Agenda and Summary of Speeches

Executive Summit: Emerging Strategic and Financial Issues in the Pharmaceutical Industry

November 1, 2016
The Yale Club at 50 Vanderbilt Avenue - New York City

11:30 a.m. **Registration**

12:00 p.m. **Luncheon and Welcoming Comments**
Peter Young, President and Managing Director, *Young & Partners*
William Looney, Editor-in-Chief, *Pharmaceutical Executive*

12:30 p.m. **Luncheon Keynote Speaker and Fireside Chat**

The Evolving Role of Prescription Benefit Management Companies
Dr. Steven Miller, Chief Medical Officer and SVP, *Express Scripts Holding Company*

A Fireside Chat with Steven Miller
Peter Young, President and Managing Director, *Young & Partners*
Dr. Steven Miller, Chief Medical Officer and SVP, *Express Scripts Holding Company*

1:30 p.m. **Challenges and Opportunities in the Pharma and Biotech M&A Market**
Peter Young, President and Managing Director, *Young & Partners*

2:00 p.m. **Orphan Drugs: Perspectives on the Past and the Future**
Dr. Gayatri R. Rao, Director, Office of Orphan Products Development, *The FDA*

2:30 p.m. **The Pharmaceutical Market: Trends, Issues and Outlook**
Doug Long, Vice President, *IMS Health Inc.*

3:15 p.m. **Coffee Break**

3:30 p.m. **Biopharma Turnarounds: Case Studies and Lessons**
Paris Panayiotopoulos, President & CEO, *ARIAD Pharmaceuticals, Inc.*

4:00 p.m. **CRISPR: Advancing the Technology**
Samarth Kulkarni, Chief Business Officer, *CRISPR Therapeutics*

4:30 p.m. **Speaker Roundtable**

Moderator: Peter Young, President and Managing Director, *Young & Partners*

Selected Topics: Alternative Pharma and Biotech Strategies; What to do about Pricing?; Innovative Approaches to R&D; The Future of Immunotherapy; Macro Trends Affecting Biopharma, Impact of the 2016 U.S. elections.

5:30 p.m. **Cocktail Reception**

7:00 p.m. **End of Conference**

The Evolving Role of Prescription Benefit Management Companies

DR. STEVE MILLER, M.D.
SENIOR VICE PRESIDENT AND CHIEF MEDICAL OFFICER
EXPRESS SCRIPTS HOLDING COMPANY

Prescription drugs are the most used and most visible portion of the health care industry for most consumers. Prescription drugs are also becoming a more important part of the health care spend – about 19% of the spending for Express Scripts' employer-based plans. Specialty drugs are expected to grow from 30% of pharmaceutical spending in 2015 to 50% in 2018. So 50% of the spending will be for 2% of the population. Brand prescription prices have grown 164% since 2008 while generic drug prices are down 60% over the last 6 years.

The good news is there are now 7000 potential drugs in human clinical testing in the U.S. The FDA has approved more drugs recently than in the last 20 years. Starting in 2010, the majority of the approvals have been for Specialty products rather than traditional oral solids. This has been great for patients, not as good for payors. Furthermore, there has been concern among payors that certain recent FDA approvals, such as those of Addyi and Sarepta's Duchenne drug, have not been based solely on the science. The introductory price of new products has skyrocketed from an average monthly price of $2000 in 2007 to $10,000 in 2015. In addition, generic savings opportunities are declining. Payors are, therefore, very concerned about their ability to continue to pay for new, innovative products. In the meantime, bad actors such as Martin Shkreli and Mylan have painted the entire industry in a negative light. Drug pricing has been a major issue over the last several years, and especially in the current Presidential election. The industry has to figure out how to address this because the current situation is unsustainable.

Express Scripts has tried to address this issue through innovative, holistic management of certain therapeutic drug classes. These involve value-based contracting rather than outcomes-based contracting, because our systems today do not allow outcomes-based contracting. One example of value-based pricing is in Hepatitis C. When Sovaldi, a cure for Hepatitis C, came to the market, Gilead priced it at $84,000 for a 12 week cycle ($140,000 with Ribavirin or Olysio). The price was 30% lower in Germany and the UK than in the US. Then, Harvoni came out and was priced at $95,000 per cure and did not require Ribavirin or Olysio, but I was still not satisfied with the price. Then, Viekira Pak came out, which had similar cure rates to Harvoni but was less convenient to use – 7 pills per day versus 1. Express Scripts went to its plans and guaranteed adherence for plans that picked Viekira Pak. Express Scripts also made it available to treat everyone, not just patients with advanced disease. Express Scripts was able to achieve 92% adherence rates for Viekira Pak using predictive models, cellphone apps, and reminders. The plans saved $1 billion the first year and Express Scripts has now treated 50,000 people and achieved cure rates of 96%. Harvoni and Sovaldi are now the only examples of drugs that are cheaper in the US than in other Western countries.

