you talk about is the importance of competition and it being one of the primary ways to reduce drug prices. Where do you think that competition is both effective at reducing prices and where does it tend to break down or not be as effective as we'd like it to be?

Rachel Sachs
Yeah, yeah. When it works, generic and biosimilar competition are some of the most powerful tools we have for decreasing prices and enabling broader patient access. In the small molecule generic drug context, we know that when multiple generic manufacturers enter the market, prices can fall to a small fraction of the original branded drugs price, 80 to 90% or more. For biosimilar competition to date, it has produced smaller discounts than generics do for small molecules, but it's still meaningful and in some cases, very meaningful. I think there's a lot of optimism that we can increase biosimilar competition with certain statutory or regulatory

changes. But as you noted, competition isn't always effective and it can break down in different places for a small molecule generics versus for biosimilars. For small molecule generics, FDA approval really is a key bottleneck. Once a generic is FDA approved, pharmacists can substitute it for the brand automatically at the pharmacy counter under state substitution laws, and competition tends to accelerate fairly quickly. That's one reason why we continue to talk about things like patent thickets, secondary patents, or other approaches that branded drug companies may use that have the effect of delaying generic launches. So if you can delay the generic launch, you don't get that downward pricing pressure, the brand can retain its market share. But for biosimilars, the challenge is a bit bigger and more complicated. We do have some of these similar challenges with FDA approval. But for biosimilars, just because you get FDA approval, that hasn't translated as directly into the kinds of price decreases we've seen in the small molecule generic context. We need insurers to decide to cover these biosimilars. In many cases, we need clinicians to decide to prescribe them. In many cases, biosimilars are not automatically substituted or even substitutable yet, like generic. So reform efforts for biosimilars that focus on approval are important, but they also need to focus on some of these other steps in the process as well.

Ellen Kelsay
In addition to competition, you mentioned at the top of our call, some of the challenges regarding the opacity of information. If you could call forward a couple areas of opportunity when it comes to increasing transparency in the context of this conversation, where would you advocate for that to occur?

Rachel Sachs
Oh, it's really hard to pick just a couple. As a law professor, I'm mostly focused on these complex legal documents, the statutes, the regulations, the guidance documents that are impacting the development of these products, but also the legal landscape against which that is occurring. You might get a different answer if you asked a health economist or a health services researcher, but one of these related questions here is about transparency across the system. Because there is so much siloing, so much fragmentation in our healthcare system between commercial, Medicare, Medicaid, you know, Affordable Care Act plans, there are different prices being charged or being paid by different payers all across the system. Having more visibility into what are those prices and how are they being passed on along the supply chain can be valuable, particularly for your listeners, and maybe enabling them to ask questions about why are they paying these certain markups on a particular specialty generic product or their negotiated price for a branded drug is higher than the price that Medicare may have negotiated in a recent drug price negotiation effort. I did work in the Biden Administration working on implementing some of the Inflation Reduction Act's Medicare drug pricing reforms. Transparency around these issues can be helpful, but different points might be helpful to different types of actors. What might be useful for your listeners might be different than what might be useful to me as an academic or policymakers.

Ellen Kelsay
Clearly, I mean, I think we've covered so many aspects of the dynamics of drugs coming to market and pricing and the different stakeholders that really do influence the outcome of how and which types of pharmaceuticals actually get developed. Is there anything that we haven't talked about relative to that that you would like to share that might be useful for the audience to be aware of?

Rachel Sachs
I think one note I would have is that these different areas of law and policy and incentives, they all relate to each other. This incentive structure for how much are we paying and for what products, it certainly affects price and access, but it also shapes these incentives to develop pharmaceuticals in the first place. So FDA approval pathways, patent availability, reimbursement, they all impact

not just innovation and access, but both sides of these at the same time. That makes it particularly interesting to work in this space, but it's also very complex. My goal as an academic is to think about the relationship between these spaces and make sure innovation is being calibrated into spaces that are beneficial for patients, but also that they can afford these drugs once they're developed.

Ellen Kelsay
What would you say are the most important pricing or policy developments that employers should keep on their radar for the next few years? I mean, certainly there is a lot going on and a lot for them to maybe be aware of when you think about employers and employer plan sponsors who are providing benefits related to drug coverage for their workforce and covered family members. Anything on the policy or even the market landscape horizon that you think are especially notable for employers to be aware of?

