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Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

# Cures Revolution May Reshape Pharmaceutical Landscape

By **David Hoffmeister, Vern Norviel, Jeff Galvin, Charles Andres, Derrick Rowe and David Knapp**
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David Hoffmeister

Vern Norviel

Jeff Galvin

Charles Andres

Derrick Rowe

David Knapp

A revolution is coming, and it will likely reshape the pharmaceutical landscape and significantly impact its many participants: including patients, both large and small drug companies, generic drug manufacturers, regulators, health insurers, venture capitalists, and federal and state governments. The revolution is a cures revolution — ushered in by therapeutics that have the ability to cure diseases rather than merely treat their symptoms.[1]

The first shot in this revolution was arguably fired in December of 2013, when the U.S. Food and Drug Administration approved Sovaldi (sofosbuvir). Sovaldi is a once-daily oral treatment for chronic hepatitis C infection.[2] Sovaldi transformed hepatitis C from a hard-to-treat, chronic disease to one that could be cured for most patients in a matter of months.[3] Indeed, and as befits a revolution, Sovaldi inventor

Michael Sofia and two other colleagues won a Lasker Award.[4]

Several facts are worth noting, as these will likely be repeated — at least initially — in the development of future therapeutics in the cures revolution.

First is the relatively high price of a course of therapy — in Sovaldi's case about $80,000. Costs for curative therapies have been priced higher, on a per-dose or course-of-therapy basis, than traditional pharmaceuticals that are administered chronically. When viewed against the therapeutic alternatives over time, however, higher priced cures may ultimately be less expensive, more efficacious and potentially safer. And as discussed below, we expect, for a variety of reasons, drug acquisition costs to decrease in the long run.

Second is falling (or downward sloping) revenue curves. Revenue curves for the majority of therapeutics, which treat symptoms but do not cure diseases, rise over time. For example, sales of the top selling drug, Humira rose from about $16 billion (in 2016) to about $18 billion (in 2017).[5] In contrast, the Sovaldi revenue curve has fallen precipitously.[6] When traditional revenue curves invert, this is another sign of a revolution. For reasons we discuss below, we believe it is possible to build a successful pharmaceutical company based on drugs that have downward sloping revenue curves.

For a given country, as the number of patients with a disease are cured, there will be fewer patients in need of treatment. This, and the effect of competitor drugs, can drive down revenue curves. This would appear less than desirable for a pharmaceutical company. But as discussed below, with appropriate adjustments, pharmaceutical companies can thrive in the cures revolution.

Third is the halting of development of many follow-on[7] drugs.[8] Traditionally, when a first-in-class drug is approved by FDA, competitors will come to market with similar drugs in the same class. For example, the FDA approved 10 angiotensin converting enzyme (ACE) inhibitors. In comparison, it would appear that fewer follow-on drugs with the same mechanism of action and drug target are likely to be developed in the cures therapeutic space. Any follow-on drug in the cures space, to be competitive, must have significant, market recognizable advantage(s),[9] and must come to market when the market is still large enough to permit profitability. The transition from many competitive drugs, to fewer follow-on drugs, is another revolutionary harbinger.

Fourth, and as yet unanswered, is whether, and to what degree, generic pharmaceutical companies will elect to submit abbreviated new drug applications (ANDAs, or generic drug applications) for drugs whose revenues curves are downward sloping. Put differently, if a population may be cured of a disease, it may not make sense to come to market as a generic,[10] and if most of a population is cured of a disease, and the disease level remains low, it may make sense for only a limited number of generics to enter the market. Uncertainty, in large amounts, accompanies revolutions.

Other observations are worth making.

Over the last decade, regulatory risk — the risk that a drug candidate will not make it through the development and approval or licensing processes — has shifted onto startup companies. In the past, deals with partners or acquirers have often being made in the later stages of clinical development (e.g., in Phase II or later).[11] We anticipate this may change for several reasons.

Investigational compounds that are in the later stages of development have a higher price tag than earlier stage assets, meaning fewer assets are ultimately acquired for a given amount of money. As the number

and diversity of cure therapeutic assets increases, and regulatory uncertainty may decrease, it will make sense for big pharma (and others) to partner with early stage development companies. This will control costs, lock up key assets in highly competitive landscapes, and hedge risks associated with not being first or best. And a pipeline of cures, in the long run, benefits both patients and pharmaceutical companies.

For example, a patient may develop cancer and be successfully cured[12] by a CAR-T cell therapy.[13] Although that patient may have been successfully cured of their original cancer, that patient, later in time, may develop a second cancer that is not susceptible to successful treatment with the original CAR-T cell therapy. A pharmaceutical company having separate CAR-T cell or oncolytic virus or gene therapy effective against the new cancer would be able to offer a successful treatment to the patient. Similarly, if the patient has an orphan disease for which the pharmaceutical company has a cure, the company can again serve the patient.[14] In essence, because of a first cure, a patient's life is significantly extended. This allows the pharmaceutical company the possibility offering, as necessary, additional cure treatments. Both the company and the patient benefit. Thus, the pipeline of the future will be weighted to contain a variety of cures targeting different disease through diverse mechanisms.[15]

Also, proof-of-concept experiments, drug development costs and development timelines for new gene (e.g., transgenic viruses, gene therapy, CRISPR), and cellular cure therapies (e.g., CAR-T cells), will decrease for pharmaceutical companies, which, in turn, will likely result in the ability to develop more cure drugs. For example, drug "constructs" and transgenic cells are at least to some extent "reusable." [16] The regulatory process will become streamlined as the knowledge base for many of these molecules and cells grows. And patient selection for clinical studies will be optimized by the use of relevant diagnostic(s).