Oncology spend has also been going up dramatically. Over the last 45 years, there has been a 100-fold increase in the introductory cost of oncology drugs. Over the last 15 years, the cost per additional month of survival has also risen. These diminishing returns are not sustainable. One example of value-based pricing in oncology is the indication-based pricing system that Express Scripts has developed. Tarceva is a drug which prolongs survival 5.2 months in non-small cell lung cancer and by 12 days in pancreatic cancer. According to Federal regulations, such as Medicaid "best price" rules, manufacturers cannot price differently by indication despite the different efficacy. Express Scripts has worked with experts to come up with ways to price based on indication. For example, Express Scripts has contracted with AstraZeneca on Iressa for lung cancer to allow patients to try it risk-free. Express Scripts will refund payment if the patient stops treatment after the first month. Express Scripts is able to do this because it has specialized pharmacists with deep clinical knowledge.

Express Scripts is beginning to use value-based pricing for anti-inflammatory drugs, now the largest pharmaceutical spend category. The average prescription costs $3000. Express Scripts has split the anti-inflammatory into seven

categories in order to reduce rebates. Patients can try these drugs with lower risk for 3 months. If a patient stops treatment in this period, they receive 2/3rds of their money back.

What do stakeholders need to do to solve the unsustainable pricing problem? It's important to do this, because the regulators will not solve this as well as the free market can. Pharmaceutical companies need to show better judgement in pricing. They also need to allow biosimilars to reach the market to provide headroom for new products. Pharmaceutical manufacturers also need to reduce international price disparities and stop patent gaming. The Federal Government needs to better fund the FDA to speed all products to market to allow competition. They also need to boost NIH research in underfunded areas such as antibiotics, reform the patent system to help biosimilars, adjust malpractice laws to help manufacturers, and bring cost into the care equation. Payers need to continue to provide coverage – Express Scripts never complains about the pricing of cystic fibrosis or hemophilia drugs, because they are worth the price. Payors also need to design plans for consumers that have lower copays and deductibles.

A Fireside Chat with Steven Miller

DR. STEVEN MILLER
CHIEF MEDICAL OFFICER AND SVP
EXPRESS SCRIPTS HOLDING COMPANY

MODERATOR:
PETER YOUNG
PRESIDENT AND MANAGING DIRECTOR
YOUNG & PARTNERS

Personal

Young: You have an unusual career history in that you have been a doctor, a clinical researcher, a hospital administrator, and now a senior executive in a corporation in prescription benefit management. How has this mix of experiences influenced and/or helped you along the way and in the job you are doing today?

Miller: My initial goal was to be a veterinarian, but I ended up going into a six year medical school program. I became a physician and focused on taking care of patients. I then moved into doing research fellowships and clinical research for a number of years, issued lots of patents, and was involved in doing drug trials. I then became the Chief Medical Officer for Washington University, which was a position that had never existed before and got on the business side. To learn business skills, I went to business school for my MBA and became Vice President of the Medical Center. By 2006 I ended up at Express Scripts. So the pattern has been to go from being a respected physician to positions that were increasingly "evil", but I had the great fortune to be exposed to a number of different disciplines.

Young: Most people have a personal passion in life that may or may not be related to what they do for a living? What is yours?

Miller: My parents got me on track after I flunked third grade by making me find a job at a ski shop which was very hard work. This helped me develop a strong work ethic, self-esteem and an appreciation for the rewards one can get from hard work.

Industry

Young: You have been involved in a project called the Bluefield Project that took a unique approach to R&D. Can you tell the audience something about that project and what it has been able to accomplish?

Miller: The Bluefield Project emanated out of the University of California San Francisco where the target was to use a finite sum of money to focus on cures for Alzheimer's disease where there is collaboration across a large number of institutions. The researchers have to share data on a weekly basis so that the cycle of discovery is very fast. This sharing across a large number of researchers has had a very positive effect and the IP issues are well defined and solved. We are making great progress and we have broken down the typical silos and reluctance to share.

