MARCH 2014 - ISSUE 1

WKMJ

World Korean Medical Journal

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Inspirational Korean American Leader

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Biopharmaceutical Report

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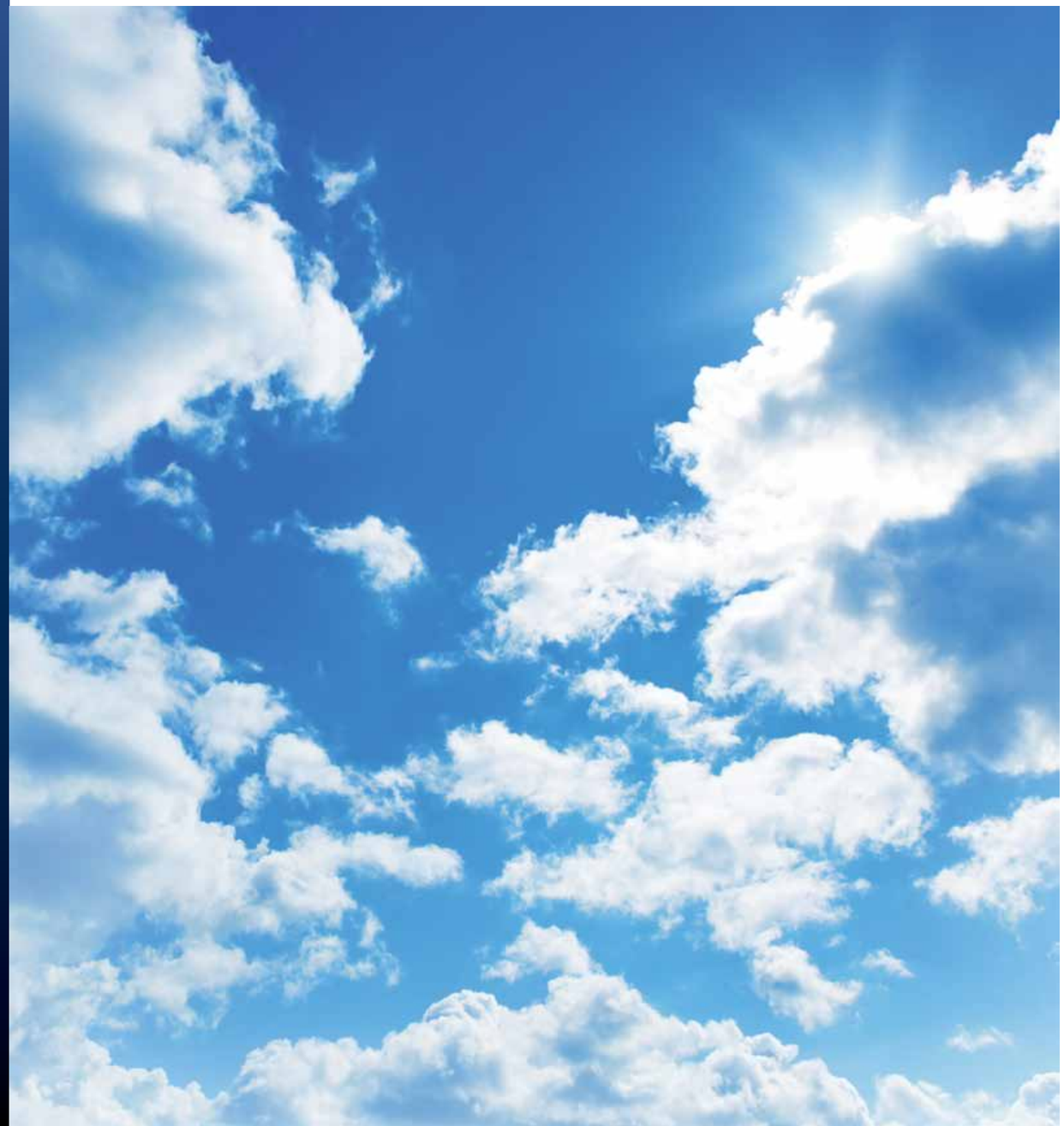
WKMJ
WORLD KOREAN MEDICAL JOURNAL



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CREATE AN ENVIRONMENT FOR *CONNECTION* AND *INNOVATION*, BRINGING POSITIVE IMPACT FOR THE ADVANCEMENT OF BIO-MEDICAL INDUSTRY & HEALTHCARE

Greetings!

I am happy to introduce the creation of the World Korean Medical Journal, otherwise known as WKMJ. Our journal is the official journal published by World Korean Medical Organization (WKMO). The goal of the World Korean Medical Journal is to present multidisciplinary perspectives on healthcare and related issues.

WKMJ is distributed to more than 38,000 physicians and organizations, including 20,000 health care professionals and bio-health industry executives in the United States. WKMJ will publish original articles, reviews, and columns, introducing the emerging issues in medicine and new trends in bio-health industry. It will encompass a wide spectrum of disciplines including medicine, technology, pharmaceuticals, healthcare management, and other subjects. In addition to updating on the notable activities of physicians of Korean heritage, the journal will also feature leaders in medical community and the pharmaceutical industry. Further, it will update its leadership on conference proceedings and new diagnostic and therapeutic products. Our aim is to provide a forum for readers to develop an integrative perspective in the complicated fields of healthcare.

As the global organization for 140,000 Korean physicians throughout the world, WKMO offers unprecedented potential to enhance global health. We look forward to partnering with you, to create an environment for *connection and innovation*, bringing positive impact for the advancement of bio-medical industry and healthcare.

Happy reading!

Chul S. Hyun, MD, PhD
Publisher
President of WKMO

WELCOME TO THE INAUGURAL ISSUE OF THE WKMJ

Welcome to the inaugural issue of the World Korean Medical Journal. Why in this age of proliferative journals do we need another? The reason is that there is need to disseminate information amongst the increasing number of Korean heritage physicians throughout the world on the activities and issues facing physicians everywhere. The creation of the World Korean Model Organization (WKMO) is timely and the journal can help with networking and presenting interesting topics. The journal focuses on Korean physicians in the myriad roles medicine offers, medical outreach to underserved areas including our kin in the North, comparing health systems, even biomedical industrial advancement, as well as featuring activities of organizations such as the World Korean Medical Student Association, the future Korean physicians.

The journal is launched in an Olympic year and we are able to feature one of the greatest Olympic physician athletes of all time. Dr. Sammy Lee is a Korean American physician who won two gold medals in diving in 1948 and 1952, as well as silver medal for the US. And he was a USC medical student, who was denied competing in the 1944 games due to World War II. It was distinct pleasure and honor to interview Dr. Lee a living legend. Dr. Lee at 94 has a sharp mind and his story is remarkable one of perseverance and accomplishment. Dr. Sammy Lee truly embodies the Olympic spirit Altius - striving higher.

WKMO had its first regional conference in Brazil which was a successful meeting. We look forward to the 3rd Annual WKMO meeting in NY on July 4th weekend so please join us to interact with Korean physicians from wide and afar. For the Korean American Medical Association 2014 is a special year as it is the 40th anniversary so come celebrate this special occasion in Hawaii in August (www.KAMAus.org). Please share this journal with your friends and colleagues. We welcome your comments and suggestions.

David Y. Ko, MD
Editor in Chief
Board Director of WKMO
President of KAMA

UNCLASSIFIED
MEMORANDUM

The World Korean Medical organization (WKMO) has a lot to celebrate since it was launched in Los Angeles, California in July 2012. I applaud WKMO's mission to facilitate medical and scientific research and improve standards of healthcare and medical training worldwide by tapping into a vast network of Koreans working or studying in various medical fields across the world.

WKMO's new World Korean Medical Journal will serve as a means to share new information and trends while supporting an expanding network of over 140,000 Korean physicians, healthcare industry leaders, and bio medicine scientists. I would like to congratulate WKMO on the launch of this journal and which the organization success in its mission to advance global cooperation in the field of health.

As the world becomes more globalized, no country acting alone will be able to successfully meet the challenges of the 21st century. To spur innovation and successfully tackle global public health issues. It will take more than hard work and long hours in the lab. Our countries need the right policy environments and our scientists and experts need to cooperate and collaborate with global partners and colleagues.

Korea and the United States share strong traditions in biomedical, medical sciences, and public health research, and we have a long history of public and private sector health collaboration. Joint efforts to advance vaccine development, pandemic influenza preparedness, liver cancer and cancer genomics, and chronic and infectious disease research have undoubtedly had a positive impact on global public health. In fact, some of our greatest tools of international diplomacy today involve science and technology partnerships, collaboration, and international exchange programs that allow us to learn from each other.

The U.S.-Korea partnership – a relationship begun in the 19th century and solidified in the 20th century – is evolving to meet the challenges of the 21st century. Like WKMO, we are working hard at the U.S. Embassy in Seoul to expand people-to-people ties through a variety of programs designed to bring people together to effect positive change in the world.

Let me again congratulate WKMO on the publication of your World Korean Medical Journal and I thank you for your contributions in the field of global health.

Sung Y. Kim
The Ambassador
U.S.Embassy Seoul, Korea

MICHAEL M. HONDA
17TH DISTRICT, CALIFORNIA

February 2014
Message from Congressman Michael M. Honda
Commemorating the First Edition of the World Korean Medical Journal

Dear Friends,

As Chair Emeritus of the Congressional Asian Pacific American Caucus (CAPAC) it is with great pleasure that I extend my congratulations to World Korean Medical Organization (WKMO) for the first issue of the World Korean Medical Journal (WKMJ). This journal exemplifies WKMO's mission of facilitating the advancement of medical and scientific research and pursuing to implement and improve higher standards of healthcare and medical training worldwide.

WKMJ will share new trends and information in public health and medicine and simultaneously strengthen the network capacity in healthcare and medicine. I am sure this journal will serve as a vital and important resource for healthcare professionals around the world – as well as strengthen the network of our global community.

Once again, I commend WKMO for its exemplary service – and I encourage you all to read this journal and use it as a guide to unite the various sectors of the global Korean medical community.

Sincerely,

Michael M. Honda
Member
Unites States Congress
Chairman Emeritus
Congressional Asian Pacific American Caucus

THE NATIONAL ASSEMBLY OF THE REPUBLIC OF KOREA

I would like to offer my sincere congratulations to the World Korean Medical Organization on its publishing of the first issue of the *World Korean Medical Journal*.

My heartfelt thanks and appreciation go to President Chul-Soo Hyun and the other WKMO officials for their dedicated hard work in promoting exchanges among Korean doctors, nurturing the next generation of talent, and globalizing Korean healthcare.

Korean people's characteristic diligence, along with our traditional virtue of mutual help in challenging times, served as a strong basis for our overseas Korean compatriots' remarkable success.

While more than 7.2 million variou s professional Korean compatriots are actively supporing their local communities of more than 150 countries around the world, and there are about 35,000 overseas Korean doctors.

Indeed, these overseas Korean compatriots made great contributions to Korea's emergence from the ruins of war to rise as one of the top 10 global economic powerhouses and to grow as a developed model democratic nation.

Our overseas Korean compatriots are still contributing to their native country in many ways. Overseas Korean doctors working around the world, in particular, are lending enormous support to the advancement and globalization of Korean healthcare with their deep love of their home country and a strong sense of unity.
From this point forward, we should join forces to achieve greater development of the Republic of Korea while contributing to the world's co-prosperity, remembering that the world's compassionate helping hands were extended to us in the past.

Above all, I would like to ask for WKMO members' active participation in helping our North Korean compatriots who are struggling to get by amid poverty and illness. After all, bringing together the South and the North is the greatest mission for all Koreans around the globe.

As a neurosurgeon-turned-politician, I will always keep in mind my original resolution of "treating our sick and ailing society" and do my best to transform the Republic of Korea into a truly 'Healthy Society'.

Once again, I extend my congratulations on the meaningful publication of WKMJ's first issue.

Thank you,

Ui-Hwa Chung, MD, PhD
Member
19th National Assembly of the Republic of Korea

KOICA 한국국제협력단
KOREA INTERNATIONAL COOPERATION AGENCY

First of all, on behalf of the Korea International Cooperation Agency, I would like to extend my congratulations on the first publication of the World Korean Medical Journal (WKMJ).

The World Korean Medical Organization has been playing the role as a focal point of Korean doctors in 12 countries across the world since its establishment in 2012. As such, I would like to offer a message of gratitude to President Hyun Chul Soo for his dedication towards encouraging the members of the WKMO while expanding the scope of work it does for the community despite various obstacles along the way.

This momentous occasion is no doubt an important milestone for the Korean medical community. Furthermore, I believe that this journal will not only be the center for various clinical and academic exchanges of Korean doctors, but also help to facilitate such discussions and cooperation. By advocating volunteerism in developing countries, WKMO shares KOICA's vision of enhancing the quality of sustainable lives as well as poverty reduction through the achievement of the MDGs.

As you might know, out of the eight targets of the MDGs, three are directly related to the health sector. As a result, the MDGs have contributed to placing the health sector as a top priority agenda and the enhancement of health care all around the world.

However, the health sectors of developing countries are still facing many difficulties and require more aid and assistance. Every year, 360,000 women across the globe die due to pregnancy-related causes, and 76 million children fall victim to death caused by malnutrition and disease. And of course, despite the global efforts, the fight against HIV/AIDS still has a long journey to go.

In this context, KOICA, as Korea's official grant aid implementation agency, provides extensive support for the development of our partner countries. As a part of these efforts, the health sector has been designated as one of our most important core sectors, and we carry out many health-related programs. In particular, maternal and child health, strengthening of health system programs, establishment of health centers and hospitals, and fostering of health workforce are some of the key programs.

