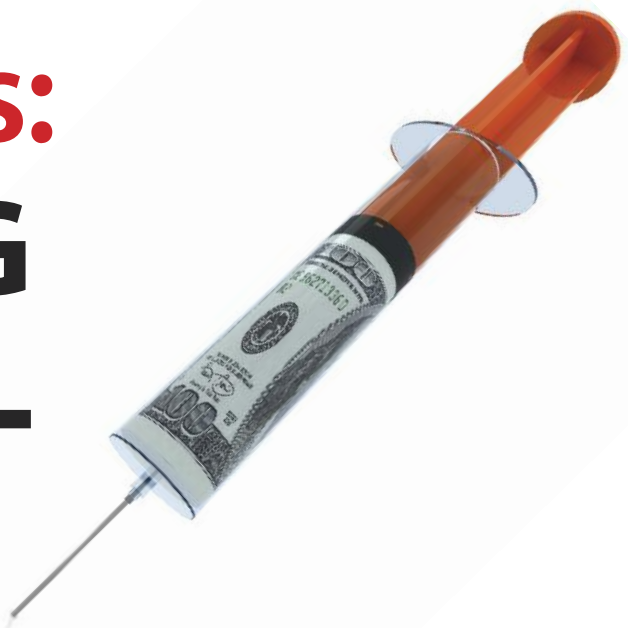
Robin Robinson

Specialty Drugs: AN EVOLVING COMMERCIAL MODEL



A changing marketplace creates new challenges and new business models for specialty medications.

At the same time the industry is increasing its focus on developing specialty drugs — a projected 40% growth by 2014 and 67% by 2015, according to Express Scripts — the reimbursement, marketing, and sales landscape of these products is also increasing in complexity.

Specialty drugs are defined as being typically high-cost, scientifically engineered drugs used to treat complex, chronic conditions that require special storage, handling, and administration, and involve a significant degree of patient education, monitoring, and management.

According to an Express Scripts report, the number of cancer drugs, considered to be speciality medicines, expected to reach the market alone is predicted to increase by 77.4% over the next three years. Spending on hepatitis C medications will grow by an incredible 465.8% by 2015. Overall, specialty drug spending is expected to more than quadruple by 2020, accounting for about $402 billion a year in sales, CVS Caremark predicts.

However, those large dollars will be hard earned, as many challenges lie ahead for the specialty drug market, including changes in the reimbursement process due to healthcare reform, financial and regulatory pressures, and the need to expand communication to all stakeholders. Addressing these hurdles will generate an evolving commercial model with little resemblance to age-old tactics.

According to Doug Moeller, M.D., medical director, McKesson Health Solutions, one of the industry's biggest challenges today is letting go of the idea that every drug developed must be a blockbuster.

FAST FACT

IN 2018, SIX OF THE 10 BEST-SELLING DRUGS BY REVENUE ARE PROJECTED TO BE SPECIALTY DRUGS, COMPARED WITH THREE DRUGS IN 2010 AND FIVE IN 2012.

EvaluatePharma World Preview 2013, Outlook to 2018

"One of the ironies of 'precision' medicine is that the success of this personalized strategy is breaking patient cohorts into much smaller and more defined groups, and 'blockbuster' status may no longer be achievable," Dr. Moeller says.

"Today's prevailing efforts in biotech's battles with viral diseases — many of which fall in the specialty market category — focus on therapies for cancers, hepatitis C, and HIV— all chronic, potentially fatal, and an unmet therapeutic need," says Bruce Robinson, a former agency medical director.

Another significant hurdle in the new model is establishing differentiation, says Amber Gilbert, executive VP, director of client services, Ogilvy CommonHealth Payer Marketing, especially since both clinical and economic value will be considered relative to competitors.

"If clinically meaningful differentiation is not established, then it comes down to economic value from the payer's perspective, which will be manufacturers' biggest hurdle," Ms. Gilbert says. "Payers will not hesitate to favor the lower-cost agent if there are no peer-reviewed/evidenced-based data justifying a higher-cost, clinically comparable agent."

Consumers will stretch the boundaries of comparable, she says.

"On the consumer side, it is entirely possible that patients will be making subjective decisions about value in the specialty pharmacy space," Ms. Gilbert says. "While payers are likely to direct use toward generics and biosimilars, patients are going to seek out products with the lowest out-of-pocket cost without compromising efficacy."