Young: As you reflect on how Big Pharma, Specialty Pharma and Biotech companies conduct R&D, what do you think is working and not working? What changes would you recommend to them with regard to how they are approaching R&D?

Miller: The biotech industry in the US is spectacular with regard to R&D effectiveness. This is not true at the large pharma companies. The large companies are focused on portfolios, not individual products. The strength of the biotech approach is a tight focus on a specific product. The large pharma companies have an advantage on the regulatory and marketing side. That is why they use M&A to acquire biotech companies or their products.

Part of the problem for the large pharma companies is that they are chasing the same therapeutic areas and are not focused on finding the areas of unmet needs that are not getting attention.

Young: How do you think the pricing battle is going to play out?

Miller: No crisis lasts forever. Someday pricing will not be on the front page. But how do we get there? Part of the solution is how the pharma companies behave and are perceived. For example, Brent Saunders of Allergan has promised not to raise the price of any drug more than 10% each year. It is going to take time and a lot of actions to get us to the right place.

Express Scripts

Young: How will PBM's have to change in the future to deal with industry and market changes?

Miller: We are focused on how to become involved in a larger part of the healthcare system, not just drugs. We're doing things that go well beyond just delivering drugs. For example, we are using our knowledge and data to become more involved in disease management by having live monitoring of patients that allow us to alert patients when we know that there is some significant blood sugar change and letting the patient know. Since we are somewhat of a virtual company, we can add these services economically as a "light rail" company.

Young: Express Scripts has put an enormous effort into data analytics and into innovation in general. Could you describe these efforts, what is driving these efforts, and what you think the benefits will be?

Miller: We have predictive models for almost any disease that you can think of. For example, we can predict if someone has a high propensity to be an opioid addict after their first prescription. We have ways to provide feedback to the patient in an appropriate way that will help them avoid these predicted problems. We think we can change the world by using our data and predictive models to change behaviors in a positive way with regard to patient health.

Young: Express Scripts has embarked on creating a chain of specialty pharmacies? Why are you doing this and will this create tension with other parts of industry?

Miller: We really have therapeutic resource centers in 21 therapeutic areas. These centers have specialists in each therapeutic area. These are not general pharmacists. That way people can talk to specialists. By setting it up this way, the patients speak with a specialist pharmacist for their disease. Obviously other pharmacists do not like this because we are getting 10% better patient adherence by having these specialists and we can do it on a large scale because we are almost a virtual company. We do not have lots of bricks and mortar.

Challenges and Opportunities in the Pharma and Biotech M&A Market

PETER YOUNG
PRESIDENT AND MANAGING DIRECTOR
YOUNG & PARTNERS

Introduction

The last few years have been a positive period overall for both the Pharma and the Biotech industries on many fronts.

Most importantly, the number of new drugs approved and under development has escalated for both pharma and biotech companies. Many of these are driven by new methods, such as Immuno-Oncology, personalized medicine, stem cells, and biologics. We are also witnessing the development of a greater number of drugs that cure diseases rather than just extend life.

The valuations of both pharma and biotech companies in the public and M&A markets soared up until the end of 2014 in part because of these positive developments, but share prices and public valuations have been volatile since then with the drug pricing controversies.

Public biotech shares have been hit particularly severely since the end of 2014, and as a result the IPO market began to cool off in the second half of last year. This is creating a difficult equity financing environment for biotech companies which, in turn, has affected the choices available to biotech companies to continue to fund their companies.

Pharma M&A

Through the third quarter of 2016, 37 deals were completed worth $117 billion compared to 56 deals completed worth $200 billion in 2015. From an annualized point of view, this represents a decrease in the dollar activity since last year, and a slight decrease in the number of deals.

There were fewer mega deals, with only two large deals completed, the $31 billion acquisition of Baxalta by Shire and the $40.4 billion acquisition of Allergan's Generics Business by Teva. Drug makers are acting as both buyers and sellers, forming strategic alliances and swapping as they shore up their core businesses, exit non-core units, and use or seek tax inversion advantages.

As of September 30, 2016, the value of the deals announced but not closed was $7 billion (20 deals), a solid number of deals, but a weaker dollar volume in the pipeline. The pipeline was $240.4 billion (16 deals) at the end of December, but the massive Pfizer/Allergan deal was cancelled.

