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xconomy

Hepatitis C Commercial Game Theory

Peter Kolchinsky | 1/1/15

Anyone either celebrating or fearing the start of a Hepatitis C drug price war should take a break from the excitement to consider that a far more nuanced and profound game is at hand, one where the rules of tacit collusion (the legal kind) constrain price erosion—and each new entrant with a "good enough" drug regimen can take a reasonable share with modest further discounts.

In this game, in which patients can be cured even if they are not taking the most convenient or best tolerated regimen, being the best is not particularly relevant. It takes many qualifying entrants in the market before "gentlemanly" conduct turns chaotic and prices fall rapidly, a process that can be slowed by consolidation.

AbbVie's (NYSE: ABBV) Viekira Pak, a combination regimen that was just approved by the FDA to treat chronic hepatitis C virus (HCV) infection, emerged with a list price only 10 percent lower than the $94,500 list price for 12 weeks of Gilead Sciences' (NASDAQ: GILD) sofosbuvir-ledipasvir combo pill (Harvoni), though some patients only need to take Harvoni for 8 weeks. Although AbbVie and Gilead offer regimens with comparable cure rates, AbbVie's is less convenient and less tolerable for the patient than Gilead's: Viekira Pak requires more frequent dosing, involves more pills, has more complex drug-drug interactions, and has more side effects than Harvoni.

Despite the disadvantages of its regimen, AbbVie just secured exclusive formulary status from the pharmacy benefit manager Express Scripts (NASDAQ: ESRX) that covers tens of millions of patients in the U.S. In the deal, Express Scripts negotiated an undisclosed discounted price for Viekira Pak. By effectively removing Harvoni from the formulary, Express Scripts is forcing physicians to choose an inferior, yet "good enough" regimen. Thus, one important lesson from the AbbVie-Express Scripts deal is that the bar for qualifying as a new entrant in HCV is not as high as people think. Regimens that match or exceed the profile of AbbVie's Viekira Pak are also "good enough," and should be able to compete on price.

The rules of civilized price competition dictate that AbbVie can only offer a winning price discount to some payers, but not all, giving it only some of Gilead's market share. In turn, Gilead has to let it happen. If Gilead cuts its price to take back the share it will lose to AbbVie, that would only trigger another round of discounting, cascading into a much anticipated price war.

In a kind of "ultimatum game," Gilead must yield some market share to AbbVie to keep AbbVie from dropping its price further. Likewise, AbbVie cannot try to grab Gilead's entire market share, or Gilead will respond with price cuts of its own. Predicting the fraction of the market each company will end up with is difficult, but a 50/50 split is unlikely. AbbVie may be content with less, especially since it likely wants to preserve pricing until it brings its more competitive next-generation regimen—which would likely still be a bit worse than Harvoni—to market. Were the U.S. a single-payer system, like the U.K., dividing the market would be impossible. But the U.S. is a fragmented market with a few large formularies (Express Scripts and CVS Caremark) and several medium and small ones; therefore, Gilead and AbbVie can split the market in a "gentlemanly" fashion. This phenomenon of neither player wanting to spark repeated rounds of discounting is called "tacit collusion," and it is legal. The practice would only potentially violate anti-trust laws if the players communicated and coordinated their pricing plans.

The emergence of additional players in the HCV market, like Bristol-Myers Squibb and Merck possibly in 2016 or 2017, will force Gilead and AbbVie to make room for more new entrants. To compete, Bristol and Merck do not need to have the best drugs; they just need to be "good enough" (i.e., well-tolerated, oral dosing for 12 weeks or less, with greater than 90 percent cure rates). Each company's debut may trigger a single round of discounting to establish the new market share equilibrium, but each party will do its best not to accidentally over-elbow the others into a frenzy of price discounts. Based on what is known about their compounds, Merck's regimen could be comparable to Gilead's, requiring only 8 weeks of dosing for most patients, while Bristol's regimen may be more like AbbVie's, requiring 12 weeks of dosing. All, though, should fall within the "good enough" spectrum.

Others are coming. Achillion Pharmaceuticals (NASDAQ: ACHN) is a small company with four HCV drugs in clinical development; it is working on a combination regimen that could come to market by 2018, maybe a year behind Merck. Even if all known HCV patients sought treatment today, due to capacity constraints and the large pool of undiagnosed patients, there will still be millions of people who

need treatment in 2018. That makes HCV a substantial and long lasting market worth fighting for. And that's even if treatments are priced at a half, or a third of the cost they are today—especially if, given the deflation expected to occur over the next few years, payers continue to drag their feet on enabling widespread access to treatments.