Rachel Sachs
Sure, sure. Maybe I'll say two and a half things. One, in response to your comment that there's a lot going on, that is certainly true. Drug pricing law and policy is actively evolving right now. This is in part because of legislative efforts through things like the Inflation Reduction Act, the Medicare drug price negotiation program, but also executive branch actions that are currently being taken, and also efforts by state governments. There's a whole range of ways that different actors are attempting to change policy in this space, and they might all interact with each other in complex ways that could have implications for employers. A second one is, and I think this is a perennial topic, is how to pay for high-cost drugs. Drugs can be high cost because the market is very large or because the individual cost of the therapy is very high. I know there's a lot of focus by your listeners on things like GLP-1s. Utilization keeps going up, these pricing structures can be changing quickly, and exactly as I mentioned, some of these new federal approaches are reshaping the payment landscape in ways that can spill over to employer coverage. But then also something like gene therapies, which can be quite unpredictable, these very large one-time costs, that can also be a major sticking point for employer plans. Then the last one is this question of price transparency or a broader direct-to-consumer or DTC pricing environment. These are obviously related to each other. So one question is whether the DTC push can lead to things like more direct-to-purchaser contracting. If you think about something like GLP-1s, where we now not only have these sort of published cash prices, but also a published negotiated price through Medicare for at least one of the products, how does that enable employers to negotiate differently with either manufacturers directly or with their PBMs, depending on what prices are being paid for these products?

Ellen Kelsay
The DTC space is a fascinating one to be watching and it seems to really be exploding just even in the past year or so. Fascinating to see how that continues to evolve. And again, the implications for all the stakeholders, for consumers, for employer plan sponsors, and then also are their unintended consequences of that too in terms of access and inequities of people who can get that and others who can't. A lot to watch in that space in particular.

Rachel Sachs
To your point about unintended consequences, there are some efforts to push more decision-making down to the patient level, the beneficiary level, to ask them to make decisions that are price conscious, that help them think about where to spend their money more effectively. But we're asking a lot of patients under some of these situations. It's not clear to me that patients always understand some of the complexities involved and whether they can use their insurance as part of some of these DTC programs, or whether even if they understand they're making an out-

of-pocket cost here, that they're not progressing through their deductible or into certain phases of their benefit. A patient could easily end up paying more through some of these DTC programs than by going through their insurance. But that's a really difficult thing to ask them to figure out, especially at a moment when they might have a new diagnosis, they might be under a lot of pressure and health-wise, family-wise, whatever it might be. Thinking about who are the actors in the system who can help people, employers, patients, make informed decisions is a really tough part of this process.

Ellen Kelsay
All right. Well, I would love to close with kind of a note of optimism. We've talked about how things are really complicated in this space and it is very technical. There's a lot of unbelievable innovation that is happening. As you said, it's kind of a very frothy, interesting time from a policy perspective. When you kind of step back and look at all of that, what are the areas that give you the most hope as you think about the future of drug development and pricing?

Rachel Sachs
Yeah. On the development side, I think to your point, it's really the science and the scientists. I spend a lot of my time thinking about the legal issues here, patents, reimbursement rules, FDA approval pathways, and we have to get that right to provide incentives for development of these products. But underneath all of that, the pace of genuine scientific progress is remarkable. We've talked about GLP-1s, gene therapies. These are incredible scientific advances to be able to have one-time treatments for conditions that used to mean a lifetime of chronic disease management. That's really giving me hope for thinking about addressing some of these health needs that patients have. On the pricing side, the glass half full version of the story is that there is so much energy being directed at this topic right now from so many different directions. There's bipartisan interest in increasing biosimilar competition. PBM reform recently became law. None of these alone solves the whole problem because of the complexity of the development process, the supply chain, and then the ability of different actors to evolve beyond some of the practices that used to be prevalent in industry, but the fact that policymakers in multiple locations and government and in industry are all actively engaged with this issue is really important.

Ellen Kelsay
Rachel, thank you so much for taking what is a very highly fluid, highly technical, extremely complex issue across a wide array of stakeholders and breaking it down for our audience in layperson's terms. So just greatly appreciate your time and expertise and sharing it with us in conversation today. Thank you.

Rachel Sachs
Thank you so much for having me. This is such an interesting conversation.

Ellen Kelsay
I've been speaking with Rachel Sachs about how the life cycle of a drug is shaped by a series of policy, regulatory, scientific, and market forces, all influencing not only the availability of treatments, but also the incentives that drive future research and competition.

I'm Ellen Kelsay, and this podcast is produced by Business Group on Health, with Connected Social Media. If you like this episode, please rate us and leave a review.