However, KOICA cannot carry out these activities alone. It continually needs the support of relevant experts as well as the cooperation of other organizations. For this reason, the cooperation between KOICA and WKMO is crucial in providing support for enhancing the health of the people of developing countries.

I once again offer my congratulations on the publication of WKMJ. I highly anticipate the great contributions it will make as a source for academic knowledge sharing in all areas of health, and hope that it will also provide a space for doctors to cooperate on working to develop the health sectors of developing countries.

Lastly, I wish for the continued success and growth of the WKMO, and may it serve a critical role in improving the lives of not only the members of the Korean community but also of those all around the world.

Thank you.

Young-mok Kim
President
Korea International Cooperation Agency

On behalf of Hanmi Pharmaceuticals, I express our respect to World Korean Medical Organization (WMKO), who has played pivotal roles for *Korean Healthcare Professionals* worldwide who have endeavored for global health and happiness, and sincerely congratulate the first publication of the World Korean Medical Journal (WKMJ) which would greatly contribute in sharing and expanding WMKO's activities. Also, we praise Chul-Soo Hyun, the President of WKMO, and his leadership team for making such progress.

Hanmi, as one of the leading Korean pharmaceuticals, has always strived to be a global company through R&D. As a result, we have developed innovative novel drugs in Oncology and Biologics, over ten of which are currently under multinational clinical trials in the US and Europe.

In addition to innovative novel drugs, Hanmi has developed a great number of Incrementally Modified Drugs (IMD) and Fixed-Dose Combination (FDC) drugs, entering global markets by collaboration with multinational companies such as Merck, Sanofi and GSK. Hanmi's "ESOMEPRAZOLE STRONTIUM Delayed Release Capsule 49.3 mg", a pharmaceutical alternative to NEXIUM® capsule 40mg for a more affordable treatment option for gastroesophageal reflux disease (GERD) in adult patients, was launched in the US market in December 2013. Esomeprazole strontium is currently marketed in the US by Hanmi's US partner, Amneal Pharmaceuticals.

All such Hanmi's R&D activities and global market expansions have been supported by Korean Healthcare Professionals worldwide. With the first publication of WKMJ as a momentum, we wish all members of WKMO collaborate closely each other and support Korean pharmaceuticals in entering global markets. Hanmi promises to do our best efforts to contribute to the activities of WKMO in the future.

May the Year of the Blue Horse bring all WKMO members health, happiness, and prosperity. Thank you.

Gwan Sun Lee, PhD
President & CEO
Hanmi Pharm. Co., Ltd.

Congratulatory Letter for World Korean Medical Journal (WKMJ)

BG Rhee, Ph.D.
President, Green Cross Holdings, KOREA
Chairman, Korea BIO

This is my great honor to acknowledge and congratulate World Korean Medical Journal for publishing its very first but remarkable issue. I truly believe that WKMJ will serve its role as the messenger of platform for a new paradigm in the healthcare industry and for the development of an active and strategic cooperation between Korea and other global markets. As you know, Korean Pharma/Bio industry is far less than global level compare to any other industry in Korea. Korean government is considering Pharma/Bio industry as one of the next generation growth engine and in this sense, I believe WKMJ will do significant role to highlight the major issues of dynamically evolving healthcare industry and to support global market entry.

Since adaptation of trendy technologies is often critical with numerous controversies, I hope WKMJ serves as a vital source for continued analysis and dialogues among the field's leading minds on pharmaceuticals, medical devices and healthcare services.

I would like to express my heartfelt support and congratulate WKMJ's new beginning and dedicated enthusiasm towards their goals of enhancing the networking opportunities, improving levels of understanding, fostering a platform for information sharing and identifying opportunities for technological/commercial collaboration among the healthcare industries.

Thanks.

Byung Gun Rhee, PhD
President
Green Cross Holdings, KOREA
Chairman
Korea BIO

Holy Name Medical Center

Dear WKMO Members, Colleagues and Friends,

On behalf of Holy Name Medical Center, I am honored to congratulate the World Korean Medical Organization on this most auspicious occasion: its launch of the *World Korean Medical Journal*. I would like to acknowledge the WKMO membership, its associated partners, and Dr. Chul S. Hyun, president of WKMO and the Director of Asian Liver Center of Holy Name Medical Center, for their vision of a global medical and scientific network that engenders fellowship and collaboration.

Working cooperatively and sharing intelligence with the goal of elevating standards of health care and medical training worldwide is a lofty mission that we at Holy Name wholly appreciate and support. The potential impact of *World Korean Medical Journal* is formidable because it will reach so many physicians, health industry leaders, biomedical scientists and others who, through their dedication, skills and insights, will find solutions to the medical challenges of today and the future.

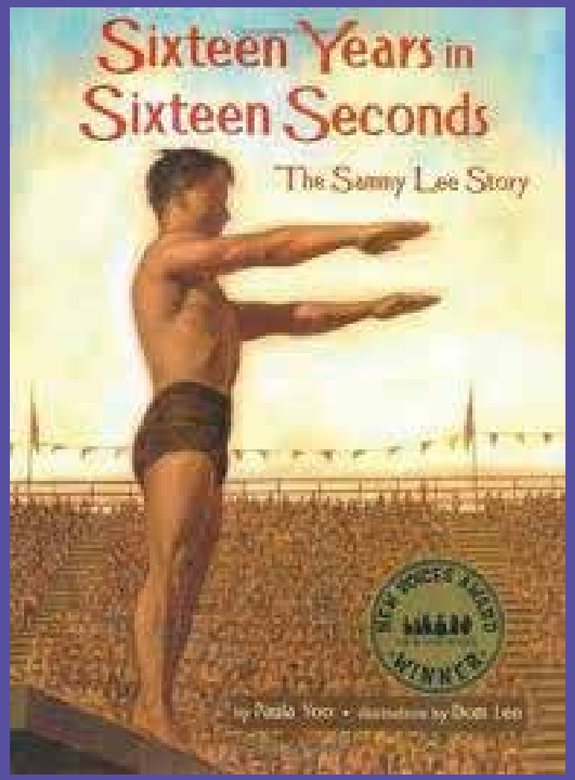
At Holy Name, we too, strive to address the medical challenges that face a diverse patient population. Our Korean Medical Program (KMP) is a linguistically and culturally sensitive healthcare initiative which, like WKMO, seeks to enhance the health status of Korean Americans and, in doing so, to advance the standard of healthcare delivery on a broader scale. With a Korean American physician staff numbering 80-plus, medical programs featuring primary care and multiple specialties, and community outreach targeted to Korean-specific needs, the KMP's patient volume has burgeoned beyond expectations, serving more than 40,000 people each year and becoming a national model for culturally focused health care.

Please accept my gratitude for your leadership in establishing a worldwide forum for information exchange, and my commendations on the inaugural issue of *World Korean Medical Journal*.

Sincerely,

Michael Maron
President & CEO
Holy Name Medical Center

Overcoming the Odds: Dr. Sammy Lee's Journey to the American Dream



Less than 5 foot 2 inches tall, it is hard to imagine this elderly man of small stature to be a two-time Olympian honored by so many accolades. Dr. Samuel "Sammy" Lee, a Korean American physician who has left an indelible mark as an American champion diver, is still a force to be reckoned with.

His achievements as a diver are well documented. He won three Olympic medals, a gold medal in the 10-meter platform and a bronze in the three-meter springboard competitions from 1948 Olympic Games in London; another gold medal was won in the 10 meter platform from Helsinki in 1952. As the oldest person to win a gold medal in diving at age 32, Dr. Lee, the first Asian American to win an Olympic gold medal for the United States, was also the first male diver to win consecutive diving gold medals. He was the first Asian American to be awarded in 1953 the James E. Sullivan Memorial Award as outstanding U.S. amateur athlete.

COVER STORY

Being a star athlete and coach was just another title to many he will receive in his lifetime. He received his medical degree from the University of Southern California (USC) in 1947, later becoming an ear, nose and throat specialist. A fervent patriot, he served in World War II and as a Major in the U.S. Army Medical Corps in South Korea from 1953–55. According to an anecdote, the Army asked Major Lee to treat then South Korean President Syngman Rhee for an ear infection. "Yes, I took care of Syngman Rhee. It was severe "otitis externa," due to his scratching," said Lee. President Rhee in turn organized a ceremony at the Blue House (Korean White House) and honored Lee for his Sullivan Award.

Living in Southern California with his Chinese American wife, Roz, Dr. Lee will be turning 94 this August.

Dr. David Ko, editor in chief of WKMJ, and Dr. Jinha Park, board member of WKMO, visited Dr. Lee to talk about his illustrious life and the time when only a few Asian Americans practiced medicine. Cheerfully welcoming them into his home, Dr. Lee reminisced fondly his old mentor. "My hero is Dr. Kihyung Kwon, who could do seven open heart surgeries a day, whereas other heart surgeons took seven hours to operate just one case," he said with chuckles. "There weren't many of us – Asian American medical doctors – back then, but we were skillful physicians dedicated to our patients and the practice of medicine. I would like to congratulate WKMO for continuing that legacy by extending tender loving care to all Americans and beyond, and showing how compassionate Koreans are."

Dr. Lee's life journey had a humble start in California's San Joaquin Valley, born to Korean parents who emigrated from Korea. The Lees had tried truck farming in Fresno, which was destroyed by fire before they moved to Bunker Hill where they opened a grocery store. Raised in Highland Park, Lee encountered many obstacles due to widespread racism and inequality in America, as people of colors, including Asians, were often discriminated. But those difficulties did not deter him from embracing his American dream, a value instilled by his father Soonkee Rhee who spoke to young Lee about inner fortitude and the importance of citizenship.

Sammy Lee in costume and on a photographers pony. ca. 1928 | Image: Courtesy of Los Angeles Public Library

Lee was a boy scout at Yorkdale Grammar School and was cheerleader at Luther Burbank Junior High School. While at Franklin High School, he became an all "A" student and voted to be the first non-white student body president in 1939. His turning point in life came when he graduated from Occidental College in 1943, the year he lost his father to a massive brain hemorrhage. He had promised his father to become a medical doctor, so he got into USC where he also joined the Army reserves to pay for his tuition.
There, he enrolled in an accelerated program that condensed a four-year medical curriculum into two years and nine months. Due to the outbreak of World War II, the United States was desperately in need of doctors. Struggling to keep up with studies, he even flunked out of school at one point.

However, helped by friends from fraternities who shared copies of past exams, Lee graduated from USC Medical School in June 1946 and was assigned to the McCornack Army Hospital in Pasadena as first lieutenant.

Dr. Lee joked that he became a great diver, because "Every time I did poorly on an exam, I would go to the pool to dive and relax." He went on to become an Olympic diving champion in 1948 along side Miller Anderson and Bruce Harlan. He would finish his residency in ear, nose and throat diseases at Letterman Army Hospital and was assigned to the 121st EVAC hospital outside of Seoul. In 1954, Lee became Goodwill Sports Ambassador for the U.S. in Southeast Asia.

He went into private practice after resigning his Regular Army Commission as Major and hoped to establish a medical practice in Santa Ana by the mid-1950s. But local doctors weren't supportive of his move, while developers in Garden Grove refused to sell him a house despite his highly respectable reputation as an Olympian. The Lees were able to secure their home only after Scott Newhall, the editor of the San Francisco Chronicle, and even conservative presses such as The Santa Ana Register and Long Beach Press Telegram came to the Lees' defense. Newhall said, "The story of Major Lee's reception in Garden Grove will embarrass our country in the eyes of the world."

Although he suffers from dementia since 2013, Dr. Lee remains in great spirit and health, with years of hard work and glory behind him. He has been honored as a member of the US Olympic Hall of Fame, with a landmark in Los Angeles' Koreatown dedicated to him as the Sammy Lee Square in 2010. Recently, Central Region Elementary School #20 was renamed the Dr. Sammy Lee Medical and Health Sciences Magnet School in 2013.

Beaming as he talks about his two children, Pamela and Sammy II, and three grandchildren he adores, he told the Los Angeles Times, "I no longer worry about heaven because I get to play with three angels on planet Earth." Dr. Lee is a true role model for rising above harsh discrimination and the naysayers who doubted that he could achieve excellence as both a physician and an athlete. Here is to his lasting legacy of the American dream and undefeated spirit that live on in all of us. W

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BIOPHARMA IN 2013: A RISING TIDE

Big launches, clinical success in key therapeutic areas like cancer immunotherapy, and renewed interest in biotech from a broad investor base floated the biopharma world through 2013's average year for FDA approvals, the rocky rollout of the Affordable Care Act, and increasing concern about drug prices.

BY IN VIVO'S BIOPHARMA TEAM

In 2013, the broader biopharmaceutical world built on the valuation gains afforded by a buoyant stock market and enthusiasm – unmatched in the history of the industry – for biotech IPOs. But this boom comes amid a reversion to the regulatory mean, as FDA approved a dozen fewer drugs in 2013 than in the standout year of 2012; the cooling of growth in emerging markets like China; and the not-so-distant drumbeat of payor demands for health care value.

Deal trends largely stayed on track from previous years, with peer dealmaking among large companies gaining steam and "innovation center fever" – **Johnson & Johnson**'s was contagious – reflecting pharma's continued push into earlier-stage, less-expensive asset and technology acquisitions. Pharma-VC collaboration also continued apace, with **GlaxoSmithKline PLC** leading the way through its Avalon Ventures tie-up. (*See "Venture Firm Avalon Turns To GSK To Share Biotech Risk"* — START-UP, *May 2013*.) There were few enormous deals, and where multibillion dollar dealmaking was concerned, Big Pharma seemed to take a backseat to increasingly aggressive specialty pharma and Big Biotech acquirers.