Therefore, by 2018, barring consolidation among these companies, there will likely be five "good enough" regimens—and potentially more—competing for a slice of a still very large pie. Other companies, notably Johnson & Johnson (NYSE: JNJ), are still working on combination treatments, but may fall short of qualifying for "good enough." And then there's Regulus Therapeutics (NASDAQ: RGLS), whose subcutaneously injected antisense drug, RG101, is showing signs in early studies that after giving a patient a single injection, a physician might only need to prescribe 4 or 6 weeks of even moderately effective oral drugs—including those that might not be considered "good enough" on their own—to ensure a very high rate of cure for patients.

Before elaborating on Achillion and Regulus, I'll pause briefly to disclose that the fund that my colleagues and I manage holds positions in both companies. We built these positions in part because of our conviction in the analysis of the HCV landscape presented here; we could certainly be wrong. While these arguments stand on their own merits and represent my views, if I, as a professional investor, held such views without owning stock in these companies, readers should question my sincerity.

While tacit collusion could potentially keep prices from eroding when there are two, three, and maybe even four players, having five or six players might just bring about a true, chaotic price war. Clearly, Gilead, AbbVie, Bristol, and Merck have the most to lose from Achillion and/or Regulus coming to market; game theory would dictate that the larger companies would just buy out the smaller ones to avoid the risk. Arguably, any other company could achieve a dominant position in the HCV arena by buying both Achillion and Regulus. Their combined market capitalization is currently $2 billion—therefore, paying even a 100 percent premium would cost little more than the $3.85 billion Merck paid for Idenix Pharmaceuticals earlier this year. Wouldn't it be interesting if a company out of left field like Alexion Pharmaceuticals (NASDAQ: ALXN) acquired Achillion for its Factor D inhibitor to protect its flank in complement disorders, while gaining a highly valuable HCV franchise in the deal?

Ordinarily, a match between an orphan disease company and the HCV market would not make sense, but the qualifications for competing in HCV are both modest and attainable for any company with enough resources and agility; therefore, the list of potential suitors is longer than you would expect.

There is some evidence that many investors and analysts are still operating under the impression that only the best drug can win. On the same day that AbbVie-Express Scripts deal was announced, Achillion released data from its HCV pipeline. Whether the data were good enough for Achillion to be competitive was subsequently debated, with most of the commentary focused on whether Achillion's nucleotide polymerase inhibitor, or "nuc," ACH-3422, had the same hallmarks of efficacy and safety as Gilead's and Merck's nucs. In a phase I trial, Achillion's nuc took a few days longer than other nucs to knock down comparable amounts of virus, which some interpreted as an inferior outcome. Achillion's nuc is just one of four HCV drugs that the company has in the clinic that it plans to combine into an effective regimen. Demanding that Achillion's nuc tie for first place within its drug class fails to acknowledge the lesson from the AbbVie-Express Scripts deal—the bar for getting to the market and competing on price is having a combination regimen that is "good enough."

Whether Achillion's regimen is better than Merck's or Gilead's is simply not that important. Achieving a 6-week cure is certainly a nice objective and indeed possible, but to get in the game, Achillion just needs to qualify with a regimen that cures most patients in 8 to 12 weeks, a modest goal by comparison that now looks highly probable. With a valuation that is 99 percent lower than Gilead's, Achillion could exceed expectations by taking even a modest 10 to 15 percent of the market, which is not unreasonable in a 5-player field.

If Achillion does emerge with a regimen that is better than AbbVie's and Bristol's, neither of which have a nuc, then these fourth and fifth place players may become unsatisfied with their market share and think about more price cutting to maintain exclusivity in at least one of the few large formularies. This strategy could spark more rounds of discounting by all players, unleashing a potentially unmitigated price war. By acquiring Achillion for its nuc and NS5A inhibitor (another drug used in HCV regimens), either AbbVie or Bristol could both strengthen its own hand and remove one player from the field, at least partially easing competitive pressure. Interestingly, by adding a nuc to its next-generation regimen, AbbVie could dilute the royalty it pays to Enanta Pharmaceuticals (NASDAQ: ENTA) for a protease inhibitor (in the expanded regimen, the protease inhibitor would represent a third of the combination instead of half, unless it were eliminated altogether); reduced payments to Enanta would partially offset the cost of acquiring Achillion.

The impact of Regulus on the market is probably the least understood scenario of all the possible futures of the HCV field and is, therefore, worth exploring in more detail. Regulus could entirely upend the above simplistic prediction of how competition in the HCV game will unfold if RG101 reaches the market in 2017 or 2018. Based on data Regulus released in October, approximately 40 percent of patients had undetectable levels of virus within 2 weeks of receiving a single injection of RG101, and they remained undetectable as of the date of the press release, in some cases months after the injection, suggesting these patients were cured.

