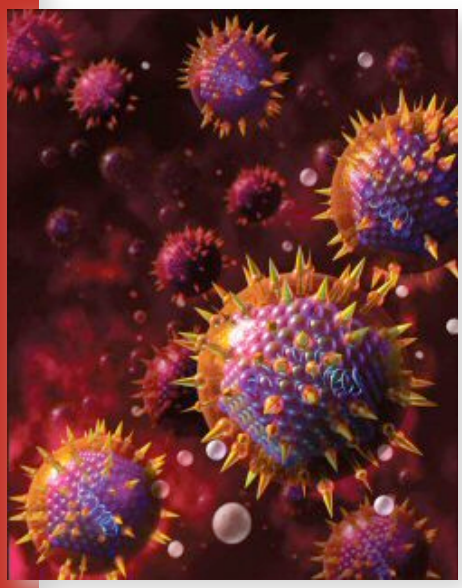
HEP-C THREATS AND OPPORTUNITIES



Contrasting Presentation Styles of KOLs in Hep C
Implications for Pharmaceutical Marketing

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Can a coterie of partisan investigators and speakers strongly contribute to market share in a larger, more fragmented, competitive market?

Companies considering entry into the chronic hep C category have doubtlessly considered the available opportunities in that class. These include substantial revenue growth, and even more attractively, exceptionally high profit margins. For example, physicians that treat the disease in the US are almost exclusively limited to a segment of gastroenterologists (GEs), thereby permitting a competitor to cover the entire national market with no more than 100 reps.

New entrants must also address the fact that the character and dynamics of this market are substantially different than those in other virology categories. The present discussion will focus on one of these differences -- the *sui generis* character of influential, national KOLs.

For almost twenty years two companies, Schering-Plough and Roche, dominated the competition among therapeutic products in hep C. Merck & Co. now owns the former, while Roche in the US is now known as Genentech, the biotech company that was wholly acquired by majority owner Hoffmann-La Roche. The standard of care in hepatitis C for most of that period has consisted of interferon-alfa plus ribavirin.

Until the interferon products transitioned to a pegylated composition in approximately 2002, Schering-Plough held as much as an 80% share of the interferon-alfa market. Then, according to S-P marketing managers at the time, the company suffered a "perfect storm" that allowed Roche to assume category leadership. The first disruption occurred in the form of a scandal involving CEO Rick Kogan who was formally charged with selective disclosure of financial information. Next, Schering lost patent protection on its top-selling product, Claritin®, in 2003.

Even as both sources of trouble took hold, investigations by numerous federal agencies resulted in >$700 million in fines and an additional +/-$500 million costs to fix manufacturing problems.

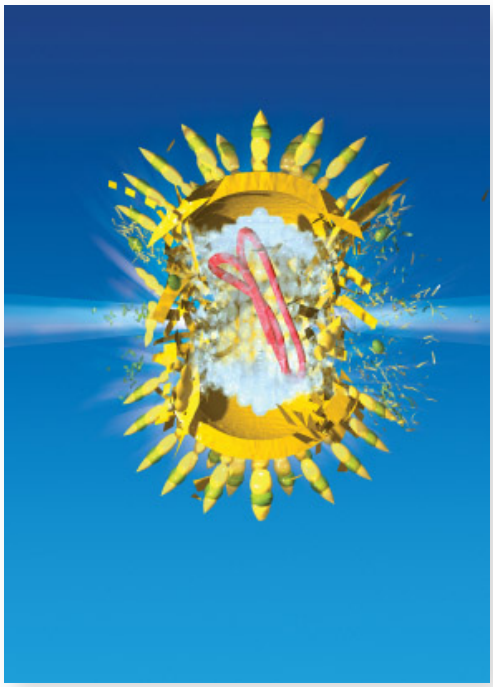
Around the same time two more scandals set S-P's efforts in hep C farther off course. An FDA criminal investigation concluded that the company's officers knowingly distributed faulty Claritin® tablets and Nasonex® inhalers. Even as the FDA probe was proceeding, investigations by the attorneys general of Massachusetts and Pennsylvania charged S-P's sales division with off-label marketing.

As a result of these multiple problems, Schering-Plough was obliged to dismiss several key people in sales and marketing, while others with strong experience in the hep C market left or were forced out for various reasons. As the interferons moved to pegylated formulations, Roche arose from its long slumber with Roferon® and developed an aggressive program for managed markets that enabled it to assume a wide lead in the category.

S-P's assorted scandals and financial setbacks jeopardized an advantage that was as responsible for their erstwhile market leadership as any other factor. That advantage was the extraordinarily close and loyal following they maintained with several of the top luminaries in academic gastroenterology.

In the early years of this decade, hep C was a small therapeutic class, in terms of absolute sales volumes, and Schering-Plough's revenue setbacks on Claritin® and elsewhere raised serious questions about whether they would continue their research support in this low-profile, arcane category. Just as those doubts emerged, Roche reanimated what had been an "empty desk," in terms of Roferon's® marketing management, by generously supporting an expansive research program. The Swiss-based company chose an alternative cohort of academic GEs to serve as principal investigators.