Many companies will be exploring the specialty drug market while also maintaining a presence in traditional medicine, a conundrum that may require two sets of management teams.

Mason Tenaglia, VP, managed markets services group, IMS Health, adds that companies with one foot in each sector will need to simultaneously learn how to manage a primary care product along side a specialty one.

"When being 'big' becomes less critical, the industry will need to learn how to be big as well as small and flexible, which is a really difficult task for pharma management," he says. "Everyone is struggling with building the new capability of the specialty drug market while trying to keep the larger drugs moving as well."

Mr. Tenaglia says the common strategy today is to keep the two pipelines separate, but underneath maintain the same management structure.

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"This is the current model that companies are defaulting to and nobody knows really if this is going to work," he says.

Mr. Tenaglia adds that specialty companies that have been acquired — such as MedImmune and Genzyme — by larger companies are examples of a new transitional model.

The Reimbursement Landscape

According to Express Scripts, 73% of total specialty sales are to independent physician-owned clinics that use the traditional buy-and-bill business model. This model can create challenges for physicians, as they buy the very expensive drugs up front but don't get reimbursed until after they have been administered — and the risk in today's reimbursement market is that they may not get paid at all.

This is a problem unique to the specialty market, says Ganesh Vedarajan, managing principal, ZS Associates.

"The challenge is that there is an increased risk to being denied reimbursement, and physicians need to have a strategy in place to deal with this," he says. "Doctors need to have education and information about prior authorization and they need assistance with knowing how to improve their chances for reimbursement."

In March 2013, budget sequestration legislated a decline in Medicare reimbursement for specialty drugs by 2%. This added further strain to oncology practices, especially community oncology practices, and is already leading many of them to change their business and clinical practices.

"The industry will need to develop new ways to improve their engagement with oncologists dealing with these reimbursement issues," Mr. Vedarajan says. "The challenges will be in discovering what any given doctor needs."

There are a variety of tactics that manufacturers are beginning to employ to help providers in the new marketplace.

"One element is helping physician offices by assisting doctors and practice managers to understand and follow through with the prior authorization process," Mr. Vedarajan says. "Some manufacturers are also contracting with providers to increase the reimbursement that they receive from administering the drug."

Payers will also be making new demands of the industry; manufacturers will need to prove the clinical value as well as the economic value of the therapy to payers, physicians, and patients.

The most fundamental premise remains that the therapy provides clinical value, but the bar has been raised beyond just a few more months of survival. For example, in cancer therapy, the endpoint is moving from progression free survival to an increased overall survival rate of the patient.

"The bottom line continues to be pushed in terms of proving clinical value of the drug," Mr. Vedarajan says.

The Marketing Landscape

In addition to reimbursement issues, companies will have to learn to expand their market research and communications to include all of the channel stakeholders in the new process, not just the payers on the public and commercial side as in the past.

"Today there is more impact by segmentation," says Randy Vogenberg, Ph.D., principal at Institute for Integrated Healthcare. "Market segmentation is different today than it was before healthcare reform and each segment requires a different value proposition."

This is a big change for manufacturers to embrace — they need to be aware of who is advising on or will be paying for the treat-

FAST FACT

SPECIALTY DRUG SPENDING IS EXPECTED TO MORE THAN QUADRUPLE BY 2020, REACHING ABOUT $402 BILLION A YEAR. FEWER THAN 4% OF PATIENTS USE SPECIALTY MEDICATIONS, BUT THEY ACCOUNT FOR 25% OF HEALTHCARE COSTS.

Source: CVS Caremark

Specialty Pharmaceuticals: A Resource Guide

Informational links to reports on general trends in use and cost, benefit design, and trends related to specialty diseases and drugs.

» **2013 Specialty Trend Management Insights Report** from CVSCaremark reports on recent specialty pharmacy prescribing trends and strategies for managing costs.
For more information, visit cvscaremarkfyi.com/insights-2013.