Although rollout of the Affordable Care Act has been anything but smooth, pharmaceutical companies will still very likely enjoy the growth in drug spending that is at least in part a result of its implementation. Nearly all drug companies are pursuing some variety of medication adherence strategy. (*See "Medication Adherence: A Positive Story You Are Not Hearing"* — IN VIVO, *November 2013*.) Some, such as **Merck & Co. Inc.** with its HMR Weight Management Services Corp. and post-hospital-discharge services company Vree Health, are very much playing the ACA angles in so-called beyond-the-pill adjacencies. (*See "Merck's "Beyond The Pill" Bet, Vree Health, Goes Commercial"* — IN VIVO, *October 2013*.)

ALLIANCES: NEW NORMAL?

Alliances in 2013 did not pick up after a weak 2012. Exhibit 2 shows the decline in total up-front cash flowing from large to small partners in biopharma deals is continuing. The number of deals potentially worth at least $10 million in combined up-front and downstream payments has seemingly bottomed out around 90 deals. This new normal is abetted by biotech corporate structures that incentivize M&A (including full acquisition of individual assets), fewer large pharmaceutical buyers, R&D restructuring at several large pharmaceutical companies, and shifting commercial priorities.

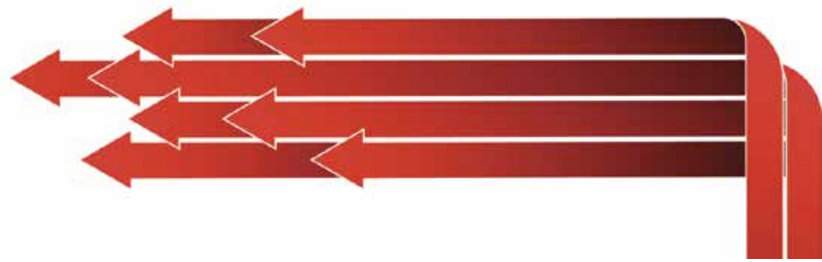
But fewer deals is not necessarily a sign of reduced interest on the sell-side, which given the year's free-flowing capital has surprised even seasoned dealmakers. **Roche**'s **Genentech Inc.** partnering chief James Sabry was expecting a dropoff in partnering interest to accompany the biotech boom last year. That hasn't happened.

"What we've noticed is, remarkably, no diminution in interest in partnering," he said in an interview during the 2014 *JP Morgan Health Care Conference*. "Ten years ago, when I was running a company, if there was a ready-made way to access capital, we would put off partnering discussions and create more value and take more risk. What I thought we'd see, but we don't see, is people saying, 'We'll talk to you in a few years when we have Phase II data.'"

And there certainly are investors eager to pour in capital by floating biotech companies on the public markets. Newly public companies – and the horde amassing in the IPO queue behind them – have the cash that might suggest they should be dealing from a position of strength, or not wanting to deal at all. (*See "On The Road And Through The Window: Inside Three Biotech IPOs"* — START-UP, *November 2013*.)

That said, although the frequency of partnership interactions hasn't changed, potential partners have predictably become more aggressive – another data point for the "this time it's different" crowd. That suggests to Sabry that smaller or newly public biotechs are perhaps justifiably concerned that the boom won't last or recognize that development is increasingly difficult. Attrition rates in the clinic are as bad, or worse, than ever, finds a study by analysts at BioMedTracker and the Biotech Industry Organization published online in January in *Nature Biotechnology*. Some of that attrition boils down to companies facing up to the fact that some drug candidates may be safe and effective – but may struggle to compete regardless.

So interest remains high, discussions are ongoing, but fewer deals are getting done. (*See "2013's Top Biopharma Dealmakers," this issue. Roche cracks the top five.*) That overall trend is reflected by Genentech's own experience. "We're passing on deals that other people are doing at crazy valuations," says Sabry. "Some of the deals you don't know about because we didn't do them because they priced themselves out of our sweet spot."



BREAKTHROUGH DRUGS: FDA HITTING STRIDE

Genentech Inc.'s *Gazyva* (obinutuzumab) represents a lot of "firsts." Formerly GA101, the chronic lymphocytic leukemia drug is Genentech's first application to go through the Food and Drug Administration's new review process under the Prescription Drug User Fee Act V. It was also the company's first "Breakthrough" designation from FDA – and the first "Breakthrough" application accepted for filing. And on November 1 it became the first "Breakthrough" product approved by the agency. (*See "FDA's First "Breakthrough" Approval Coming; Won't Break Speed Records"* — The RPM Report, *October 2013*.)

"The approval reflects the promise of the breakthrough therapy designation program, allowing us to work collaboratively with companies to expedite the development, review and availability of important new drugs," FDA Office of Hematology and Oncology Products director Richard Pazdur said in the agency's announcement of the approval. (*See "Roche's Gazyva Clears FDA, But First Breakthrough Approval Breaks No Speed Barriers"* — "The Pink Sheet," *November 4, 2013*.)

Gazyva, however, is not a true test of the program's impact. Because the designation wasn't available during GA101 development –Genentech requested it at the time of the BLA submission – the company missed out on the program's opportunities for accelerating drug development. But it's unlikely industry will have to wait too long to witness the full potential of the program to accelerate development of industry's most impressive product opportunities. (*See Exhibit 3*.)

> FDA approved 27 NMEs in 2013, down from 39 in 2012. FDA's statistics would suggest 2013 is the more "normal" year. Meanwhile, FDA review times for new drug and biologic therapies continued their downward trend in 2013, even though just over half of CDER's novel approvals in the year were subject to the longer review timetables under what the agency calls "the program" for NME and novel biologic reviews.

Among the first wave of breakthrough therapies – the second to get FDA's nod – is **Johnson & Johnson** and **Pharmacyclics Inc.**'s expected oncology blockbuster *Imbruvica* (ibrutinib). (*See "Pharmacyclics/Janssen Offer Suite Of Patient Support Programs For Imbruvica"* — "The Pink Sheet," *November 18, 2013*.)

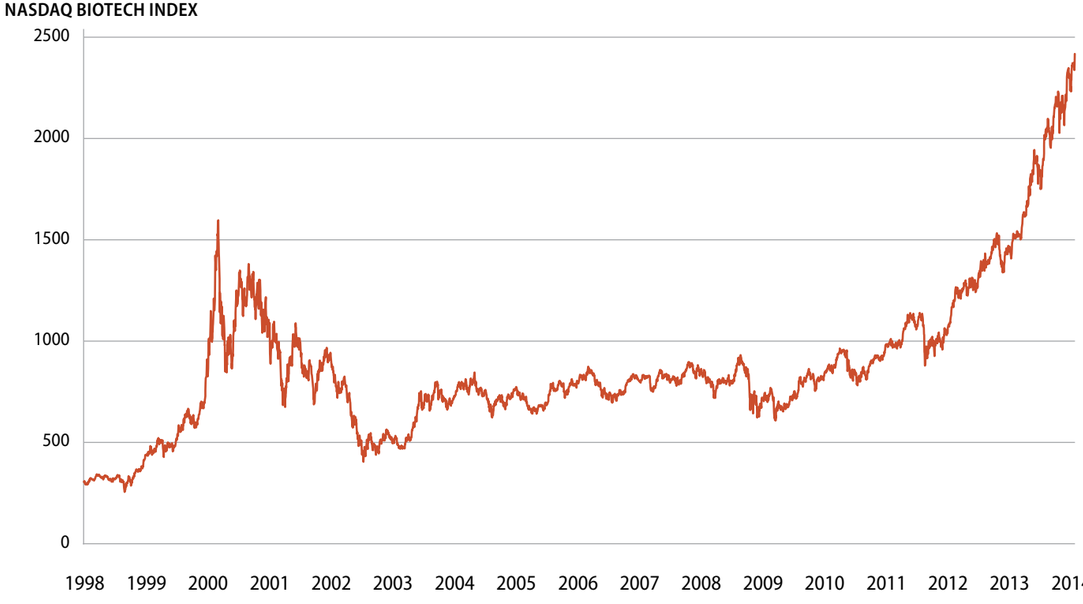
SPECIALTY PHARMA TOP BUYERS IN 2013

Although 2012 and to a lesser extent 2013 gave large pharmaceutical companies new product approvals to drive future growth, current trends in R&D productivity make it unlikely that organic growth alone will be sufficient to boost Big Pharma revenue to the extent that the group can keep up with faster growing specialty pharma and biotech companies. M&A is essential, analysts at Ernst & Young pointed out this year.

Unfortunately, just when Big Pharma

Exhibit 1

Bull Market Or Bubble Market?



The soaring Nasdaq Biotech Index has exceeded the most optimistic expectations over the past year. Whether or not 2014 brings more of the same frothiness remains to be seen, but heading into January's conference season the general sentiment remained, reflecting a "this time it's different" mentality. The boost extended beyond the components of the NBI – 2014's early star was Intercept Pharmaceuticals Inc.*, which added more than $7 billion to its market capitalization in two days in early January after announcing a surprisingly successful Phase II trial for a liver disease therapy. Intercept's valuation has since drifted back to earth a bit, but it remains $4 billion higher than before the news broke.*

SOURCE: Yahoo! Finance

most needs growth through acquisitions, its resources to conduct such transactions have become more constrained. To quantify this phenomenon, E&Y developed a measure of "firepower" – the financial resources a company has available to execute M&A or alliances. Firepower is directly correlated with market value, cash, and equivalents, and is inversely correlated with debt. E&Y's analysis, published in *IN VIVO* in June 2013, looked primarily at acquisitions, for the simple reason that most alliances cannot be expected to provide a meaningful boost to revenues in the near term. (*See "Biopharma M&A In An Era Of Elusive Growth, Capital Triage, and New Competitors"* — IN VIVO, *June 2013.*)

To the extent Big Pharma was a major player on the business development scene in 2013, it was largely through early-stage dealmaking and outreach to scientific hotspots like Boston or San Francisco. The wheelers and dealers writing big checks tended to be from specialty pharma companies such as **Valeant Pharmaceuticals International Inc.** (*See Exhibit 4.*)

Valeant has been telling investors (most recently during the January 2014 JP Morgan gathering) that it plans to be a "top five" pharma business by 2016 – which would essentially mean adding more than $100 billion in market cap over the next few years. Meanwhile, what excites analysts most about the Pfizers and Mercks of the world is whether they'll get smaller – through divestments or spin-offs of businesses like consumer or animal health. Big Biotechs such as **Biogen Idec Inc.**, **Celgene Corp.**, and **Gilead Sciences Inc.** are growing much faster than traditional large pharmaceutical players and have enjoyed the year's most explosive launches. As such, it's easy to wonder whether the current crop of Big Pharma players will be eclipsed by these upstarts sooner rather than later.

TECFIDERA: 2013'S BREAK-OUT STAR

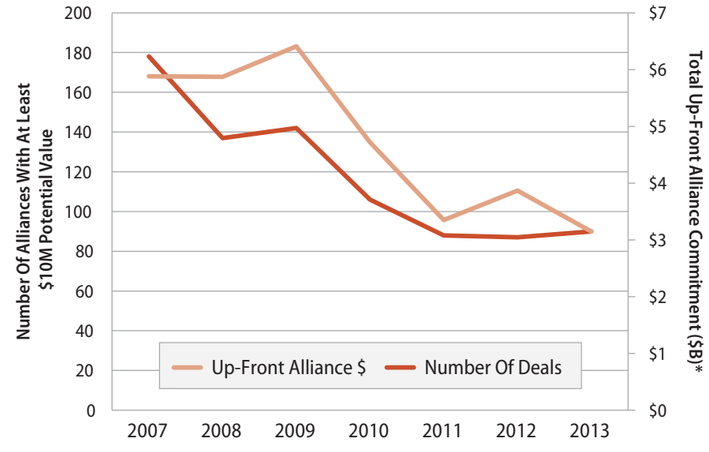
Biogen Idec's *Tecfidera* (dimethyl fumarate) stands as proof that the blockbuster drug is alive, if perhaps not exactly kicking, in 2013. The drug was the break-out star among the new drugs that launched during the year and the only one to stand out from the group on sales metrics.

Tecfidera, an oral pill for multiple sclerosis, appears to have generated sales approaching $1 billion in 2013 after just nine months on the market (official annual sales tallies aren't yet available).

The drug brought in $478.5 million for Biogen Idec from its launch in April through September, surpassing analyst expectations and Biogen's own internal forecasts. It's likely to outpace first-year sales of **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) for age-related macular degeneration, regarded as one of the most successful recent drug launches. Eylea debuted in late 2011 and generated sales of $838 million in 2012. Tecfidera appears on track to surpass $1 billion in sales in its first 12 months on the market.

Exhibit 2

Alliances Continue To Lag



**Biotech/Pharma alliances where total potential value is at least $10 million.*

SOURCE: *Strategic Transactions*

Exhibit 3

"Breakthrough Therapy" Designation Requests

	REQUESTS RECEIVED	REQUESTS GRANTED	REQUESTS DENIED
CDER (as of 1/3/2014)	**121***	**36**	**59**
CBER (as of 1/3/2014)	**20**	**1**	**13**
FDA Total	**141**	**37**	**72**

** At least six applications have been withdrawn.*

SOURCE: FDA

It was the exception in 2013, not the rule. No other new drugs flew out of the gates with as much speed, and only one other generated more than $100 million in sales in the first months of launch.

The early success of Tecfidera harkens back to **Vertex Pharmaceuticals Inc.**'s hepatitis C drug *Incivek* (telaprevir), which generated $950.9 million in sales in 2011 following its mid-year launch. Vertex hasn't been able to sustain the sales momentum for Incivek, however, as "warehoused" patients were treated and as other patients await the first all-oral regimens, the first of which – Gilead's *Sovaldi* (sofosbuvir) – was approved in December 2013. Incivek generated only $447 million in the first nine months of 2013, less than half what it generated in the first nine months of 2012.