Many of the newer cure therapies will have narrow therapeutic effects and cleaner safety profiles, likely resulting in reduced failure in human trials. Finally, FDA and regulators are, and will continue to work with, companies to smooth the path to market for therapeutics that cure diseases.

We also predict that venture capitalists, and other investors that provide capital for drug development, will — for new therapies as opposed to repurposed uses of approved drugs — emphasize being first, or if not first, having a marked recognizable advantage over an approved therapeutic in a market that is still large enough to justify the resources deployed to enter. Investors will demand a clear understanding of how a follow-on drug will be able to surmount therapeutic first mover market advantage, and reason(s) why insurers and governments will reimburse the cost of the drug.

This is especially important as "efficacy pricing" is becoming more common.[17] As described above, while the initial costs of cure therapies can be high, we expect the price of these therapies to decrease over time, because of: increased knowledge, reusability, streamlined clinical pathways, increased favorable clinical outcomes, a favorable regulatory environment, and efficacy based pricing. And for those cure therapies that retain higher prices, the higher prices may be justified by comparing the therapeutic result (a cure) to years of therapy that, at best, may prevent a disease from progressing and at worst, may only add a few days or months of life.

From a patient perspective, the cures revolution will be life changing and affirming. Patients who may otherwise have died — with a significantly reduced quality-of-life in the interim — will go on to have many more productive and high-quality-of-life years; without, for example, the need to constantly and repeatedly undergo treatments (e.g., dialysis), and to periodically suffer life disrupting bouts of fatigue.[18] Indeed, historian Yuval Noah Harari, in his book Homo Deus, lists two goals of this century as perpetual happiness and amortality.

The cures revolution will present significant growth opportunities for pharmaceutical companies who embrace it. The cures revolution should create therapeutic products whose revenues dwarf current revenues. Also, with the transition to a cure-based model, pharma and consumer interests will be even more aligned. This transition will allow for curative therapies and a drug pricing model that incentivizes innovation, drives pharma profitability, and makes patient lives better and longer.

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*David Hoffmeister and Vern Norviel are partners at Wilson Sonsini Goodrich & Rosati PC.*

*Jeff Galvin is the founder and CEO of American Gene Technologies.*

*Charles Andres, Derrick Rowe and David Knapp are associates at Wilson Sonsini.*



[1] This is not to say that there were no past cures e.g., antibiotics, and some vaccines and cancer drugs. But the scope and diversity of the cure revolution will dwarf these great historical achievements.

[2] See, e.g., https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=204671.

[3] See, e.g., D. F. Maron, "Inventor of Hepatitis C Cure Wins a Major Prize—and Turns to the Next Battle", Scientific American (2016); available at: https://www.scientificamerican.com/article/inventor-of-hepatitis-c-cure-wins-a-major-prize-and-turns-to-the-next-battle/.

[4] The Lasker Award, sometimes called the American Nobel, can be a prelude to winning a Nobel Prize.

[5] A. Philippidis, "The Top 15 Best-Selling Drugs of 2017", Genetic Engineering & Biotechnology News (2018); available at: https://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2017/77901068.

[6] See, e.g., N. Pigliarulo, "Gilead Forecasts Steep Slide in 2018 hepatitis C revenues", Biopharmadive (2018); available at: https://www.biopharmadive.com/news/gilead-hepatitis-c-revenues-slide-fourth-quarter-earnings/516494/.

[7] In different contexts, the term follow-on drug can have different meanings. Here, we define a follow-on drug to be a drug (biologic or small molecule) that has the same mechanism of action and the same target as an earlier approved or licensed therapeutic.

[8] See, e.g., R. Staines, “Janssen axes hep C development with Achillion”, pharmaphorum (2017); available at: https://pharmaphorum.com/news/jj-axes-hepatitis-c-drug-rd-deal-achillion/.

[9] For example, AbbVie’s hepatitis C treatment Mavyret, which was launched after Sovaldi, had cost and time-of-treatment advantages that justified bringing Mavyret to market. See, e.g., “FDA approves Mavyret for Hepatitis C”, FDA (2017); available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm570038.htm, and n5, supra.

[10] E.g., polio or small pox.

[11] For example, Ceptaris Therapeutics was acquired by Actelion only after Ceptaris received FDA approval for the anti-cancer drug Valchlor.

[12] Cure can have different meanings. In the cancer context, we describe a cure as at least five years of remission.

[13] M. Leiser et al., “CAR T-cell therapy approval huge step for oncology, but only ‘beginning of story’”, Healio HemOnc today (2017); available at: https://www.healio.com/hematology-oncology/leukemia/news/print/hemonc-today/%7B33119631-5996-45cf-9be6-8e36466ded9e%7D/car-t-cell-therapy-approval-huge-step-for-oncology-but-only-beginning-of-story.

[14] Orphan diseases represent a significant opportunity both in the number of orphan diseases, variously estimated to range from 6,000 to 8,000, and because of incentives for developing orphan therapeutics (e.g., the Orphan Drug Act).

[15] Therapeutic cures, in the age of regenerative medicine, will not be limited to small molecules and traditional biologics. For example, in the near future, it may be possible to replace or supplement entire organs with manufactured organs that will not trigger rejection by the human immune system. See, e.g., http://www.miromatrix.com/.

[16] See, e.g., https://www.americangene.com/.

[17] E.g., a payer only pays when the drug is efficacious in a particular patient.

[18] M. Jhamb et al., “Fatigue in Patients Receiving Maintenance Dialysis: A Review of Definitions, Measures, and Contributing Factors,” Am J Kidney Dis. (2009); available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582327/.