» **Aon Hewitt Health Care Trends Survey** summarizes forecasted healthcare trend data (medical, dental, pharmacy, vision benefit trends for various plan types) based on information from leading healthcare vendors.
Fore more information, visit aon.com/attachments/human-capital-consulting/2013_Health_Care_Survey.pdf

» **EMD Serono Specialty Digest** is a report based on compiled survey results and used by healthcare decision makers to benchmark their management of specialty pharmaceuticals against their peers. Each digest provides a comprehensive overview of managed care challenges and opportunities as well as current and future trends in managing specialty pharmaceuticals. Survey results come from various private and public health plans and pharmacy benefit managers.
For more information, visit specialtydigest.emdserono.com/

» **Magellan Pharmacy Solutions' 2012 Medical Pharmacy & Oncology Trend Report** provides a source for trends and benchmarking statistics for injectables paid under the medical benefit. By surveying 50 top U.S. commercial health plans, representing almost 160 million lives, the report leverages three years of trend report benchmarking data.
For more information, visit icorehealthcare.com/icore-resources/trend-report.aspx

» **Managing MS: Trends, Issues and Perspectives.** This Biotechnology Healthcare report outlines the impact of the entry of oral medications for multiple sclerosis into the marketplace and challenges for all stakeholders from the high cost of biologic drugs.
For more information, visit ncbi.nlm.nih.gov/pmc/articles/PMC3138383

» **Multiple Sclerosis Trend Report**, 2nd Edition is the National Multiple Sclerosis Society and Teva Neuroscience survey of key stakeholders, physicians, MCOs, and specialty pharmacies on their views of the management of MS in the managed care environment.
For more information, visit nationalmssociety.org/research/research-news/ms-trend-report/index.aspx

» **Walgreens Specialty Pipeline Report** provides a summary of the specialty medications that may be approved by the FDA within the next few years.
For more information, visit walgreens.com/pdf/newsletterreport/Pipeline_Report_4Q2013.pdf

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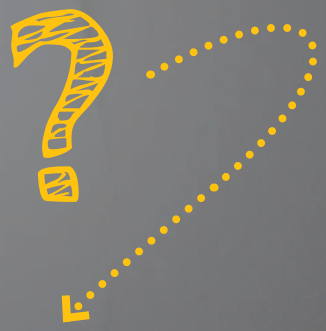

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>
> **MICHAEL ZILLIGAN**
> Ogilvy CommonHealth
> Specialty Marketing

> "The cost of specialty drugs is going to raise a lot of challenges for employers and insurers."
>
> **MASON TENAGLIA** / IMS Health

ment, and what their perspective is on identifying value. Dr. Vogenberg says most companies have not begun to do the market research or analysis necessary to be able to identify and properly address each one of these new segments that impact coverage decisions.

"The industry has never had to address the landmines that are associated with what each individual stakeholder thinks the value prop is," he says. "It's always been straightforward. They may have worried about distribution channels, but now the whole marketplace is looking at making decisions from a different point of view."

Healthcare reform has completely changed the marketplace from a predominantly clinical perspective to include financial or economic impact perspectives.

"This has become a big challenge for pharma companies because in the past their whole message has been clinical, and the whole voluntary pharma code was about putting clinical data before economics, but the market now is about economics first, and clinical second," Dr. Vogenberg says.

A good example of this shift is represented by the new Gilead drug Sovaldi for hepatitis C treatment. According to Forbes, one pill will sell for $1,000, and the treatment is taken once a day for 12 weeks for a total cost of $84,000.

Mr. Robinson says of the viral sciences' leaps and bounds prayed for by patients and caregivers, hepatitis C therapies of late seem to really deliver. (For more information related to the hepatitis C market, please see the digital edition: Hepatitis C Round-Up.)

"Sovaldi appears to be extremely effective in eradicating the disease, but the cost may be a stumbling block for patients," Mr. Tenaglia says. "The cost of the drug is going to raise a lot of challenges for employers and insurers, and if they do pay for it, they are going to want to make sure patients take it effectively."

The Sales Landscape

The industry needs to prepare for the challenges ahead by making changes to its current commercial model. Ms. Gilbert says the biggest change needed in commercial strategies is to purposefully address more audiences with a clear cost-benefit value proposition. Payers are continuing to shift costs to patients at a rapid rate through higher deductibles and a broader use of percent-based co-insurances.

This means that patients will have to bear a significant portion of out-of-pocket costs for specialty drugs. That said, the co-pay card element is likely to be a key piece of any consumer strategy, at least for commercially covered patients, in the near term. If the product is not differentiated clinically, then a dynamic contract offering that delivers added value to payers will be even more critical. One example could be up-front discounts rather than rebates or performance-based contracts.