Biotech M&A

Biotech M&A activity has almost always been modest historically, with small spurts of activity from time to time.

Through the third quarter of 2016 there were 29 biotech M&A deals completed worth $14 billion compared to 31 deals worth $19 billion completed in 2015.

2016 activity is on track to exceed 2015 in terms of the number of deals. The dollar volume trajectory is less clear. The pipeline is very weak. As of September 30, 2016, the value of deals announced but not closed was very modest at only $0.6 billion on only 1 deal.

Outlook – Pharma M&A

M&A activity through the first three quarters of 2016 has been below last year's dollar pace, and about the same on a number of deals basis.
Young & Partners expects Pharma M&A activity in 2016 to fall relative to that of 2015 in terms of both dollars and number of deals. The shutdown of the large inversion deals has contributed to the dollar slowdown. However, volume will still be significant, driven by restructuring and strategic needs of the pharma companies and the residual impact of what has been a feeding frenzy. This is being fueled by the massive business restructuring that is happening in pharma and the consolidation that is occurring both on the generic and non-generic sides of the business.

Pharma companies are modifying their business portfolios to focus on leading positions and to exit weaker positions, and non-core and mature/established products, to search for growth, to attempt to replace lost or soon to be lost revenues, and to drive for scale and cost reduction through consolidation.

Outside of M&A, the need to fill the shrinking drug pipeline is also facilitated by in-licensing arrangements and the formation of partnerships and joint ventures involving both pharma and biotech companies.

Therefore, in spite of the headwinds from the current ruckus about drug pricing, we believe there will be strong pharma M&A volume ahead of us, but moderately curtailed on a dollar basis by the inversion rules now in place.

Outlook – Biotech M&A

The primary biotech M&A theme has been pharma and big biotech acquisitions of biotech companies for pipeline enhancement.

The most promising biotech companies over the previous three years were able to go public first and attract significant interest and high prices later. The surge in IPOs gave biotech companies more flexibility as to whether and when they exit via a sale. However, the recent slowdown in IPOs will drive many companies to either sell themselves or raise funds via partnering deals or discounted private placements.

Therefore, M&A volume and partnering deals will be modest relative to pharma, but will increase significantly.

Implications for Senior Management

For ethical pharma companies, there will continue to be a wide variety of tools to acquire revenues and pipeline drugs, but the valuations are challenging, particularly for promising drugs in late stage clinical trials and for companies with strong products.

The challenge will be to pick the right overall mix of M&A, licensing, and partnering to accomplish corporate strategic goals and defend and deliver shareholder value.

The generic pharma companies will continue to face a number of industry challenges. This will result in a continuation of the current industry consolidation and selective strategies around diversification.

Time will tell whether the very public attack on drug pricing will force changes in the industry.

Orphan Drugs: Perspectives on the Past and the Future

DR. GAYATRI R. RAO, M.D., J.D.
DIRECTOR, OFFICE OF ORPHAN PRODUCTS DEVELOPMENT
FOOD AND DRUG ADMINISTRATION

The Orphan Drug Designation Program was created by congress in 1983 to address real needs in the patient community. The program created financial incentives for the development of drugs in spaces that had little drug development activity. The primary incentives created by the program include a 50% clinical trial tax credit, a waiver of marketing application fee when they submit to FDA (the current fee is $2 million), and eligibility for 7 years of marketing exclusivity. Although these are the traditional incentives, orphan designation has taken on a life of its own as time has passed, and is now tied to novel incentives such as 340B drug discount pricing and branded prescription drug fees, both of which are under the Affordable Care Act.

The process for receiving orphan drug designation begins with a sponsor sending the orphan drug designation request to the Office of Orphan Products Development (OOPD). At this point there will either be an issuance of deficiency/denial letter or a grant designation. Grant designations also result in the eligibility to receive financial incentives. The next step is to develop the product, and this is where the financial incentives kick in. The products that we designate are usually early stage. They often have animal model data or early clinical data, but in some rare cases we designate on in-vitro data with mechanism of action data. The idea is to designate liberally because we want the science to weed out safe and effective drugs from those that are not safe and effective.

During the clinical development stage applicants take advantage of the tax credits for clinical trials. The next major step is to submit a Marketing Application, and if the product has orphan designation then the user fee is waived. These applications go to the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER). If an applicant makes it past this step and receives approval to market their product they must apply for Orphan Exclusivity Determination. This decision is made by the OOPD in tandem with CDER and CBER. Designation is not permanent, and can be revoked, but it happens very rarely. If there is evidence that the product was ineligible for designation at the time that the request for designation was granted, then it can be revoked.