The potential impact of Regulus' agent on the HCV market has

been downplayed. Some investors and physicians argue that there is no place for an injectable drug in what has become an all-oral playing field. In the past, patients with HCV objected to injections of another therapy called interferon because it made them feel terrible, causing flu-like symptoms, and had to be self-administered over 6 to 12 months. The interferon injections and RG101 are hardly comparable. Unlike interferon, RG101 so far appears to be safe and well tolerated, even after repeated injections at higher doses.

If more data support those already reported for RG101, then a simple and highly effective "sandwich" regimen becomes plausible—a single physician-administered injection of RG101, followed by a 4 to 6 week prescription of an oral regimen, possibly ending with another injection of Regulus' drug. With RG101 alone knocking down the virus for a prolonged period of time, it may not matter which oral regimen is used in the sandwich. In other words, RG101 may prove a great equalizer; anyone's drugs may prove "good enough" when sandwiched between two injections of RG101 for 4 to 6 weeks. By potentially enabling more players to become competitive, Regulus threatens the market share of both Gilead and AbbVie. In addition, if RG101 enables, for example, a 4-week sandwich regimen, the shortened dosing time (from 8 to 12 weeks, to 4) would cut Gilead's revenues by 50 to 67 percent and AbbVie's by 67 percent. This revenue reduction could be captured in Regulus' pricing of RG101, keeping the cost per cure the same, but shortening the treatment regimen.

Regulus could also pursue a response-guided treatment paradigm that, if successful, would have far more impact on established HCV players. In that scenario, all patients would start with a shot of RG101. After 4 weeks, a patient would see their physician again to get a blood draw and a second shot of RG101. The blood draw would be analyzed, and, if the patient's virus was undetectable (this is called an "RVR4" response), he or she would not need any other treatment. If the patient still had detectable virus, then the physician would prescribe a 4 to 6 week oral regimen, such as Harvoni or Viekira Pak, to ensure a cure.

This scenario is reminiscent of prior regimens in HCV, where patient response after 4 weeks of treatment (i.e., RVR4) with Vertex Pharmaceuticals's (NASDAQ: VRTX) telaprevir (Incivek) or Merck's boceprevir (Victrelis) determined whether patients received an extra 6 months of treatment. Such a response-guided regimen would be judged by the overall cure rate and not just by the cure rates seen with RG101 alone; as long as the cure rates were similar to the roughly 95 percent of other regimens, it would likely be approved and used. If 40 percent of patients had undetectable levels of virus after 4 weeks of treatment, as was the case in the phase 1 data released in October, then 40 percent of patients would be treated with just RG101 and 60 percent would get the add-on oral therapy for 4 to 6 weeks. That would result in an overall reduction in the number of oral doses of 75 percent for Gilead and 80 percent for AbbVie, with a similar drop in their revenues.

Those still doubting that there is room for an appropriately priced, injectable drug in future HCV regimens should also consider the incentives of physicians, who want to remain relevant to their patients and monitor their progress. By administering an RG101 injection, physicians would be more actively involved (and more relevant) in the care of their patients, and they would also be paid for their efforts. Under current reimbursement conventions, physicians would be compensated at 6 percent of RG101's price, just as oncologists and rheumatologists are paid 6 percent of the costs of the injected and infused drugs they administer. Physicians are not compensated for prescribing oral medications. Whether such incentives should influence how a physician treats a patient is an entirely separate question, but these incentives do exist; thus, they have to be taken into account when anticipating RG101's impact on the HCV market.

With only a modest amount of clinical data, Regulus is considered a long shot at the moment; therefore, Abbvie, Gilead, Bristol, Merck, Achillion, and any other HCV player should first optimize their all-oral regimen strategy. In other words, there is still strategic sense for AbbVie and Bristol to vie for Achillion to ensure their competitive positioning against Gilead and eventually Merck, and to keep Achillion out of another player's hands.

Assuming that happens and only Gilead, AbbVie, Bristol, and Merck are left, these four players will all still need to worry about Regulus—and the company that wins Regulus could end up with the best regimen. For the ones that do not, even an all-oral, 12-week regimen will likely be considered "good enough" to compete if it is offered at a big enough discount. But competing on price has not been the traditional aspiration of pharmaceutical companies; therefore, those projected to bring up the rear need to up their game, while those currently leading in quality should be thinking about how to stay ahead.

—Peter Kolchinsky is RA Capital's founder, Managing Director, and Portfolio Manager.