Sovaldi is very likely to be 2014's launch of the year – and with analysts talking about a potential billion-dollar quarter for the drug in its first full quarter on the market, perhaps the launch of the decade or longer.

REIMBURSEMENT: PBMS PLAYING HARDBALL

The coming year could see increased intensity in drug pricing negotiations between some brand drug manufacturers and the largest pharmacy benefit managers, as **Express Scripts Inc.** and **CVS Caremark Corp.** weigh adding more drugs to their "not covered" lists.

The formulary exclusion lists, especially Express Scripts', were a particularly important development in the reimbursement world in 2013. (*See "Express Scripts Tightens Commercial Formulary Control With "Not Covered" List"* — "The Pink Sheet," *October 7, 2013.*) The lists were developed as part of the PBMs' 2014 recommended national formularies for commercial insurance plans and are noteworthy because they are expected to solidify the presence of more restrictive formularies in employer-sponsored insurance.

Express Scripts and CVS Caremark are expected to announce the next iteration of their national formularies for the 2015 plan year, including lists of "not covered" drugs, around late summer/early fall. Both firms have said they see room to expand their "not covered" lists, particularly in the area of specialty drugs.

Express Scripts' "not covered" list includes 48 branded products – 44 drugs and four diabetes test kits – and was launched for the first time in 2014. CVS Caremark's list includes even more products, a total of 76, including a number of diabetes test strips and kits. (*See "CVS Caremark Formulary Exclusion Program Expected To Save $1 Bil. In 2014"* — "The Pink Sheet" DAILY, *December 20, 2013.*) CVS Caremark first introduced a "not covered" list in 2012; the current version includes 25 new products and the rest are carryovers from the previous year.

The concept of a "not covered" drug list was not new in commercial insurance when

THE *IN VIVO BLOG'S* DEALS OF THE YEAR

Our editors nominated half a dozen pharma deals in three categories, and blog readers cast their votes

☑ **M&A OF THE YEAR: AMGEN/ONYX**

62% OF THE VOTERS CHOOSE AMGEN/ONYX – and we'll all be watching *Kyprolis* (carfilzomib) to see whether the price was right.

☑ **ALLIANCE OF THE YEAR: CELGENE/ONCOMED**

63% OF THE VOTERS CHOOSE CELGENE/ONCOMED – Their cancer stem cell alliance claimed the top spot.

☑ **FINANCING OF THE YEAR: GSK/AVALON**

48% OF THE VOTERS CHOOSE GSK/AVALON – This one was a squeaker, but GlaxoSmithKline and Avalon Ventures' company-creating partnership carried the day.

Express Scripts introduced its 2014 list during the latter half of 2013. Nevertheless, the move sent shockwaves through the biopharma industry.

What was striking about the Express Scripts "not covered" list is that it demonstrated a more aggressive approach than had been taken by CVS Caremark. For one thing, it targets more high-profile drugs, such as GSK's *Advair Diskus* (fluticasone/salmeterol) and Novo Nordisk AS's *Victoza* (liraglutide), on the basis that the dosing advantages offered by the products are not enough to ensure a place on formulary.

Express Scripts also includes more specialty drugs on its list, such as treatments for hepatitis C, multiple sclerosis, and inflammatory disease, and growth hormone products. CVS Caremark's list covers just one specialty class – growth hormones.

The Express Scripts list also illustrates a different approach to exclusion and one that is potentially more worrisome for drug firms. It targets brands with branded drug alternatives in the same class and not just brands that have generic competition in the same class, like CVS Caremark has done. Express Scripts' approach thus drives branded manufacturers to compete with each other for a spot on the formulary through bigger price concessions and rebates.

The moves underscore the importance of incorporating payor perspectives into drug development plans as early as is practical. Doing so should also increase potential deal values for biotech firms shopping their wares to commercial partners. (*See "Surpassing Expectations: Increasing Deal Value Through Better Drug Value Propositions"* — IN VIVO, *November 2013*.)

TACKLING CANCER DRUG PRICING?

The time has come for Roche to revise its approach to oncology drug pricing, Pharmaceuticals Division chief operating officer Daniel O'Day stated at an analyst briefing held at the American Society for Clinical Oncology Annual Meeting June 2. Payment will need to move away from volume, especially as expensive combinations become more widespread in treating cancer, O'Day suggested. "The days of looking at per-milligram price, I think for us in many countries, and certainly when we look at the next three years, it's unsustainable," he acknowledged. "It's unsustainable to suggest that we're just going to simply add another therapy at $8,000 to $10,000 a month on top of [existing costly therapy] and expect constrained health care systems to be able to pay for that. So we have to be a bit more creative about it," he said. (*See "Roche Experimenting With New Pricing Models In Oncology"* — IN VIVO, *June 2013*.)

The company's new pricing focus will include indication-based pricing, pricing for combination therapy, and eventually, in some countries, outcome-based models, O'Day indicated. Roche has started this shift, "but it will advance," he said. In Germany, where novel medicines must show an added benefit as they go through a two-tier system of health technology assessment, Roche uses a capitation program where everything over 10 grams in an annual period is covered by the company. A similar program is used in Italy, and the idea is similar to the price cap in the US (for labeled indications only). However, "there is no one size fits all here," O'Day cautioned. "Every health care system has different dynamics; they have different needs." Risk-sharing arrangements that make payment contingent on pre-specified outcomes are also part of the *Avastin* (bevacizumab) policy in Italy for the first dosing schedule. Indication-based pricing is facilitated by stronger data sources at the country level, and the approach allows Roche to monitor patients by indication.

GSK PROBE SLOWS CHINA JUGGERNAUT

It is not surprising that Big Pharma sales hit the wall in the third quarter of 2013 in China as widespread compliance probes cooled down marketing activities during the period. Overall, the top 10 Big Pharma in China reported an average 1% sales growth in Q3; in contrast, these companies grew 18% in Q2, 24% in Q3 last year, and 23% for the full year in 2012.

GSK, which is in the eye of China's compliance storm, reported a 61% sales decrease in the country for the quarter. (*See "Public Security Ministry Claims Evidence Of GSK Bribery In China; Several Execs Arrested"* — PharmAsia News, *July 11, 2013*.) Excluding GSK, average growth of the other nine companies was still only 8% (or 9% if excluding Pfizer Inc.'s transfer of products to its joint venture with Zhejiang Hisun Pharmaceutical Co. Ltd.), poor growth for an emerging powerhouse like China.

Most companies' revenue growth was down 6% to 10% compared with Q2 numbers. Roche dropped 18% from the previous quarter but still kept a relatively high year-on-year growth of 16%. Merck was the largest victim after GSK with a 21% drop from the previous quarter and a year-on-year sales decrease of 8%. (*See "Behind The Ugly Numbers From The Compliance Crisis Fallout: China Big Pharma Roundup"* — PharmAsia News, *November 7, 2013*.)

A#2014800012

COMMENTS: Email the editor: *Chris.Morrison@Informa.com*

Exhibit 4

Blockbuster M&A – Billion Dollar Club Sees Few Big Pharma Members In 2013

DATE	DEAL	TOTAL VALUE (INCLUDING BIOBUCKS)
June 2013	Amgen buys Onyx Pharmaceuticals	$9.2 billion
May 2013	Valeant buys Bausch & Lomb	$8.7 billion
July 2013	Perrigo buys Elan	$8.3 billion
May 2013	Actavis buys Warner Chilcott	$8.1 billion
November 2013	Shire buys ViroPharma	$3.3 billion
December 2013	AstraZeneca buys BMS out of diabetes JV	$2.7 billion ($4.375 billion)
November 2013	Bayer buys Algeta	$2.6 billion
November 2013	Salix buys Santarus	$2.1 billion
February 2013	Mylan buys Agila	$1.6 billion ($1.85 billion)
November 2013	Endo buys Paladin	$1.5 billion
June 2013	AstraZeneca buys Pearl Therapeutics	$560 million ($1.15 billion)
June 2013	J&J's Janssen buys Aragon Pharmaceuticals	$650 million ($1 billion)

SOURCE: *Strategic Transactions*

CMS SEES NO END TO DRUG SPENDING GROWTH

In 2009, prescription drug spending was $254.6 billion, according to the Centers for Medicare and Medicaid Services' National Health Statistics Group. Thirteen years later, in 2022, drug spending is projected to be $455 billion for that single year – a difference of about $200 billion and one that paints a picture of solid annual growth in prescription spending in the 5% to 7% range over an extended period of time.

RELATED READING

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"FDA's First "Breakthrough" Approval Coming; Won't Break Speed Records" — *The RPM Report,* October 2013 [A#2013500123]

"Roche's Gazyva Clears FDA, But First Breakthrough Approval Breaks No Speed Barriers" — *"The Pink Sheet,"* November 4, 2013 [A#00131104018]

"Pharmacyclics/Janssen Offer Suite Of Patient Support Programs For *Imbruvica"* — *"The Pink Sheet,"* November 18, 2013 [A#00131118014]

"Drug Spending Expected To Rise By $200 Bil. In 2022 Compared To Pre-ACA Levels" — *The RPM Report,* September 2013 [A#2013500113]

"Express Scripts Tightens Commercial Formulary Control With "Not Covered" List" — *"The Pink Sheet,"* October 7, 2013 [A#00131007006]

"CVS Caremark Formulary Exclusion Program Expected To Save $1 Bil. In 2014" — *"The Pink Sheet" DAILY,* December 20, 2013 [A#14131220002]

"Surpassing Expectations: Increasing Deal Value Through Better Drug Value Propositions" — *IN VIVO,* November 2013 [A#2013800199]

"Roche Experimenting With New Pricing Models In Oncology" — *IN VIVO,* June 2013 [A#2013800116]

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BRIEF SUMMARY

ESOMEPRAZOLE STRONTIUM

delayed-release capsules 49.3 mg

For oral use only

Rx Only

BRIEF SUMMARY of Prescribing Information

INDICATIONS AND USAGE

Treatment of GERD in Adults: Esomeprazole strontium is indicated for the short-term treatment (4 to 8 weeks) for healing and symptomatic resolution and maintenance (controlled studies do not extend beyond 6 months) of confirmed erosive esophagitis (EE), the short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults. **Risk Reduction of NSAID-Associated Gastric Ulcer in Adults, *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence in Adults, and Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults.**

CONTRAINDICATIONS

Esomeprazole strontium is contraindicated in patients with known hypersensitivity to proton pump inhibitors (PPIs). Hypersensitivity reactions, e.g., angioedema and anaphylactic shock, have been reported with esomeprazole use. For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with esomeprazole strontium, refer to the **CONTRAINDICATIONS** section of their package inserts.

WARNINGS AND PRECAUTIONS

Concurrent Gastric Malignancy: Symptomatic response to therapy with esomeprazole strontium does not preclude the presence of gastric malignancy.

Atrophic Gastritis: Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer.

***Clostridium difficile* Associated Diarrhea:** Published observational studies suggest that PPI therapy like esomeprazole strontium may be associated with an increased risk of *Clostridium difficile* associated diarrhea. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with esomeprazole strontium, refer to **WARNINGS** and **PRECAUTIONS** sections of those package inserts.

Interaction with Clopidogrel: Avoid concomitant use of esomeprazole strontium with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using esomeprazole strontium, consider alternative anti-platelet therapy.

Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesemia: Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Concomitant Use of esomeprazole strontium with St. John's Wort or Rifampin: Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole strontium with St. John's Wort or rifampin.

Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Providers should temporarily stop esomeprazole treatment before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Concomitant Use of esomeprazole strontium with Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of esomeprazole strontium has been established from adequate and well-controlled studies of esomeprazole magnesium.

Adults: The safety of esomeprazole magnesium was evaluated in over 15,000 patients (aged 18 to 84 years) in clinical trials worldwide including over 8,500 patients in the United States and over 6,500 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, esomeprazole magnesium was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in 4 randomized comparative clinical trials, which included 1,240 patients on 22.3 mg of esomeprazole magnesium (equivalent to 20 mg of esomeprazole), 2,434 patients on 44.6 mg of esomeprazole magnesium (equivalent to 40 mg of esomeprazole), and 3,008 patients on 20 mg of omeprazole daily. The most frequently occurring adverse reactions (≥1%) in all three groups were headache (5.5%, 5%, and 3.8%, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium or omeprazole. Additional adverse reactions that were reported as possibly or probably related to esomeprazole magnesium with an incidence <1% are listed below by body system: **Body as a Whole:** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; **Cardiovascular:** flushing, hypertension, tachycardia; **Endocrine:** goiter; **Gastrointestinal:** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; **Hearing:** earache, tinnitus; **Hematologic:** anemia, anemia hypochromic, cervical lymphadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; **Hepatic:** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; **Metabolic/Nutritional:** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; **Musculoskeletal:** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; **Nervous System/Psychiatric:** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; **Reproductive:** dysmenorrhea, menstrual disorder, vaginitis; **Respiratory:** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; **Skin/Appendages:** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; **Special Senses:** otitis media, parosmia, taste loss, taste perversion; **Urogenital:** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; **Visual:** conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse reactions include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

In two placebo-controlled studies, 710 patients were treated symptomatic GERD and the most common adverse reactions possibly or probably related to esomeprazole magnesium were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%). **Combination Treatment with Amoxicillin and Clarithromycin:** In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no additional adverse reactions specific to these drug combinations were observed. Adverse reactions that occurred were limited to those observed when using esomeprazole magnesium, amoxicillin, or clarithromycin alone. The most frequently reported drug-related adverse reactions for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse reactions were observed at higher rates with triple therapy than were observed with esomeprazole magnesium alone. For more information on adverse reactions with amoxicillin or clarithromycin, see their package inserts, refer to **ADVERSE REACTIONS** sections.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of esomeprazole magnesium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system: **Blood and Lymphatic:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastrointestinal:** pancreatitis, stomatitis, microscopic colitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; *Clostridium difficile* associated diarrhea; **Metabolism and nutritional disorders:** hypomagnesemia; **Musculoskeletal and Connective Tissue:** muscular weakness, myalgia, bone fracture; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal and Urinary:** interstitial nephritis; **Reproductive System and Breast:** gynecomastia; **Respiratory, Thoracic, and Mediastinal:** bronchospasm; **Skin and Subcutaneous Tissue:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS

Interference with Antiretroviral Therapy: Concomitant use of atazanavir and nelfinavir with PPIs is not recommended. Coadministration of atazanavir with PPIs is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Coadministration of saquinavir with PPIs is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. *Reduced concentrations of atazanavir and nelfinavir:* For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75%, respectively for nelfinavir and M8. Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. *Increased concentrations of saquinavir:* For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported, with an increase in AUC by 82%, in C_{max} by 75%, and in C_{min} by 106%, following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily coadministered days 11 to 15. Clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.