"We'll continue to see stakeholders push back on manufacturers for premium pricing of drugs that they perceive as offering minimal efficacy over competing therapies," says Michael Zilligan, president, Ogilvy CommonHealth Specialty Marketing. "For example, Express Scripts took an aggressive stance toward pricing the new hepatitis C therapies when it suggested the manufacturer had 'inadequate justification' for higher pricing versus less convenient therapies that produce similar efficacy."

Another change will be the importance of collecting and using data to prove better health outcomes through CRM programs, Mr. Tenaglia says.

"Patient behavior will need to be tracked so the loop can be closed and data can be collected on what companies are spending on keeping patients adherent, and what that means to overall health costs," he says. "Whether it's claims data or data from copay card suppliers or data from CRM, the biggest management challenge for the next five to 10 years will be how to integrate all of those data sets and infer the results, because results are what's going to matter in the future."

This need will drive the significance of CRM programs more than ever. Companies may seek to create websites that engage specialty drug patients and provide them with financial subsidies, drug information, and even adherence devices.

"Devices such as the Fitbit are going to be incredibly important in the coming years in making the link between adherence and results," Mr. Tenaglia says.

To keep pace with the transitioning marketplace, drug companies will need to become more strategic in their planning, rather than tactical, says Dr. Vogenberg.

"Traditionally, the industry has planned ahead tactically each year at a time, but with the market resetting itself every year due to the effects of healthcare reform, companies can no longer afford to operate that way," he says. "If a commercial strategy is not in sync with what healthcare reform is doing in the market, that company is going to be headed out of business."

Dr. Vogenberg predicts it will be another three to five years before the marketplace becomes more solid and easier to predict. During this transition, companies need to factor in healthcare reform into their strategies, and begin focusing not only on what's happened in the market but also anticipate what will change.

"Most companies today do not have this type of strategy," he says. "They are preparing to launch products into a market they haven't anticipated; I know one company that plans to launch a product sometime next year and before that time the market will have shifted twice before the launch, so the launch strategy will be 50% to 60% incorrect at launch. This situation is totally avoidable."

The current R&D model focuses on a long-term development plan and getting FDA approval and the drug to market, but in the meantime it must closely monitor the changes being made in healthcare coverage, or else it may produce a drug that will not be reimbursed.

"In today's environment, by the time the product receives FDA approval, the traditional commercial insurance market might be shut down and become a defined benefit, which means the company won't be able to sell the product, or at least not at the price they intended," Dr. Vogenberg says. "It sounds sur-

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prising, but many companies do not know the fundamentals about how the healthcare market and insurance work. They don't have a basic understanding on market fundamentals, such as that there is a finite amount of money and if the drug's value doesn't make sense to those who are paying, then it has no value."

The commercial model for specialty drugs is very different from the model for primary care, and drug companies with new specialty drugs will need to adjust their strategy, Mr. Vedarajan notes.

There are four elements that differ greatly between the two commercial models, he says. As already noted, reimbursement has become much more complex, for one. Identifying the needs of the specialty physician is another difference, he says. Discussions with specialty clinicians are much more detailed than the clinical discussions with primary care physicians. Also, specialty physicians can no longer be lumped together as one group as in the past.

"There was a time when specialists were considered as all the same, but today, every oncologist is different and every practice setting is different," Mr. Vedarajan says. "While PCP visits are typically 10 to 30 seconds long, specialty appointments are scheduled months in advance and the discussion can last 10 to 30 minutes, during which a lot of clinical data are supplied through multimedia detailing techniques. There is also a lot of support provided to the practice, especially to the nurses who must anticipate side effects of a patient during infusion care and to practice managers to help them bill the hundreds of thousands of dollars of claims correctly. The clinical and sales support to sell the specialty drug is significantly more intense and complex than sales for a primary care drug."

Distribution strategies are very different as well. PCP patients go into a pharmacy and pick up their drugs, but specialty drugs are either buy and bill through the physician or sold from a specialty pharmacy to the physician or the patient.

And lastly, many specialty drugs need to be tested before they are implemented to determine if the drug is right for each patient, which creates new challenges for physicians and manufacturers. Drug companies will have to create a way to support this testing.

One of the biggest overall changes in strategy, however, is the move from a product-focused model to a solutions model.

There will soon be a time when payers will contract not just on volume but on the outcome along the patient journey.

"This is an important change for practices because they will not be measured on volume of

"A significant hurdle in the new commercial model is establishing differentiation."