We had 466 requests for Orphan Drug Designation in 2015, this is approximately double that of 2009. Typically two-thirds of the requests receive designation. This year we are well on our way to surpassing the number of requests from last year. Interestingly, 50% of novel drugs which were approved were drugs with an orphan designation. I am not sure that these numbers will continue, but I do not foresee a significant drop off in the near future.

We are always asked whether precision medicine is driving this increase in orphan drug designation. Precision medicine can be defined as a drug or biologic with a mechanism that acts specifically to treat a genetically or molecularly defined subset of a disease population. Although we are still looking at data, the preliminary analysis shows precision medicine is not responsible for this dramatic increase in orphan drug designations. In order to get an orphan designation of a drug that is the "same" as a drug which already has approval, a plausible hypothesis of clinical superiority must be provided. To get orphan exclusivity, regulations require that sponsors demonstrate that their product is clinically superior. However, the framework for obtaining orphan exclusivity is currently under litigation. When talking about the ongoing litigation and its potential implications we are really only talking about 5% of the drug applications for orphan exclusivity.

Looking at orphan drug designation request data, there seems to be a strong interest in orphan drugs and biologic developments. Oncology related designations continue to dominate what we are seeing. A significant number of novel drug approvals are orphan. They are approved through flexible reviews and really take advantage of expedited pathways. The vast majority of these drugs receive exclusivity upon approval, but there is uncertainty with regards to the current orphan exclusivity framework.

The Pharmaceutical Market: Trends, Issues and Outlook

DOUGLAS M. LONG
VICE PRESIDENT, INDUSTRY RELATIONS
IMS HEALTH, INC.

Year-to-date pharmaceutical spending growth is 6.3% in 2016 YTD, down from double digit growth in 2014 and 2015 as we are now at the tail end of the growth in Hepatitis C drugs. Nominal drug industry sales are now over $430 billion. Over the past 30 years, we have moved from the Blockbuster Era to the Generics Era and are now in the Specialty Era. Specialty drug sales growth is 23% compared to traditional drug growth at 7.8% YTD and specialty medicines now account for 36% of all pharmaceutical spending. New brand spending increased by $21.5 billion in the last 12 months, and $13.6 billion of new brand spending is on specialty medicines. Prescription growth increased 1% in 2015 due to higher prescribing of generic drugs offset by lower prescriptions of narcotics due to rescheduling of controlled substances. Nearly all of the prescription increases are in Medicaid and Medicare Part D.

Generics now account for 15% of spending and 84% of prescriptions. This will grow to 85-86% by 2018-19. The great sweet spot of the generics industry was 2000 to 2014. Savings from generics over the last 10 years totaled $1.7 trillion. This provided the headroom to pay for the new specialty drugs. The savings from generics has been slowing substantially; although $87 billion in small molecule brand sales are facing patent loss over the next 5 years, only $19 billion of this is in 2019-2020. Whereas generic inflation was substantial in 2014 and 2015, generic prices have been flat in 2016. The large opportunity to provide headroom to pay for new drugs over the next several years is with biosimilars. Many key biologics products have lost or will be losing patent protection by 2020. One key launch to watch is Pfizer's infliximab, its Remicade biosimilar, expected later this year. Biosimilars have been approved in Europe since 2006, while the US only has one approved so far. There is great potential for biosimilars in the US and most of the competitors are brand name companies rather than generics companies.

New Brand spending was in the $6-7 billion per year range from 2011-2013 and then exploded beginning in 2014 when Sovaldi was introduced. Spending on brands launched in the last 24 months has been over $20 billion per year over the last couple of years. In 2014, half of the spending was in Viral Hepatitis but more recently spending is also in Oncology, Autoimmune and Diabetes, among others. An unprecedented 225 new drug products are expected to be introduced between 2016 and 2020. List price growth has been in the high single to low double digits. In 2015, invoice prices rose 12.2% to $425 billion, while net prices rose 8.5% to $310 billion. Payers have become more concentrated and more powerful and are receiving higher rebates. There will be a need for more collaboration between pharmaceutical manufacturers and PBMs as new products are introduced, many of which will be high-priced specialty medicines.