Drugs for Which Gastric pH Can Affect Bioavailability: Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g. ketoconazole, atazanavir, iron salts, and erlotinib can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (30% in two subjects). Esomeprazole is an enantiomer of omeprazole. Coadministration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Patients may need to be monitored when digoxin is taken concomitantly with esomeprazole.

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways: Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, quinidine, clarithromycin, or amoxicillin. Although drug interaction studies have not shown that esomeprazole has a clinically significant interaction with warfarin, post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of esomeprazole strontium with clopidogrel. When using esomeprazole strontium, consider use of alternative anti-platelet therapy. Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in a cross-over study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. A dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, who may require higher doses up to 240 mg/day, dose adjustment may be considered. Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolisers (C_{max} and AUC decreased by 37.5% and 37.9%, respectively) and extensive metabolisers (C_{max} and AUC decreased by 49.6 % and 43.9%, respectively). Avoid concomitant use of St. John's Wort or rifampin with esomeprazole strontium.

Interactions with Investigations of Neuroendocrine Tumors: Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels, which may interfere with investigations for neuroendocrine tumors.

Tacrolimus: Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.

Combination Therapy with Clarithromycin: Coadministration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions [see **WARNINGS** and **PRECAUTIONS** in prescribing information for clarithromycin]. Because of these drug interactions, clarithromycin is contraindicated for coadministration with certain drugs [see **CONTRAINDICATIONS** in prescribing information for clarithromycin].

Methotrexate: Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

SPECIFIC POPULATIONS

Pregnancy: *Pregnancy Category C:* There are no adequate and well controlled studies of esomeprazole strontium delayed-release capsules in pregnant women. Teratogenicity was not observed in an embryofetal developmental study in rats with either esomeprazole strontium or esomeprazole magnesium at equimolar oral doses up to 280 mg esomeprazole/kg/day (about 57 times the daily maximum recommended human dose (MRHD) of 40 mg on a body surface area basis). When administered as either the strontium or magnesium salt, changes in bone morphology and physeal dysplasia were observed in pre- and postnatal developmental toxicity studies in rats at doses equal to or greater than 138 mg esomeprazole/kg/day (approximately 33.6 times the daily MRHD of 40 mg on a body surface area basis). Because of the observed effect at the high doses of esomeprazole strontium on developing bone in rat studies, esomeprazole strontium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Limited published data indicate that esomeprazole and strontium are present in human milk. Because of the effect of esomeprazole strontium observed at high doses on developing bone in rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of esomeprazole strontium delayed-release capsules have not been established in pediatric patients. Strontium is known to compete with calcium for intestinal absorption and is incorporated into bone. Use in pediatric patients is not recommended because adequate safety studies have not been performed.

Geriatric Use: No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Use in Patients with Renal Impairment: No dosage adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of strontium in patients with severe renal impairment has not been studied and, therefore, use in this patient population is not recommended.

OVERDOSAGE

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - **ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose contact a Poison Control Center at 1-800-222-1222.

Please see package insert for full prescribing information.

More detailed information is available upon request.

For more information about esomeprazole strontium contact:
Amneal Pharmaceuticals at 1-877-835-5472.
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amneal PHARMACEUTICALS

Entrepreneur Interview

John Martin, CEO of Gilead Sciences, Inc.

1. We admire the efforts of Gilead Sciences to find right ways to overcome the major threats of human health, and challenges of diversifying its areas into cancer, HIV, hepatitis and beyond. What are Gilead's major business philosophy and strategies?

"Gilead's decision-making is guided by science and by the needs of patients. By understanding the needs of patients, we can focus research where our efforts will have the greatest future impact and apply scientific knowledge to those areas."

2. You have a science background and still, you had been recognized as one of the best CEOs among Fortune 500 companies, by many reputable media. What are the pros and cons of being a scientist trained CEO in the biotech company?

"The biotechnology industry is unique in that it is a blend of science and business. Having a foundation in science plus business education and experience allows one to make sound business decisions based on confidence in scientific data and principles."

3. You recently had a huge success in launching Hepatitis C medication and we've seen many innovative activities of Gilead. What makes Gilead a better innovator than other companies? In addition to that, what are your plans on launching Sovaldi in Korea, China and other Asian markets?

"By focusing on science and patient needs, we are able to identify the most important projects with the greatest likelihood of success, and those that will have the greatest future impact on patients' health.

In the area of HIV, the once-daily medications and single tablet regimens that Gilead has developed help to simplify treatment for patients. And while simplifying treatment has significantly benefited millions of patients worldwide, we continue to look at how we can improve on existing treatment options. The ultimate goal is to find a cure.

In the area of hepatitis B, we introduced Viread in Korea in 2012. We have been working in partnership with the medical community there, and around the world, to increase awareness of HBV and its link to liver cancer, and to expand access to treatment.

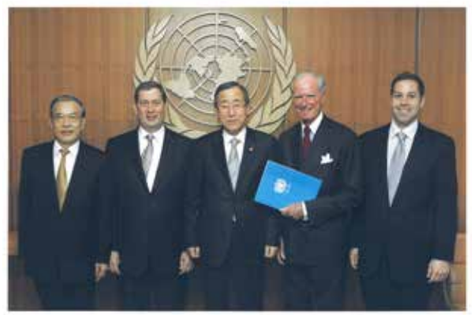
Hepatitis C is an international health challenge, and we're currently working to secure approval for Sovaldi around the world, including in Asian countries.

Over the years, Gilead has focused on bringing together teams of talented people with deep experience in their fields and a personal commitment to patients. When we opened our Seoul office in 2011 and our Tokyo office in 2013, we focused on recruiting experienced local professionals to lead our work in those markets. This will continue to be a critical component of our success as we expand our presence internationally."

4. The World Korean Medical Organization (WKMO) recently established a consulting subsidiary named W Medical Strategy Group to maximize utilization of knowledge and expertise of our member physicians in achieving our goals of enhancing quality of human life. What do you think the roles of physicians and also roles of organization such as ours are in developing new therapeutics?

"Scientific breakthroughs are almost always the product of collaboration, which is why Gilead works with a broad network of partners, including many researchers and clinicians who participate in clinical trials that are essential to therapeutic innovation. Healthcare professionals also play a critical role in identifying future needs, educating patients and helping them access the best treatments. Healthcare advocates are a strong voice in support of innovation."

5. Gilead is also known for supporting emerging countries to treat their major health threats. As the physician organization, we also focus on outreaching programs to contribute to the betterment of human health in emerging countries. What are your thoughts behind Gilead's huge support on those countries?



"Gilead makes it a priority to increase access to its medicines for people who can benefit from them, regardless of where they live or their ability to pay. Unfortunately, diseases like HIV/AIDS and viral hepatitis are taking the heaviest toll in countries with limited resources and limited healthcare infrastructure. In terms of treatment access, we apply the same focus on innovation and collaboration that drives Gilead research efforts. Today, 4.8 million people living with HIV in low- and middle-income countries are receiving Gilead antiretroviral medicines through our initiatives, and that is the result of partnership with governments, public health experts, patient advocates and generic manufacturing groups."

6. As a scientist, a CEO, and a leader in healthcare arena, what would be your advice to medical students in our organization who are expected to be physicians in few years?

“The accelerating pace of technological and medical innovation is very exciting. It’s critical to be agile – to be able to seize new opportunities quickly and change direction when circumstances warrant. It’s also critical to be perseverant. Effecting change – whether through scientific innovation or delivery of healthcare – doesn’t happen overnight. I’d say that these characteristics, and getting the right balance between them, are a part of success in many different professions.”

7. WKMO is a global organization of physicians with Korean heritage. Do you have any personal memories or relationships with Korea or Korean?

“A close friend and colleague of mine, Choung Kim, is a Korean national and chemist who worked at Bristol-Myers and Gilead for more than 30 years. He is an inventor of Tamiflu, the first oral antiviral for the treatment and prevention of influenza. Over the years I have appreciated his insight and advice.

Additionally, many of our therapeutic advances have been in the area of liver disease, including hepatitis B, which disproportionately affects Asians. I’ve had the opportunity to meet regularly with Korean physicians around the United States and at conferences around the world to seek their perspectives on the clinical management of chronic hepatitis B and C. I’ve also traveled to South Korea and worked with leading experts and health officials in the country to identify how we can partner to meet the needs of physicians and patients in South Korea.”

Bio

John Martin, CEO of Gilead Sciences, Inc.

GILEAD

Dr. Martin joined Gilead Sciences in 1990 and currently serves as Chairman of the Board of Directors and Chief Executive Officer. He served as President and Chief Executive Officer from 1996 through May 2008. Prior to joining Gilead, Dr. Martin held several leadership positions at Bristol-Myers Squibb and Syntex Corporation.

Dr. Martin is a member of the Board of Directors of the California Healthcare Institute. He also serves on the University of Southern California Board of Trustees.

Dr. Martin previously served as President of the International Society for Antiviral Research, Chairman of the Board of Directors of BayBio and Chairman of the Board of Directors of the California Healthcare Institute. He served on the National Institute of Allergy & Infectious Diseases Council, the Board of Directors of the Biotechnology Industry Organization, the Board of Trustees of the University of Chicago, the Board of Trustees of Golden Gate University and the External Scientific Advisory Board of the University of California School of Global Health. Additionally, Dr. Martin served on the Centers for Disease Control/Health Resources and Services Administration’s Advisory Committee on HIV and STD Prevention and Treatment and was a member of the Presidential Advisory Council on HIV/AIDS.

Dr. Martin holds a PhD in organic chemistry from the University of Chicago and an MBA in marketing from Golden Gate University. He has received the Isbell Award from the American Chemical Society and the Gertrude B. Elion Award for Scientific Excellence from the International Society for Antiviral Research. In 2008, Dr. Martin was inducted into the National Academy of Engineering of the National Academies.

212.524.5000 212.524.5050 info@jmfnylaw.com

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JACOB, MEDINGER & FINNEGAN, LLP

1270 Avenue of the Americas
Rockerfeller Center
New York, NY 10020

T 212.524.5000
F 212.524.5050
info@jmfnylaw.com

212.524.5000 212.524.5050 info@jmfnylaw.com

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JACOB, MEDINGER & FINNEGAN, LLP

1270 Avenue of the Americas
Rockerfeller Center
New York, NY 10020

T 212.524.5000
F 212.524.5050
info@jmfnylaw.com

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Life science industry's record-setting pace of deals unlikely to end anytime soon

- Recent IPOs have started to lose some steam, one banker notes
- Tax inversion key theme enabling specialty pharma M&A

As the life sciences sector continues its record-setting levels of industry financing and public offerings, industry experts discuss whether this trend will continue.

Small-to-mid-cap biotechs have been strong outperformers year to date, and the NASDAQ Biotech Index recently reached a new high, said Noel Brown, managing director, healthcare investment banking, RBC Capital Markets.

"There has been no slowing of activity in biotech financings," Brown explained. "It continues at a level we've not seen in the past 10 years. The deal pace continues to be bolstered in part because of the activity of generalist investors."

In terms of the basic categories of investors, there are the healthcare specialist funds, healthcare-dedicated mutual funds and the generalist funds seeking high, defensive growth wherever they can find it. "While the generalists may not comprise the largest pool of money, their role in recent markets is not insignificant because there [is] now this other pool of money competing to have its orders filled against the usual participants in the biotech market. This provides some leverage for issuers and their investment bankers to price deals at better valuations," Brown explained.

It is great to have generalist investors, who have been largely absent for a decade, Brown noted. "But our fear is not that this pool of capital is frightened off by some Phase III failure or a commercial launch flop, but rather, strong performance in other sectors, say consumer, technology, industrials, etc., with which those investors have more familiarity," he said. In that scenario, generalist investors could find growth that is achievable without the learning curve or risk profile of biotech.

This year represents a big opportunity for antibody drug conjugates. Both pivotal and earlier-stage readouts are expected from **Seattle Genetics** (NASDAQ:SGEN), **ImmunoGen** (NASDAQ:IMGN), **Endocyte** (NASDAQ:ECYT), Celldex (NASDAQ:-CLDX) and Roche (VTX:ROG), said Brown.

"Other areas of interest are antibiotics, as evidenced by Cubist's (NASDAQ:CBST) acquisition of **Optimer** and **Trius**, which we financed and **The Medicines Company's** (NASDQ:MDCO) acquisition of **Rempex**, on which we were the exclusive advisor to Medicines," Brown said.

Orphan drugs continue to be an area of much excitement, he added. Companies also continue to show interest in solid tumors like melanoma as well as liquid cancers like chronic lymphocytic leukemia and acute myeloid leukemia, Brown said. "Ophthalmology is seeing an era of revitalization, and new companies in both front and back of the eye diseases are progressing," he added.