AMBER GILBERT
Ogilvy CommonHealth
Payer Marketing

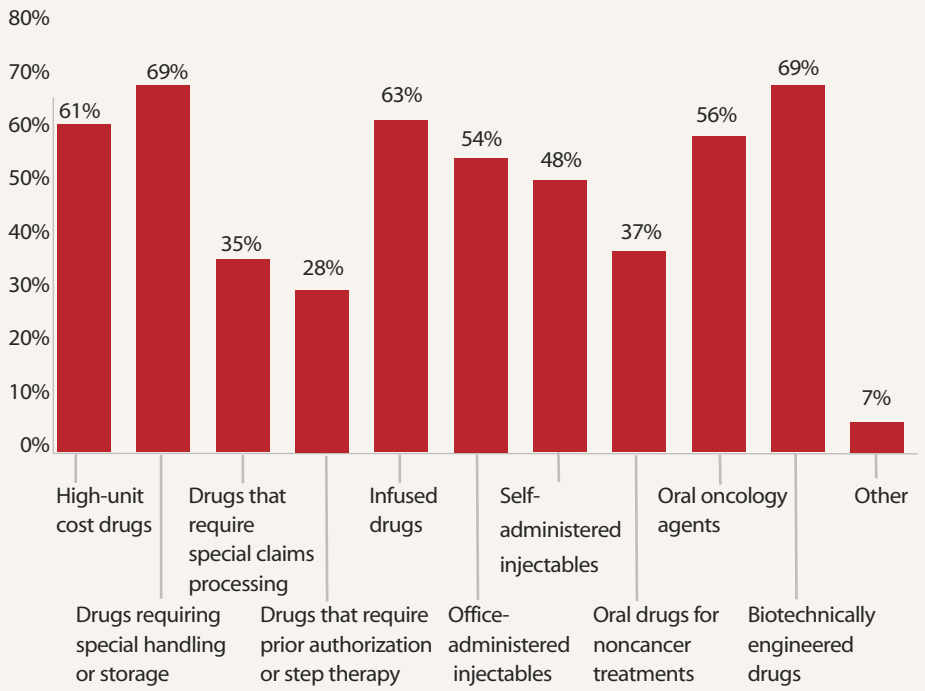
"The industry will need to develop new ways to improve its engagement with oncologists; the challenge will be discovering what any given doctor needs."

GANESH VEDARAJAN / ZS Associates

Defining Specialty Drugs

Defining the term "specialty drugs" can be a challenge. Each key stakeholder has a different perspective and may also have a slightly different definition. For example, the Centers for Medicare & Medicaid Services define specialty drugs as those that cost more than $600/month. Meanwhile, the Food & Drug Administration, employers, and other healthcare stakeholders have their own ways of defining this fastest-growing drug category.

When asked to define specialty drugs, PBMs and specialty pharmacy executives provided a number of responses as indicated below:



There is a general consensus that the following elements currently define specialty drugs:

- Treat complex chronic and/or life-threatening conditions
- Have a high cost per unit
- Require special storage, handling, and administration
- Involve a significant degree of patient education, monitoring, and management

Source: 2011 Digest Report on managed care published by Kikaku America, Washington, D.C.

services but on patient outcomes and they will be looking to share this responsibility with the manufacturers, who will in turn need to change the business model to a more outcome or solutions based mindset," Mr. Vedarajan says.

According to Dr. Moeller, the single most important change will be more transparency and consensus regarding the evidence-based criteria for adding emerging technologies — diagnostic and therapeutic — to accepted clinical care protocols.

"Unfortunately, emerging means just that," he says. "We don't quite have enough reliable, objective information to approve this test or therapy as fully approved. Even so, competitive pressure and anti-trust provisions should not prevent a marketplace from establishing thoughtful and useful quality-of-care criteria and measures."

According to Mr. Zilligan, the industry can prepare for the future and the new commercial model by creating strong relationships with patient advocacy groups and developing a deep understanding of the sociology, psychology, and economics of the disease state as it relates to not just one patient — personalized medicine is becoming more of the norm in oncology, for example — but all typical patient types.

"Companies will need to approach and work with all stakeholders as if they operate in a common ecosystem and master all of the functional variables that impact each key player, for example, a nurse navigator," he says.

Mr. Zilligan says as the specialty space moves to a more "mature" point in its evolution, payers will demand lower pricing, likely through more aggressive contracting. And incremental value will flow from the use of technologies — digital pill boxes, Web-based solutions, etc. — that can be integrated into adherence strategies.