The pharmaceutical industry has to deal with the current political environment. Pharmaceutical spending is approximately 14% of total healthcare spending (19% according to Express Scripts). The bulk of spending is on hospitals and other provider costs. The pharmaceutical industry is a convenient target, however, and the industry has hurt itself with Turing and Valeant and Epipen, for example. Adherence to medicines lowers total health spending – over $200 billion could be saved annually in the US if medicines were used properly. Prescription drug deductibles are increasing causing challenges for consumers. A minority of patients account for the vast majority of healthcare costs – the top 1% account for 26% of spending and the bottom 50% accounts for only 3.3%. This bottom 50% have not signed up for the Affordable Care Act in sufficient numbers to offset the sicker patients in the health exchanges.

In the meantime, there are several "tsunamis" on the horizon. The first was the new Hepatitis C drugs and we are now experiencing the rise of immuno-oncology drugs. We will soon have the expansion of PCSK9 inhibitors and respiratory biologics. Further out, is Alzheimer's. Independent bodies like ICER and some European countries have been involved in the debate over new drug pricing. We will likely see new payment models in the future to pay for innovation, including pricing by country income, pricing by indication and pricing by performance. Real

world evidence will be key and a number of collaborations are looking at this. In the future, outcomes will equal income, and if your drug delivers no outcomes, you will have no income.

The therapeutic classes with the largest growth are autoimmune, diabetes, monoclonal antibodies, HIV and anticoagulants. This growth was funded in part by classes where sales were falling substantially including antipsychotics, proton pump inhibitors, A2 antagonists, and Alzheimer-type dementia. Many of the leading products by sales are facing potential biosimilar or generic competition in the near future or, in the case of Harvoni, fewer new patients.

Payers are concerned about the exploding costs of specialty drugs. Consumers are concerned about the rising costs to them of pharmaceuticals. This potentially leads to lower compliance as people choose not to fill prescriptions. Manufacturers are becoming more specialized and continue to focus on developing oral specialty and orphan drugs.

As we look ahead, the decelerating dollar growth for pharmaceuticals is continuing. Most recently, growth for retail and mail is running at about 6%. The difference between list and net prices continues to grow. Prescription trends are improving and are now running at about 2%. Mergers are continuing – there is uncertainty about whether the announced Walgreen's/Rite Aid merger will be completed. The effect of the upcoming election and continuing public anger about drug prices remains to be seen.

Biopharma Turnarounds: Case Studies and Lessons

PARIS PANAYIOTOPOULOS
CHIEF EXECUTIVE OFFICER, PRESIDENT AND DIRECTOR
ARIAD PHARMACEUTICALS, INC.

I have done turnarounds in Japan, Western Europe, North America and Switzerland where I did a large global restructuring for Merck KGaA. Every situation is different and it is difficult to be formulaic.

With ARIAD Pharmaceuticals, the company had accumulated losses of $1.4 billion. It had invested $1.3 billion in R&D. The revenues were all being invested into R&D. The cash position at the end of the first quarter of 2016 was just over $160 million and the company was planning to spend $400 million for all of 2016. ARIAD was struggling to remain sustainable, let alone fund the fantastic science that is ultimately the company's greatest asset. ARIAD developed and commercializes ponatinib, a treatment for refractory Chronic Myeloid Leukemia (CML) and Philadelphia-chromosome positive Acute Lymphoblastic Leukemia (Ph+ ALL), treating a small population of rare cancer patients with no other treatment options. The company also developed brigatinib, which received the Breakthrough Therapy designation from the FDA for the treatment of patients with crizotinib-resistant ALK+ Non-small cell lung cancer, and developed an early-stage Immuno-Oncology research platform. So how do you push these projects forward with limited cash?

The first step is to "diagnose" the problem by listening to people from all functions within the organization. The second step is to "decide & execute" as many wins as you can. Finally, "refine & focus" that execution strategy over time to assure effectiveness. Communication is essential to the entire turnaround process. Barriers and hierarchy must be broken down quickly and formality must be kept to an absolute minimum. At ARIAD, we spent time trying to understanding the previous strategy, operational plans, culture and strengths. We made ourselves very accessible across the entire organization.

We organized the strategic review across five areas; these were geographic reach, commercial maximization, R&D portfolio, cost efficiencies and business development. At the time, we were operating in the USA and Europe and were working through partners in the rest of the world. We had the potential launch of brigatinib upcoming as well as the commercialization of ponatinib. We had an R&D portfolio of a number of programs that could bring hope to patients but limited financials to do so. Finally, there was some business development potential which, given our financial position, would need to be out-licensing rather than in- licensing. We undertook a long, quantitative exercise to evaluate our various options.