IPO market starting to cool

One industry banker noted almost all the biopharma IPOs that launched recently are flat or less than the offering price, he added. "Seven IPOs that I followed earlier this month are either at or below IPO price," he said. "The IPO market is cooling down, and low-quality companies are taking this opportunity to go public, but they're not ready yet," the industry banker said.

Dicerna Pharmaceuticals (NASDAQ:DRNA), an RNA interference company, is an example of a firm that is extremely overvalued, the industry banker said. The company has a pipeline of preclinical and Phase I drugs. The company's share price increased 170% on the listing date.

There have been 35 IPOs priced so far this year across all sectors, a 75% increase from last year, according to Renaissance Capital's US IPO Marketwatch.

"One thing is certain: Biotech rallies often end with an over-issuance of equity. Phase I and preclinical IPOs in biotech have a tapered history," said Les Funtleyder, consulting partner at investment firm BlueCloud Healthcare.

Brown added he believes the IPO pace will change in terms of slope but not general trajectory. "While I think the market is due for some level of correction, current activity shows no sign of near-term abatement," he noted.

The IPO frenzy should continue until the major oncology meeting in June -- the American Society of Clinical Oncology (ASCO) meeting, said Funtleyder. However, he noted the lack of expected catalysts and thus he expects less event-driven news flow in the fall, after this scientific meeting. While it is tough to predict when the IPO frenzy will end, Funtleyder said he would be surprised for the cycle to continue at the current pace. Some of the recent IPOs within the life sciences sector will probably delist, the industry banker added.

Lock-up expirations will definitely be an issue to manage for many of the newly public companies, explained Brown. "It could create some instability in trading if not managed in the aftermarket. Much of this newly available supply should get absorbed by other investors," he explained.

After the lock-ups from the initial group of IPOs, it will become clear if the market can absorb all the biotech shares available, Funtleyder noted. As the capital markets cool down, companies will look for alternative areas to raise financing and find shelter, he added.

On the pharma side, we continue to see some interesting evolution of business models.

Tax inversion, capital allocation

Tax inversion is a key theme that has been enabling specialty pharma M&A. RBC Capital Markets will be hosting a keynote panel discussion at the 2014 RBC Healthcare Conference with tax inversion expert Robert Willens, president, Robert Willens LLC, and Eric Jacobs, RBC Capital Markets Global M&A managing director, to understand expectations for more tax inversions and inversion-driven M&A within specialty pharma and healthcare more broadly.

"On the pharma side, we continue to see some interesting evolution of business models. Pharma has become a slow- to no-grower, and many are struggling with where the business goes over the next decade," said Brown.
Years ago, pharma was the source of innovation, but now R&D productivity at pharma cannot provide sufficient growth and pharma is going to have to acquire that innovation to stay at the forefront, said Brown.

"We should also expect continued divestitures and spin-outs from pharma as they work to focus themselves in areas of excellence – both current areas of strength or where they may not now be a leader but see the need to lead in the future" he added.

Capital allocation will also be a big theme for large-cap biotechs over the next couple of years. "Amgen already has a growing dividend. We expect there to be discussion with other large cap biotechs regarding what needs to happen for them to get comfortable with issuing a dividend, and whether that could bring in new income-style investors to these stocks, like what we saw happen with Amgen in 2011," Brown said.

Kimberly Ha
Global Editor
Biopharm Insight
A Financial Times Group product

AstraZeneca's Phase I/II AZD9291 shows promise in EGFR inhibitor refractory patients - oncologists

"Targets T790M mutation to overcome EGFR inhibitor resistance
Could be effective in the first-line setting as well
Selectivity particularly promising for a better side-effect profile"

AstraZeneca's (LON:AZN) AZD9291 has generated high hopes for non-small-cell lung cancer (NSCLC) patients resistant to marketed EGFR inhibitors, according to oncologists. The selectivity of the drug makes it an attractive choice and could mean it has a better safety and tolerability profile, they added.

AZD9291 is under investigation in a 233-patient, open-label Phase I/II trial, with Phase I results expected at the American Society of Clinical Oncology (ASCO) annual meeting from 30 May to 3 June. It is a third-generation oral, irreversible inhibitor of both the sensitising EGFR mutation and the resistance mutation, T790M, according to a company spokesperson.

The drug has been specifically designed to target the classical EGFR mutations, but also the T790M mutations, said Dr Edward Kim, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, North Carolina. The T790M mutation appears after resistance occurs to EGFR inhibitors, such as Roche's (VTX:ROG) Tarceva (erlotinib), and is known to be the primary driver of resistance for these patients, he explained.

EGFR-refractory and first-line potential

Resistance means that patients cannot progress onto another first- or a second-generation EGFR inhibitor, such as Tarceva, AstraZeneca's Iressa (gefitinib) or Boehringer Ingelheim's Gilotrif (afatinib), Kim said. AZD9291 targeting the T790M mutation makes it an attractive and viable choice to patients with resistance, he added.

T790M occurs in roughly 50%-60% of patients after taking EGFR inhibitors, meaning this is a huge unmet medical need, Kim added. AstraZeneca's NSCLC candidate fits into an area where there are no approved agents; i.e., for those who have progressed after another EGFR inhibitor, said Dr Giorgio Scagliotti, professor, respiratory medicine, University of Torino, Italy. If AZD9291 gets approved, patients with EGFR mutations would be able to take a first- or second-generation EGFR inhibitor followed by AZD9291, increasing the potential of long-term control, said trial investigator Dr Federico Cappuzzo, director, medical oncology, Ospedale Civile, Livorno, Italy.

AZD9291 has shown to be effective in Tarceva-resistant patients, said Dr James Chih-Hsin Yang, director and professor, Cancer Research Center, National Taiwan University, Taipei. Preliminary results from the ongoing Phase I part of the study demonstrated partial tumour shrinkage (as defined by response evaluation criteria in solid tumours (RECIST) criteria) in 12 of 26 patients, or a response rate of 46%, according to a poster presentation at the European Cancer Congress (ECC) 2013 [Abstract#33LBA].

A response rate this high is encouraging at an early stage in development as it suggests the drug has activity in a significant proportion of NSCLC patients with EGFR mutations, according to an oncologist.

The T790M mutation is also found de novo in a very small population of patients (1%-2% of patients with EGFR mutations), said Kim. These patients, who have the de novo T790M mutation, could benefit from AZD9291 in the front-line setting, said Scagliotti. There is significant activity in T790M+ tumours but also activity in T790M-negative tumours, he noted. Preliminary Phase I data showed that of the 12 who responded, seven had the T790M mutation, a response rate of 58% in the T790M-positive group, the poster stated. There were 12 patients in all who were T790M positive.

AZD9291 will likely be more potent than Tarceva because the mode of action is to suppress resistance as well as EGFRs, said Dr Ross Camidge, associate professor, University of Colorado School of Medicine, Denver. The drug's response rates look very good and it is likely to be the next blockbuster drug in NSCLC, said Kim.

It is yet not known is whether AZD9291 will be utilised in the first-line setting, said Camidge. One of the questions that has to be answered to figure out AZD9291's first-line potential is whether the benefit in survival time is greater if patients take AZD9291 in the first-line or take a first- or second-generation EGFR inhibitor and then AZD9291 once resistant, said Camidge. Median survival time for patients taking Tarceva was 10.5 months in the Phase III registration trial leading to approval, according to a Roche press release.

The Phase I/II trial is assessing AZD9291 in patients with advanced NSCLC who have progressed on at least one prior therapy with an EGFR inhibitor, according to ClinicalTrials.gov.

At the moment, AstraZeneca is targeting refractory patients, as this setting is a faster route to approval, Camidge noted. Additionally, the company would not want to compete with its own product Iressa, he said. Whether AstraZeneca attempts the front-line setting may depend on the status of its competitor's compound, Clovis Oncology's (NASDAQ:CLVS) CO-1686, and what setting Clovis targets, he added. On 13 January, Clovis announced plans to launch a Phase II/III registration trial in first-line EGFR-associated NSCLC with CO-1686, also a third-generation EGFR inhibitor in development.

Early data suggests improved selectivity

Initial clinical data suggests that AZD9291 is well tolerated and the typical EGFR-related side effects like severe rash (Grade 3 or higher) are not seen, said an oncologist. Preliminary Phase I results showed no reported dose-limiting toxicities, according to the ECC poster. Additionally, across the three dose cohorts, only Grade 1 diarrhoea and rash was reported, the poster stated.

The fact that severe rash was not reported in this group is very encouraging at an early stage because it has been such a prevalent problem with drugs such as Gilotrif and Tarceva, said another oncologist. This would suggest the drug is highly selective, which should indicate that this drug will demonstrate good safety and tolerability in a larger population, he added.

Preclinical data showed AZD9291 to be more selective than marketed EGFR inhibitors such as Tarceva, said Cappuzzo. Selectivity is important because AZD9291 is able to avoid targeting wild-type EGFR; therefore toxicity is lower than with first- or second-generation EGFR inhibitors, Cappuzzo and Yang added. The lack of off-target toxicities is clinically relevant because you have fewer side effects compared to other EGFR inhibitors, especially in terms of skin and gastrointestinal toxicities, said Scagliotti.

Lower toxicity could be very important for the future of targeted agents, as it is likely that these agents will be combined to improve efficacy, said Cappuzzo. Targeted agents cannot be combined now because of the excess in toxicity, he added.

AstraZeneca's market cap is GBP 50bn (USD 83bn).

BioPharm Insight

Hamish McDougall

World Korean Medical Organization

Hosts an International Forum to Discuss Korea-Brazil Medical Collaboration

Photo session for speakers. Drs. Jinha Park(US), Sangchoon Cha(Brazil), Sungho Joo(Brazil), Dohyun Cho, Claudio Lottenberg(Brazil), Chul Hyun, honorable Amb. Koo, Drs. Youngman Lee(Brazil), Dongwon Lee(Brazil), Hyung Kwon Kim(Brazil), David Ko(US), Sanghoo Kim(Korea), Yoonkyo Ahn(Australia) and Heejung Kang(Paraguay).

Entitled “WKMO Global Leadership Series 2014”, the forum was held in Sao Paulo Hilton on Feb. 6 attending by more than 100 physicians, including Dr. Chul Soo Hyun , President of World Korean Medical Organization(WKMO), Dr. David Ko, president of Korean American Medical Association (KAMA), Dr. Heejung Kang, president of Korean Paraguay Medical Association(AMCP), Dr. Taemo Jeong, vice president of Korean Brazilian Medical Association(KOBRAMA), and other WKMO board member physicians from Korea, US, Brazil, UK and Australia.

Drs.Chul Hyun, Hyung Kwon Kim, Claudio Lottenberg, Dohyun Cho are providing speeches respectively

Forum Held in Sao Paulo, Brazil
Attended by 100 Plus Korean Physicians
Largest Brazilian Hospital Group, Enthusiastic for Possible Acquisition of Korean Medical Products

In his congratulatory remarks, Ambassador to Brazil Bonwoo Koo said, “It is very much meaningful to see Korean physicians all around the world gathering together not only to remember their root but also discuss ways to contribute to Korea.” “I ask all [Korean] physicians to help support the success of Korean technology and products in Brazilian market where needs for medical areas are high.”

WKMO Global Leadership Series 2014 at Hilton Sao Paulo, Brazil on Feb. 6, 2014

Especially, President Claudio Lottenberg, the Chairman of ‘Sociedade Beneficente Israelita Brasileira Hospital Albert Einstein’ which is Brazil’s largest hospital Einstein Group at the event stated that “I have much admiration for Korea and confidence for its technology. I will enthusiastically consider Korean products that are ready to reach Forum Held in San Paulo.. Attended by 100 Plus Korean Physicians Largest Brazilian Hospital Group, Enthusiastic for Possible Acquisition of Korean Medical Products World Korean Medical Organization (WKMO) held an international medical industry forum and discussed the collaboration between Korea and Brazil. Brazilian hospitals.”Additionally, Korean Brazilian physicians such as Dr. Sangchun Cha who twice served as president of the Brazilian Ultrasound Society of nearly two million members to Dr. Dongwon Lee, professor of Sao Paulo University of Medicine to and the first Korean Brazilian physician Dr. Youngman Lee promised at the event to assist Korean companies entry into Brazil via various channels, including Brazilian politicians and medical institutes.

WKMO Board Roundtable

Wonyoung Lee, President of Vatech Brazil, confirmed a recent successful completion of onsite inspection by ANVISA’s GMP and expressed his hope for positive outcome given Einstein Group’s interest in purchase itself is valuable.

As part of the forum, technologies and products by several Korean pharmaceutical companies for hopeful entry into Brazil were introduced.

This event, hosted by WKMO and organized by W Medical Strategy Group, was concluded on Feb. 8th.

Executive visit to Hospital Israelita Albert Einstein

Not an actual patient, but is representative of a real patient type. Models are used for illustrative purposes only.