> **"Market segmentation is different today than it was before healthcare reform, and each segment requires a different value proposition."**
>
> **DR. RANDY VOGENBERG**
> Institute for Integrated Healthcare

"For pharma, the benefits will be the ability to command premium pricing for genuine superiority; the risk will be no-holds-barred commoditization and heavy payer restrictions on products deemed as having too high a price for the benefit offered," he says.

Success will stem from a strong R&D strategy, with input and alignment between medical and commercial teams, as well as strong business-to-business relationships, which will open doors to new sources of real-world data.

Advanced and real-time analytics will become critical to ensure that the clinical and economic value story communications are being resourced and targeted in the correct channels and segments. A strong partnership model will evolve in the contracting environment, Mr. Zilligan predicts.

"One the biggest differences in the next five or 10 years may depend on the timing of biosimiliars in the United States," he says. "The strategies pharma develops and deploys to address these pending lower cost market entrants will no doubt be critical. Companies need to guard against having market leadership and then confronting either a low-cost or higher-quality competitor and being caught flat-footed when a clear strategic response was called for." PV

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Oncology Most Restrictive Specialty For Second Year

Oncology remains the most restrictive specialty for sales representative access this year for the second year in a row. A ZS Associates report found that about 65% of oncologists in the United States placed moderate-to-severe restrictions on visits from sales reps. By comparison, only 17% of oncologists restricted access to reps in 2008. About 58% of cardiologists and 47% of primary care physicians restrict rep access to the same degree.

Oncology is the most restrictive of the 20 common medical specialties noted in the report.

Source: ZS Associates

Hepatitis C Round-up: A Specialty Drug Overview

Investigational therapeutic clinical trials make for great headlines, failure or success notwithstanding, according to Bruce Robinson, former medical director in the medical strategy division of Fingerpaint. Gilead Sciences, for instance, has a fine leverage: its business model addresses three diseases, and arguably quite successfully. Gilead's recent FDA approval for Sovaldi, its hepatitis C first all-oral combination, and has been in the press since filing its NDA letter in April 2013. Vertex Pharmaceuticals recently effected a two-year trip to orbital proportions, then quickly fizzled with its hepatitis C therapy Incivek.

Of the viral sciences' leaps and bounds prayed for by patients and caregivers, hepatitis C therapies of late seem to really deliver. A virus that copies itself 1 million times a day in the afflicted hepatocytes while affecting varied genotypes in its offspring, HCV has finally succumbed to the keen microscopes at AbbVie, Merck, Vertex, Janssen, BMS, and Gilead, to name a few. The molecular workings of this little devil have revealed themselves in unprecedented illumination, and the first successful IND application in the form of VX-950 arrived at the FDA in November 2005. Vertex stated VX-950 "was well tolerated and possessed potent antiviral activity in a 14-day study in patients with hepatitis C virus (HCV) infection." It went on to become Incivek. This is a big-dollar, transformative medicine; a potential eradication to a silent, often fatal virus.

> **"Today's prevailing efforts in biotech's battles with viral diseases — many of which fall in the specialty market category — focus on therapies for cancers, hepatitis C, and HIV— all chronic, potentially fatal, and an unmet therapeutic need."**
>
> **BRUCE ROBINSON**
> Former Agency Medical Director


Bruce Robinson

Baby Boomers

The Centers for Disease Control and Prevention (CDC) estimate worldwide HCV infection at 17 million with an annual mortality of 350,000. The U.S. HCV infection prevalence claims more than 5 million infected individuals; most (76%, or three out of four) are baby boomers born between 1945 and 1965. That's one in every 30 baby boomers. What was their risk? Nothing really so different as from the more recently born. Removed from the liability pool are those who have had blood transfusions post 1987 and organ transplantations post 1992; otherwise, needle sharing, HIV-plus status, tattoo needles, and sexual activity in which blood is transferred present opportunities for this most common (U.S.) of blood-borne infections to gain traction.

In the body, HCV can replicate while undetected for many years. Most of today's HCV-plus were infected between 20 and 40 years ago. The disease is greeted by clinicians who fail to screen, simply because HCV's symptoms lay hidden. And concurrently, most PCPs are not tuned in to the disease's striking prevalence. Hidden from gross anatomical view, HCV's liver damage may progress insidiously to fibrosis, cirrhosis, and scarring, paving a way for hepatocellular carcinoma or end-stage liver disease. Chronic HCV infection is a leading reason for liver transplantation in the United States. So, if you believed HCV does not kill, you were mistaken. It is terminal in people who do not clear it naturally or pursue some form of therapy.