The period that started with Rick Kogan's waning, lame duck tenure as CEO, and lasted until his successor, Fred Hassan, recommitted to hep C, was long enough to enable a complete reversal of market share positions between S-P and Roche. When Hassan did re-establish the company's presence as a major funder of hep C clinical research, he revived the company's extraordinary relationships with several, top KOLs in the field.



The two, most important, annual meetings for hepatitis C are AASLD (American Association for the Study of Liver Disease) in the US and EASL (European Association for the Study of the Liver) for Europe. Even casual observers of the hep C market competition who have seen Schering-Plough's top stars speak at satellite symposia, oral sessions and dinners at these meetings couldn't fail to notice some unusual things about Schering's major exponents.

KOLs in most therapeutic classes typically accept research funding from several competitors within a class, ostensibly as a means of demonstrating objectivity and deflecting charges of paid partisanship. While the Schering stars perform research and other services for small competitors in hep C, for years none of them did any business with Roche. This research/financial exclusivity was accompanied by their extraordinary partisanship up on the dais.

Clinical KOLs during their speaking engagements are usually careful not to denigrate products that compete directly with those of their sponsors. People may honestly disagree whether this results from a desire not to antagonize additional funders, or if such restraint is simply part of the pose to maintain academic objectivity and disinterest. In any case, Schering's leading KOLs in hep C, such as John McHutchison of Duke University and Ira Jacobsen of New York Presbyterian/Weill Cornell, demonstrated no such reluctance. Their presentations were baldly partisan. In fact a few of their students, hoping to emulate the success of McHutchison and Jacobsen in securing generous grants, gave talks that were even less impartial. On a few occasions, casual onlookers actually mistook the academic followers of McHutchison and Jacobsen for district sales managers.

Roche never held such fervid loyalty and partisan commitment from its top investigators. KOLs such as Michael Fried of the University of North Carolina and Mitchell Shiffman at Virginia Commonwealth would ably defend their research on behalf of Pegasys® and Copegus®, but they never assumed the role of attacking Peg-Intron®.

For the years that Schering-Plough held sway in the hep C field and Roche lacked an energetic approach, a loyal partisanship among its KOL investigators helped to maintain hegemony in the category. After Schering's disarray caused them to lose the leadership position to Roche, the loyal, partisan relationships with key investigators mitigated further share loss and at least kept S-P in the game.

As the new decade unfolds, different conditions exist in the hep C competition. Merck has now absorbed Schering-Plough and, while ex-Schering people retain prominent positions in the hep C franchise, the Merck culture and operating style will clearly prevail. Merck's marketing approaches, including relationships with investigators, differ markedly from Schering's, as veterans of the Merck/S-P joint venture for Vytorin® can attest.

Another change involves the fact that more competitors, big pharmas and small ones, now recognize the attractive margins and growth potential in hep C. Novartis, J&J, Pfizer, and AstraZeneca are among big pharmas that seek substantial positions in the hep C market, while Gilead, a virology force with capitalization exceeding that of Schering-Plough or Wyeth, also has auspicious compounds in the pipeline. As of last summer, the PhRMA's website showed 51 compounds in development for HCV while the website of a leading patient advocacy group revealed 83 active projects in development.

The future of interferon-alfa plus ribavirin as the standard of care for hep C also appears open to question. Some of the therapeutic mechanisms and compounds under study for treating the disease, as of last year, include:

- Protease inhibitors (e.g., Vertex/J&J's telaprevir and Schering-Plough's boceprevir)
- Nucleoside polymerase inhibitors (e.g., Roche/Pharmasset's R-7128 and Idenix's IDX-184)
- Non-nucleoside polymerase inhibitors (Pfizer's PF-868554, Gilead's GS-9190)
- Interferon boosters (e.g., Anadys's ANA-773)
- NS5A inhibitors (e.g., Bristol-Myers Squibb's BMS-790052 and Arrow/AstraZeneca's A-831)
- Cyclophilin inhibitors (e.g., Debiopharm's Debio-025)

It remains, then, an important question -- can a coterie of partisan investigators and speakers strongly contribute to market share in a larger, more fragmented, competitive market? A fact that leaves little room for doubt, however, is that conventional marketing research can offer negligible help in answering this question. In the multitude of surveys, focus groups and individual interviews conducted by marketing researchers on this issue over the years, physicians routinely express their disdain for highly partisan investigators and speakers. This conclusion is strikingly similar to those reached by the same methodologies for questioning voters about negative ads in political campaigns. Here too, the respondents give socially correct answers and express their preference for "high-minded information." Despite such studies, a stubborn fact remains true, whether the subject is political candidates or antivirals. Negative campaigns work when properly conceived and executed.

As competitors such as BMS and Novartis seek to stake out major positions in the hepatitis C market, they would do well to ponder alternative approaches for assessing appropriate tactics and presentation styles for its leading investigators and advocates in academic medicine. Neglecting such analysis risks the prospect of a lost decade or more while the company remains mired in a competition for single-digit market share.

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