IN THE TREATMENT OF CHRONIC HEPATITIS B (CHB) IN ADULTS WITH COMPENSATED LIVER DISEASE

TAKE A CLOSER LOOK AT LAMIVUDINE (LAM) RESISTANCE

MORE THAN 50% of Americans living with CHB are Asian and Pacific Islanders[1]

NEARLY 70% of Asian Americans were born or have parents born in countries where CHB is common[1]

70% of patients receiving lamivudine develop resistance at 5 years[2]

2% of patients in the United States use lamivudine; **up to 88%** in Asia[3]

Indication and Usage

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on data from treatment of subjects who were nucleoside–treatment-naïve and treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

Important Safety Information

BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

Warnings and Precautions

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of VIREAD. In all patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, including those who previously experienced renal events while receiving adefovir dipivoxil, additionally monitor serum phosphorus, urine glucose, and urine protein. In patients with CrCl <50 mL/min, adjust dosing interval and closely monitor renal function. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in HIV-infected patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function
- **Coadministration with other products:**
  - Do not use in combination with other products containing tenofovir disoproxil fumarate
  - Do not administer in combination with adefovir dipivoxil
- **Patients coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with VIREAD. Consider assessment of BMD in adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for bone loss. In a clinical trial conducted in pediatric subjects 12 to <18 years of age with chronic hepatitis B, total body BMD gain was less in VIREAD-treated subjects as compared to the control group. In patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms, hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered

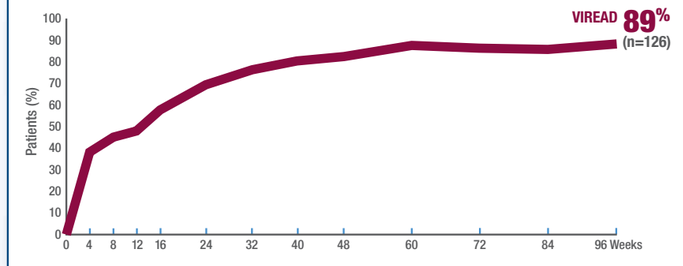
Adverse Reactions

- **In HBV-infected subjects with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash

TAKE A CLOSER LOOK AT VIREAD

LAM-resistant VIREAD patients (Study 121)

achieving viral suppression (HBV DNA <400 copies/mL) at 96 weeks of treatment[4,5]



Study 121 was a randomized, double-blind, active-controlled 96-week trial evaluating the safety and efficacy of VIREAD (n=141) compared to an unapproved antiviral regimen (n=139) in subjects with CHB, persistent viremia (HBV DNA ≥1000 IU/mL), and genotypic evidence of LAM resistance. The primary endpoint in Study 121 was HBV DNA <400 copies/mL (69 IU/mL) at Week 96.[4,5]

- As a secondary endpoint, **no HBV resistance (0%)** was detected at **96 weeks** in CHB patients with LAM resistance[4]

Important Safety Information (cont'd)

- **In HBV-infected subjects with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

Drug Interactions

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD and in patients weighing <60kg, the didanosine dose should be reduced to 200 mg once daily when coadministered with VIREAD
- **HIV-1 protease inhibitors:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations; use atazanavir given with ritonavir. Coadministration of VIREAD with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity
- **Drugs affecting renal function:** Coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

Dosage and Administration

- Recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), for the treatment of chronic hepatitis B: one 300 mg tablet, once daily, taken orally, without regard to food
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Safety and efficacy in pediatric patients <12 years of age or weighing <35kg with chronic hepatitis B have not been established
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with baseline creatinine clearance <50 mL/min

Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.

[b]Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in these patients
- No data are available to make dose recommendations in pediatric patients with renal impairment

Please see Brief Summary of full Prescribing Information, including **BOXED WARNING**, on the adjacent pages.

References: 1. CDC Web site. CDC Features-August 2011: Chronic hepatitis B and Asian & Pacific Islanders. Centers for Disease Control and Prevention. http://www.cdc.gov/Features/ChronicHepatitisB/. Accessed June 26, 2013. **2.** European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. *J Hepatol.* 2012;57:167-185. **3.** Data on file, Gilead Sciences, Inc. Gilead HBV LAM assessment, IMS MIDAS data. May 2013. **4.** Data on file, Gilead Sciences, Inc. 0121 CSR. **5.** VIREAD Prescribing Information, Foster City, CA: Gilead Sciences, Inc.; October 2013.

300mg tablets®
Viread®
tenofovir disoproxil fumarate

VIREAD® (tenofovir disoproxil fumarate) tablets

Brief summary of full Prescribing Information. Please see full Prescribing Information including Boxed WARNING. Rx only

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *(See Warnings and Precautions)***
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *(See Warnings and Precautions)***

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *(See Adverse Reactions)*
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease *(See Adverse Reactions)*
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

DOSAGE AND ADMINISTRATION: For the treatment of chronic hepatitis B the recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), is one 300 mg tablet, once daily, taken orally, without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients <12 years of age with chronic hepatitis B weighing <35 kg have not been established. **Dose Adjustment for Renal Impairment in Adults:** Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD tablets 300 mg should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *(See Warnings and Precautions)*. No dose adjustment of VIREAD tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose and urine protein should be performed in patients with mild renal impairment *(See Warnings and Precautions)*.

Dosage Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients. No data are available to make dose recommendations in pediatric patients with renal impairment.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *(See Adverse Reactions)*. It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil , it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of VIREAD, and periodically during VIREAD therapy. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *(See Dosage and Administration)*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *(See Drug Interactions)*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products ATRIPLA®, COMPLERA®, STRIBILD® or TRUVADA® since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with adefovir dipivoxil *(See Drug Interactions)*. **Patients Coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

Bone Effects

Bone Mineral Density: In clinical trials in HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD *(See Adverse Reactions)*.

Clinical trials evaluating VIREAD in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the VIREAD-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *(See Adverse Reactions)*.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects: Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of VIREAD *(See Adverse Reactions)*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *(See Warnings and Precautions)*.

ADVERSE REACTIONS: Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease: *Treatment-Emergent Adverse Reactions:* In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with adefovir dipivoxil. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile was observed with continued treatment with VIREAD for up to 240 weeks.

Laboratory Abnormalities: in Studies 0102 and 0103 (0–48 Weeks) laboratory

Brief Summary (cont'd)

abnormalities (Grades 3–4) reported in ≥1% of subjects treated with Viread (n=426) and adefovir dipivoxil (n=215), respectively, were: any ≥Grade 3 laboratory abnormality (19%, 13%); creatine kinase (M: >990 U/L; F: >845 U/L) (2%, 3%); serum amylase (>175 U/L) (4%, 1%); glycosuria (≥3+) (3%, <1%); AST (M: >180 U/L; F: >170 U/L) (4%, 4%); and ALT (M: >215 U/L; F: >170 U/L) (10%, 6%). Laboratory abnormalities (Grades 3–4) were similar in subjects continuing VIREAD treatment for up to 240 weeks in these trials.

The overall incidence of on-treatment ALT flares (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and adefovir dipivoxil (2%). ALT flares generally occurred within the first 4-8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4-8 weeks without changes in study medication. The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with VIREAD were consistent with those observed in other hepatitis B clinical trials in adults. *Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease:* In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus <2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥10 and MELD score ≥14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 week trial.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B: Assessment of adverse reactions is based on one randomized study (0115) in 106 pediatric subjects (12 to less than 18 years of age) infected with chronic hepatitis B receiving treatment with VIREAD (N = 52) or placebo (N = 54) for 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults. In this study, both the VIREAD and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in VIREAD-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the VIREAD group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to VIREAD were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving VIREAD for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV-infected patients, skeletal growth (height) appeared to be unaffected *(See Warnings and Precautions)*.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS: Didanosine: Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving VIREAD with didanosine 400 mg daily. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD. In patients weighing <60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with VIREAD. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). For additional information on coadministration of VIREAD and didanosine, please refer to the full Prescribing Information for didanosine.

HIV-1 Protease Inhibitors: VIREAD decreases the AUC and C_{min} of atazanavir. Viread should not be coadministered with atazanavir without ritonavir. Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving VIREAD concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *(See Warnings and Precautions)*. In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with adefovir dipivoxil.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category B:* There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed. *Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. *Animal Data:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. **Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.** Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD. Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with estimated creatinine clearance <50 mL/min or in patients with ESRD who require dialysis *(See Dosage and Administration)*.

For detailed information, please see full Prescribing Information. To learn more call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com.

SPECIAL REPORT II

Medical Consulting Firm
W Medical Strategy Group Launched

W Medical Strategy Group Opening Celebration was held in Yale Club NYC on Feb. 11, 2014. Launch Event was attended by 100 Plus from Medical and Pharmaceutical Industries

Medical consulting firm 'W' Medical Strategy Group (CEO Dohyun Cho) held the company's launch event at the Yale Club in Manhattan, NY. The event was attended by medical industry and Korean American leaders, including Dr. Chulsoo Hyun, president of the World Korean Medical Organization (WKMO); Mark Paxton, vice president of W Medical Strategy Group; Amb. Se-Joo Son, the Korean Consul General New York; Keelin Kavanagh, Managing Partner of JMF lawfirm, Larry Slatky, COO of NUMC Healthcare System, Dr. Augustine M. K. Choi, Chairman of Medicine at Weill Cornell Medical College and Physician-in-Chief at NewYork-Presbyterian/Weill Cornell Medical Center; David Ko, president of the Korean American Medical Association (KAMA), Kyungryul Lee, president of Hanaro Medical Foundation; Bonghyun Nam, Attache of Korean Ministry of Food and Drug Safety; Dongseok Kim, director of the Korean Voters Rights Center.

Feb. 11, Launch Event Held in Manhattan, NY...Attended by 100 Plus from Medical and Pharmaceutical Industries

Additionally, many executives from top pharmaceutical and medical device companies, American corporations and finance consulting firms, including Merrill Lynch and PWC, attended the event showing much interest in the launch.

CEO Dohyun Cho of W Medical Strategy Group said, "Healthcare industry in the United States is continually developing and expanding, in which an increasing number of Korean medical personnel serves daily." "These human resources will play a key role for Korean pharmaceutical and medical device companies' global market entry."

Amb. Sejoo Son emphasized through his remarks that "Korean medical technology and products are of excellent qualities and for the Korean medical industry to be successful in the U.S. market, Korean American doctors' enthusiastic support can make a huge difference."

Managing partner of Jacob, Medinger & Finnegan law firm Keelin Kavanagh congratulated by saying, "I am hopeful that W Medical Strategy Group will be a conduit for introducing Korea's quality technology and products to the U.S. market."

Dohyun Cho, CEO of WMSG(on left) and Chul Hyun, president of WKMO are presenting the featuring functions of WMSG

During the panel moderated by Joe McMenamin, vice president of W Strategy Group, the Group's vital function and synergy effects on leading healthcare issues were discussed with specialists from various medical industries.

'W Medical Sttrategy Group' Tape cutting ceremony. From left to right, David Ko (President of KAMA), Dohyun Cho (CEO of WMSG), Kyungryul Lee (President of HMF), Amb. Sejoo Son (Consulate General of ROK, NY), Keelin Kavanagh (Managing partner of JMF), Joseph McMenamin (Exec. Advisor of WMSG), Chul Hyun (President of WKMO), Larry Slatky (COO of NUMC Healthcare System), Mark Paxton (Exec. Advisor of WMSG)

Panelists for the medical products session, including investor Les Funtleyder, Bonghyun Nam of KFDA, science advisor Dr. Doug Yoon and others, illuminated on the main trends in pharmaceutical and devices industries. During the panel, they discussed W Medical Strategy's market development and analysis, and its collaborative impetus. Especially, attendants reacted enthusiastically to the Group's introduction to American pharmaceutical companies' competitive strategies by size and U.S. regulatory restriction trends. Medical services debate featured respected panelists, including Professor Jinha Park, the City of Hope Medical Center; President Kyungryul Lee, Hanaro Medical Foundation; President Larry Slatky, American College of health Care Administrators; and Professor William Ventura, St. Joseph Medical Center.

During the session, the panelists addressed various specialty areas such as preventative medicine, community outreach and medical R&D and how W Medical Strategy Group together with WKMO can contribute much to these areas.

The event also held a ribbon-cutting ceremony and welcomed mezzo soprano Gloria Park and tenor Youngbae Yang for musical performance to celebrate the launch.

Exec. McMenamin of WMSG is explaing the featuring function of WMSG to Hanseong Bang of JW Holdings

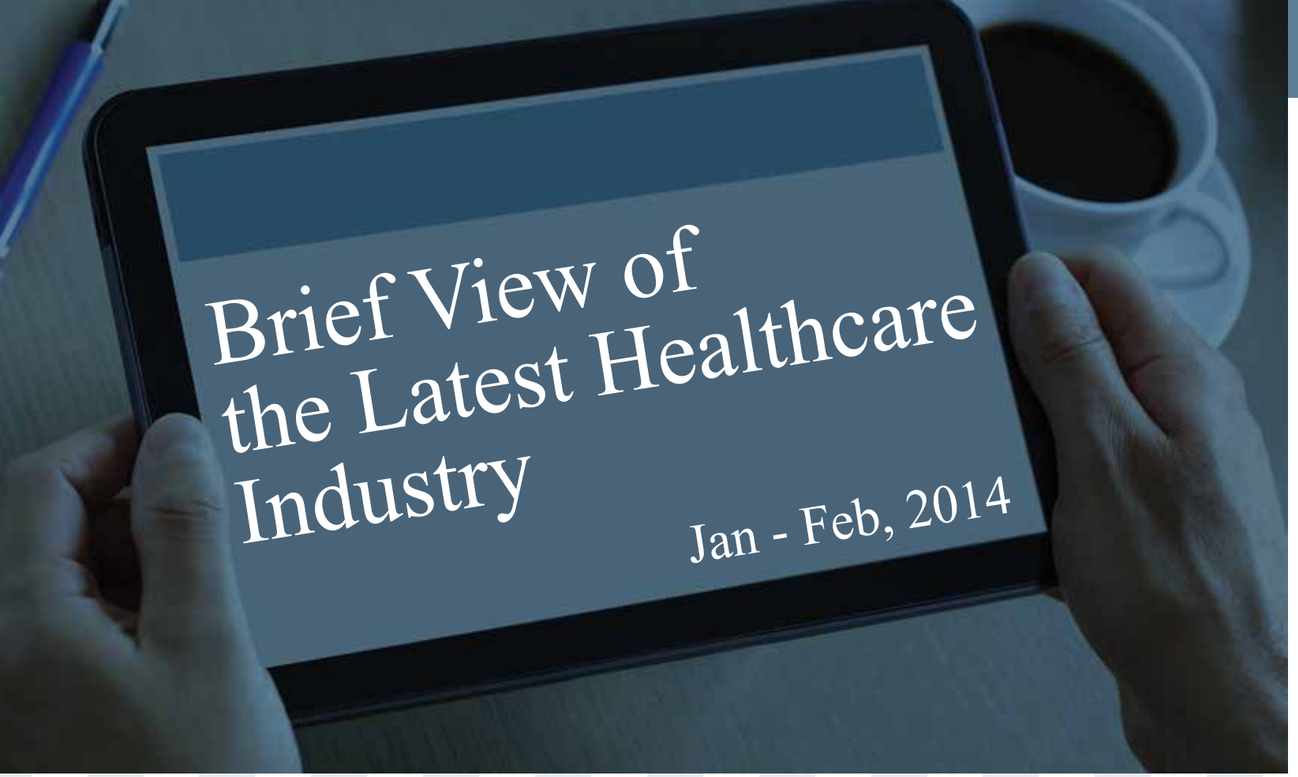
Augustine Choi, the chairman of WCMC on left is listening to the panel discussion

Les Funtleyder of Bluecloud Group is speaking about the key trend in pharmacutical industry

Larry Slatky, COO of NUMC Health System is presenting the key issues in hospital management

Bonghyun Nam of KFDA is presenting the latest trend of medical devices in US

Special musical performance was presented by Mezzo-soprano Gloria Park, and Tenor Yungbae Yang



"U.S. Medical Research Spending Drops While Asia Makes Gains"

01/03/2014

The U.S. accounting for over ¾ of world's research spending is a story of the past, as its share has been dropping over the past 5 years. Researchers found that the U.S. comprised 51% ($131B) of global research spending in 2007, decreased to 45% ($119B), while China and Japan increased $6B and $9B respectively.