Juan: A Patient Perspective

Juan R. (his name is changed for privacy) was diagnosed with HCV after a prison fight. He was incarcerated in New York's penitentiary system for second-degree murder. Formerly a gang member, today he is on parole, a certified counselor to at-risk individuals, and loving life. His smile is infectious, as well as his presence when immersed in the story of how HCV was eradicated from his system, like his past behavioral inclinations.

Juan discusses his initial treatments with combined interferon and ribavirin, which at that time were the only therapies available for HCV. An injectable and not a pill, interferon's weekly shot belied the discomfort of months on this potent cytokine. For the regimen's duration — a seemingly endless 48 weeks — flu-like symptoms kick in: body aches, fever, headaches, skin rash, nausea, diarrhea, and fatigue. Juan endured these side effects with stoic aplomb. He was in prison, so perhaps he had no choice. But as with 40% to 60% of interferon/ribavirin patients, the regimen failed to produce sustained virologic response (SVR) and Juan was, one painful year later, stuck where he started, virally speaking.

That was then.

HCV Therapies

HCV clinical science advances leave almost nothing to the imagination: isolated in separate laboratories, two protease inhibitors came to light around the same time, both novel in efficacy to the most common HCV genotype 1 (GT-1). At long last, therapies that show efficacy in null-responders to interferon/ribavirin, HCV relapsers, and treatment-naïve patients. After years of hit and mostly miss, two contenders revolutionized the pharmacy benefits manager's arsenal against HCV, and one was out of the blocs and received FDA approval in record time. Incivek went straight for the gold and never peeked over its shoulder: it claimed the world's fastest drug launch ever at $1.56 billion in its first four quarters, knocking Celebrex off the ranking podium. So the market is obviously hot.

Issues such as patient comfort, safety, and adherence drove Sovaldi's development. The pharmaceutical headlines of 2013 buzzed during its clinical trials. Touted through every press announcement as the de rigueur medicine for genotypes 2 and 3 and maybe 4, the

FDA included approval on GT-1; an imprimatur to the four major genotypes. Sovaldi patients will experience fewer side effects, an easier mode of administration (an all-oral combination therapy except when interferon is indicated), and possibly shorter durations of treatment.

Incivek, in stark inverse to its big-dollar ascension, flattened out precipitously as caregivers warehoused their HCV-plus patients. It's an easy choice for a patient and a clinician.

Enter big pharma's Merck. They re-toned their stride post Victrelis with recent announcements about combination therapy MK-5172, an NS3/4A protease inhibitor, and the NS5A treatment MK-8742. Response rates ranged from 96% to 100% among small groups of genotype 1a and 1b patients. The pipeline finally looks promising for Roger Perlmutter's R&D division with this well-reviewed contender, even if late to the start line.

Hepatitis C Therapeutics on the Market

Brand name	Compound	Marketer	Indication	Approved
1. Intro A	Interferon alph-2b	Schering-Plough	**INTRON A** has been approved for extension of therapy for chronic viral hepatitis C for 18-24 months. Intron A therapy for 18-24 months has been shown to nearly double patients' sustained response rates, compared with six months of treatment (the previously indicated treatment regimen), according to studies submitted to the FDA.	1997
2. Pegasys	Interferon alph-2a	Genentech	**PEGASYS**, peginterferon alfa-2a, alone or in combination with Copegus, is indicated for the treatment of patients 5 years of age and older with chronic hepatitis C (CHC) virus infection with compensated liver disease and have not been previously treated with interferon alpha. Efficacy has been demonstrated in subjects with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and in adult subjects with clinically stable HIV disease and CD4 count greater than 100 cells/mm3.	2002
3. Copegus	Ribavirin	Genentech	**COPEGUS** in combination with Pegasys (peginterferon alfa-2a) is indicated for the treatment of patients 5 years of age and older with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha.	2002
4. Incivek	Telaprevir	Vertex	**INCIVEK** (telaprevir), in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers	2011
5. Victrelis	Boceprevir	Merck	**VICTRELIS** (boceprevir) is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including prior null responders, partial responders, and relapsers	2011
6. Olysio	Simeprevir	Janssen	**OLYSIO** is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. » Olysio efficacy has been established in combination with peginterferon alfa and ribavirin, in HCV genotype 1 infected subjects with compensated liver disease	2013
7. Sovaldi	Sofosbuvir	Gilead	**SOVALDI** is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. » Solvadi efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection	2013