"Medicaid Raises Emergency Room Visits by 40% compared to the Uninsured"

01/07/2014

A study found that people on Medicaid are more likely to go to the emergency room (ER) for cases that weren't emergent. This result is likely to dismiss arguments to expand Medicaid, as the common argument was that individuals would no longer have to rely on uncompensated care at the emergency room.

"Baxter initiates worldwide voluntary recall of select lots of 5% Dextrose injection, USP and 9% Sodium Chloride injection, USP, IV solutions."

01/06/2014

Due to particulate matter found in solutions, Baxter International announced it has initiated a voluntary recall to select lots of injectable. "Injecting a product with the particulate matter may result in blockages of blood vessels; which can result in stroke, heart attack, etc."

"FDA and EMA launch joint Generic Inspections Initiative"

01/08/2014

The U.S. FDA and the European Medicines Agency have announced the launch of a joint initiative to share information on inspections of bioequivalence studies submitted in support of generic drug approvals. Their collaboration with the EMA and EU improves ability to leverage inspection resources and help meet needs of globalization of drugs as well as streamlining the inspection process.

"Intercept Pharma, Backed by Former Billionaire, Triples After Drug Test Results"

01/09/2014

Intercept Pharmaceuticals shares almost tripled (surges over 280%) today after the announcement of early stoppage of its liver disease when primary endpoint of trial was met. Market capitalization of the company jumped to over $5.2 B.

"Drug buyers sue Novo Nordisk over 'wrongful' delays to diabetes generic"

01/14/2014

Novo Nordisk has been sued by a group of healthcare purchasing companies in the U.S. for allegedly wrongfully keeping generic copies of its Prandin diabetes drug off the market: also known as pay-for-delay deals.

"Eli Lilly & Co.: Lilly falls off second patent cliff"

01/14/2014

Eli Lilly and Co. on Dec 11 fell off its second patent cliff as Cymbalta, its best-selling drug, saw its U.S. patents expire. Due to the loss of $5 billion in revenue sales of Cymbalta, J.P. Morgan analysts are not anticipating a near-term outperformance, but could lead to a longer-term opportunity for LLY shares for the company's next-generation product portfolio. *Combined with 2010 patent exp. of cancer drug Gemzar, 2011 patent exp. of antipsychotic Zyprexa, Lilly will suffer from more than $9 billion in annual revenue by the end of 2014.

"Merck recall depletes supplies of new cholesterol drug"

01/15/2014

Merck's Liptruzet, a cholesterol lowering drug, was voluntarily recalled by the drug maker after only being on the market since last May. The company said the recall "will deplete all available supply in the U.S., and stock-outs are expected." The reason for the recall was that there was a potential packaging leak that could affect its potency.

"Look for an M&A scramble in 2014, with pharma chasing deals at ever-higher prices"

01/15/2014

Analysis from Ernst & Young reports that Big Pharmas have more money in their pockets for deals and are willing to spend it ASAP to prepare for post-patent-cliff rebuilding. The Big Pharmas didn't really score big on R&D, so the need for deals remains strong from last year.

"Novartis may finally face generic competition for Diovan"

0116/2014

Novartis' blockbuster Diovan will be facing competition for the first time in nearly 18 months since its patent expiration in September 2012. Although there were some delays in seeking an approval from the regulator, Ranbaxy Laboratories, an Indian drug maker, retained 180 days of exclusive marketing rights for the generic version of Diovan.

"FDA Advisory Panel Votes In Favor of Approval For Merck's Vorapaxar"

01/15/2014

The FDA's Cardiovascular and Renal Drugs Advisory Committee voted 10-1 in favor of approval for vorapaxar, Merck's thrombin receptor antagonist.

"New technique targets specific areas of cancer cells with different drugs"

01/07/2014

Researhcers at N.Carolina State University and University of N.Carolina at Chapel Hill have developed a technique for in cancer treatment that allows nanoparticles to carry two different cancer-killing drugs and have them be delivered to separate parts of the cancer cell. Early results have been promising and showed significant improvement in cancer tumor reduction compared to conventional treatment techniques.

"The FDA granted Soliris with an orphan drug designation."

01/22/2014

Alexion Pharmaceuticals announced that the FDA granted Soliris (eculizumab) with an orphan drug designation. Soliris is used to prevent delayed graft function (DGF) in patients who undergo kidney transplant surgery. DFG refers to new organ not responding or functioning properly immediately after it has been introduced to the body.

"Teva's New Copaxone Formulation For MS Patients Approved By FDA"

01/29/2014

The FDA approved the new formulation of Copaxone. The new formulation offers relapsing fomrs of multiple sclerosis (MS) the option to dose less frequently. (now available in 40mg/mL in a three-times-a-week dosage)

"NIH, drug companies will partner to expedite new medication"

02/04/2014

The National Institute of Health announced a partnership with some of major drug companies on a project to reduce the time to create and market medications that treat debilitating diseases. The "Accelerating Medicines Partnership aims to fasten what is now an average 14-year process to create new drugs, and save billions of $. New approach would help pharmaceutical companies pick the right targets in earlier stages of drug development as failure rate for new drug is 95% currently.

"Singapore fling: AbbVie says a plant in Asia is just what it needs. "

02/06/2014

Whilst looking for a new production capacity, Abbvie (the developers of best-selling drug in the world, Humira) has found a location in Singapore for a $320 million manufacturing plant. As they will soon face a significant revenue gap from patent cliff of Humira in 2016, the company is working on a new medicine to fill at least some of the gap. Most anticipated is interferon-free hepatitis C product that can cure up to 90% of the patients with the virus when used in combination with other drugs.

"Merck, Samsung Bioepis To Develop & Commercialize Insulin Glargine Candidate"

02/10/2014

Merck & Co. Inc. announced that it's partnering with Samsung Bioepis to create a generic version of Sanofi SA's bestselling insulin drug, Lantus. This agreement threatens Sanofi's victory against Eli Lilly & Co. in a patent infringement suit over the diabetes medicine. As a result, Eli is likely to hold off their generic version until 2016, but if Merck's version goes through, it's going to hurt Sanofi's market share.

"What's Big Pharma's latest hot spot? The Middle East"

02/11/2014

Wall Street Journal reports that the multinational pharma's latest trend lies in the Persian Gulf. Drugmakers with ambiions are beginning to move into second, third-tier emerging markets as the top-tier BRIC (Brazil, Russia, India, and China) countries are slowing down. The Gulf region has much to offer especially for companies with strong in diabetes, as diabetes is a fast-growing problem across the region.

"J&J, Pharmacyclics get CLL approval for Imbruvica"

02/12/2014

The FDA expanded the approval of Imbruvica, Johnson & Johnson and Pharmacyclics' new drug for CLL, Chronic Lumphocytic Leukemia (a rare disease), to those who received at least one previous therapy. This allows the former rare disease treatment reach the blockbuster status. Analysts forecast annual sales reaching $1.3 billion in 2018.

"Biosimilars Market by Product & Application - Global Forecast to 2018"

02/13/2014

Increasing prevalence of oncology along with the rise in aging population and the changing lifestyles are what makes oncology the largest and fastest-growing segment of the global biosimilars market. By 2018, global market will be worth $2.0 billion growing at a Compound Annual Growth Rate (CAGR) of 20.1% during 2013-2018.

"Forest Laboratories to discontinue NAMENDA® tablets effective Aug. 15,2014 "

02/14/2014

Forest Laboratories is discontinuing Namenda (Memantine HCl) 5mg and 10mn tablets on August 15, 2014. The company announced that the oral solution of Nameda and once-daily Namenda XR capsuels will continue to be available. Both are indicated for treatment of moderate to severe Alzheimer's disease. The company is discontinuing Namenda tablets not because of lack of benefits of the drug but because the patent for the drug goes off in April of 2015, which means low cost generics will flood the market and replace the original.

"BioMarin and its patients coaches are ready to roll on Vimzim launch"

02/17/2014

The FDA approved BioMarin Pharmaceutical Inc.'s drug Vimzim to treat a very rare genetic disorder Morquio A Syndrome According to FDA, only about 800 patients in the U.S. have Morquio A syndrome, an enzyme deficiency that causes joint abnormalities and other bone problems. With no other treatments in the market, analysts figure Vimzim could reach at least $500 million in sales.

Congratulations

WKMO & CHUL S. HYUN, MD

"As we Honor his Commitment to the Medical Community"

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North American Partners in Anesthesia

Stephen P. Winikoff, M.D.

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William Ventura, M.D.

napa

WKMJ

WORLD KOREAN MEDICAL JOURNAL

World Korean Medical Journal (WKMJ) is a bi-monthly journal, which better support the community. WKMJ introduces the emerging issues and new trends of healthcare industry while also providing the best therapeutic products and medical devices available in the US market. WKMJ is delivered throughout 11 countries in the world: Korea, Brazil, China, Japan, Paraguay, Canada, Australia, Singapore, UK, France and Germany

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WORLD KOREAN MEDICAL ORGANIZATION

The 3rd WKMO Annual Convetion

CULTURAL COMPETENCE IN HEALTHCARE
'Overcoming barriers and ethnic disparties'

JULY3-5, 2014
LE PARKER MERIDIEN AT 57TH , NY, USA

WKMO
WORLD KOREAN MEDICAL ORGANIZATION

The 3rd WKMO ANNUAL CONVENTION

NEW YORK, July 3-5, 2014

Dear Colleagues:

World Korean Medical Organization (WKMO) is proud to host its **"The 3rd WKMO Annual Convention"** in New York City at Le Parker Meridien Hotel, July 3-5, 2014.

The convention, which will commence with a reception on the evening of July 3rd, aims to rekindle the spirit of solidarity amongst all the physicians of Korean heritage. As we expect over 400 physicians, medical students and leaders from healthcare industry from all over the world, this Convention will again aim to promote Korean interest and leadership in global medical community.

We will focus on a general theme- *"Cultural Barriers and Ethnic Disparities in Healthcare"* and will feature cutting edge medical and surgical specialty symposia on various topics. In addition, there will be separate sessions on Global Healthcare, Community Outreach and Worldwide Networking for Korean Physicians and Medical Students (WKMSO) with opportunities for exchange of ideas and discussion.

The WKMO Convention in the Big Apple provides a great venue and a wonderful opportunity to network with colleagues from various parts of the world and to reconnect. The details on the exact programs are in progress and we will update you soon with any new developments. Meanwhile, we hope you will make a plan ahead of time to attend this lifetime memorable event- **The 3rd WKMO Annual Convention.**

Sincerely

Chul S. Hyun, MD, PhD
President, WKMO

Hyungkwon Kim, MD
Convention Chair

The WKMO Convention Program

	July 3rd	July 4th	July 5th	
8:00- 8:30 AM		(Breakfast)	(Breakfast)	
8:30-11:30 AM		Session A Stomach Cancer: Epidemiology and Treatments	Session D Models to Improve Cultural Competence in Health Care	
11:30-12:30 PM		(Lunch)	(Lunch)	
12:30-3:00 PM		Session B Mental Health of Geriatric Immigrants	Session E Pharma Forum	Session F Future of Medical Imaging
3:00-3:30 PM		(Coffee Break)	(Coffee Break)	
3:30-6:00 PM	Registration	Session C Impact of Telemedicine in Healthcare	Session G Hepatitis B: Epidemiology and Treatments in Asian Population	
6:30-9:30 PM	Opening Reception Dinner	WKMSO Forum and Gala	WKMO Gala	

WKMO- its mission is to establish global Korean medical leadership.

The general purposes of the Organization are

- to engender and enhance the fellowship of its members and others through active participation in forums, symposia, and other professional meetings;
- to facilitate medical and scientific research and advancement;
- to provide scholarship and financial/educational assistance to needy physicians and medical students;
- to promote outreach activities in the underdeveloped communities throughout the world;
- to implement and improve higher standards of healthcare and medical training worldwide; and
- to develop collaborative activities with bio-medical industry


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