The Hepatitis C Pipeline

Product	Indication	Developer
2336805	Hepatitis C virus inhibitor	GlaxoSmithKline
HCIG	Hepatitis C immunoglobulin	Biotest
Faldaprevir	NS3/4A protease inhibitor	Boehringer Ingelheim
Miraversen	Antisense phosphorothioate	Santaris
Setrobuvir	(non-nucleoside polymerase inhibitor)	Genentech
Ledipasvir	NS5A inhibitor	Gilead

Analysts predict a best-in-category battle to be waged for the hepatitis C market between the biotech Gilead and big pharma's Merck. The win-win fallout? Patients will convert from one to the other if the first proves ineffective. But will interferonologists? It's time for researchers to delete HCV infections from their repertoire of applicable diseases (for most of the HCV population); interferon is just plain tough to tolerate, and Merck and Gilead are listening.

Micro RNAs (miRNA)

And the science just keeps getting better. Perceive, if you might, of an all-encompassing, every-genotype- and subtype-variant effective, low-side-effects therapy hepatitis C superstar? Not as of yet spouting such hyperbole, Santaris Pharmaceuticals submitted miravirsen to clinical trials and, to date, has shown substantive therapeutic efficacy and safety endpoints. The agent has enviable characteristics positioning it to contend with issues of adherence, pill-burdens, side effects, polypharmacy (think drug-to-drug interactions), and, most especially, genotype/subtype variants. This is an unparalleled repertoire of strategic benefits.

Successful HCV RNA propagation requires the host's own micro RNA-122 (miRNA-122), a short, non-coding sequence essential to healthy liver cells' growth, differentiation, and viral infection reaction. In a twist of viral brilliance and adaptation, miRNA-122 actually binds to HCV RNA and safeguards HCV's genome from host nucleolytic cleavage. By binding to the 5' untranslated region (UTR) of the viral genome, the miRNA-122/HCV RNA dimer deters endogenous immunogenicity, thus rendering an immune attack ineffective. Not only do the host's cells' polymerases and infrastructure parlay the successful proliferation of HCV, but endogenous miRNA-122 binding protects this intruder from innate immunologic defenses.

Mr. Robinson says the industry could not devise a better invasion rife with Benedict Arnolds on the opposing side.

As the miRNA-122 interference strategy, miravirsen plays bait and switch to miRNA-122's selective HCV RNA binding by offering itself up as a more appealing, higher affinity ligand. An antisense, locked nucleic-acid modified DNA phosphorothioate, simply stated, it binds efficiently with miRNA-122 and quarantines it from associating with the HCV genome. This, in turn, inhibits viral replication. No more hepatitis C viruses equates to eradication of the virus in the infected individual.

Santaris has enjoyed Phase 1 success with miravirsen, demonstrating significant drops in hepatitis C viral plasma levels Of potentially inestimable consequence for HCV therapy targets, the substrate to miravirsen, miRNA-122, knows no prejudice to which HCV variant or subtype it will bind. 5' UTR sequences are conserved across every HCV variant: the sequence on type 1 is identical through type 7, as well as every super family subtype. The implication? Miravirsen just might prove effective for all hepatitis C viruses and prevent escape mutations.

New Horizons

Juan R. was one of the fortunate many to benefit from the market entry of Incivek back in May 2011. A null-responder to interferon coupled with ribavirin, Juan's course of therapy part deux comprised the trio of peg-interferon, ribavirin, and Incivek, and success was the offing. He has achieved sustained virologic response, and monitors his blood every six months.

Juan did not have the option to warehouse himself; the science for these consequential new therapies had not yet come to light. Today's hepatitis C patients will find numerous options offering replacement therapies as redundancies. And the future? Look for an effective HCV vaccine. The market is as open and fertile as the R&D, and the dollars to be made may just supplant Incivek as the record-holding fastest launched therapeutic. PV

Contributed by Bruce Robinson, former medical director, medical strategy division, at Fingerpaint. Mr. Robinson can be reached at macmasterrobinson@gmail.com

(Editor's Notes: Miravirson Section: Janssen, HLA (Harry) et al. Treatment of HCV infection by targeting microRNA. N Engl J Med 2013.368;18:1685-1694.)

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