Ultimately, we decided to sell our European operations. That bolstered our position. We also made the difficult decision to restructure the organization. Most importantly, our goal was to be able to continue our development programs. We did not terminate any of our clinical programs. Our new vision is to continue to lead the discovery, development, and commercialization of precision therapies for patients with rare cancers. Our new strategy entailed commercializing in the USA, working through partners ex-USA, investing further in the early discovery Immuno-Oncology platform and driving a more sustainable operation. For now, we are in a position to continue to innovate and develop for the rare cancer patient population that depends upon us.

CRISPR: Advancing the Technology

DR. SAMARTH KULKARNI
CHIEF BUSINESS OFFICER
CRISPR THERAPEUTICS

CRISPR/Cas9 exploded onto the scene in 2011 when Emmanuelle Charpentier figured out how bacteria use the Cas9 enzyme to cut viral DNA. These bacteria insert the viral DNA into their own genome and used it as a defense mechanism against future viral phage attacks. Emmanuelle Charpantier, the scientific founder of CRISPR Therapeutics, figured out how to utilize CRISPR/Cas9 as a programmable, gene-editing system. There are labs all over the world editing genomes via the CRISPR/Cas9 system.
The underlying science is very efficient, specific and versatile. The challenge comes when advancing the technology into the clinic. Delivery, pharmacology and process development will need to be addressed.

CRISPR-based therapeutics can be developed both ex vivo (outside of the patient's system) and in vivo (within the patient's system). In an ex vivo setting, the patient's cells are harvested, treated with CRISPR/Cas9 in a separate location then reintroduced to the patient's system. In an in vivo setting, the CRISPR/Cas9 therapeutic is packaged in a delivery vehicle and introduced into the patient's system. Our company tends to be lumped together with gene therapy companies. However, if you think about the programs we are developing today, we are really a cell therapy company. Our pharmacological product is a cell or collection of cells. We are de-risking by pursuing ex-vivo treatment options initially. As we develop delivery technologies, we will explore in-vivo treatment options and become a gene therapy company. Ultimately, however, as we pursue regenerative medicine, we will return to ex-vivo treatment options.

CRISPR-based therapeutics will allow for the ultimate "personalization" of medicine. This concept can be applied to treatments for Duchenne muscular dystrophy. The recently approved Eteplirsen from Sarepta works via skipping the faulty exon to bring muscle functionality back. The challenge Sarepta faces is that even if the exon skipping concept is effective in one exon, the trials must be repeated for all 13 possibly defective exons to demonstrate effectiveness to the regulators. CRISPR's concept cuts out the faulty exon permanently at the genomic level. Autologous therapies, another potential CRISPR application, rely on harvesting a patient's own cells, editing them and reintroducing them back to the patient creating an individualized therapy for each patient. Approval would only be required for the process and quality control.

We are now in a paradigm where supply chain is becoming more critical than manufacturing. The logistics of collecting the patient's cells, creating and shipping leukopaks, editing the cells, re-creating the leukopaks, returning them to the site of therapy, and reintroducing the cell into the patient, are very complicated. The manufacturing scale up challenge is relatively limited because the indications we are exploring are so rare.

Commercialization will be a challenge. The marketing channels will need to be high specialized. The different types of indication will warrant innovative pricing models based on pharmaco-economic analysis. A number of the payment models currently being discussed will produce outputs that do not justify the R&D investment by biotech companies. Curative therapies have upended the standard methodology of modeling revenue for a disease. The "bolus" effect of patients suffering from the disease is reached quickly after launch. There is a huge advantage of being first-to-market.

The Pharma P&L model needs to evolve. Most of the expenditure is in marketing and sales while COGS and R&D are relatively limited. In the future, the COGS will increase tremendously as supply chain costs of autologous therapies will be much higher on a per patient basis. Niche marketing will be the key to effective launches. When there are very specialized marketing channels, sales costs will be limited. This will allow for greater R&D spend to fill the pipeline. This is how the pharma model can become sustainable again against the overhang of the pricing crises.

Speaker Roundtable – A Selection of Questions and Answers

MODERATOR:
PETER YOUNG
PRESIDENT AND MANAGING DIRECTOR
YOUNG & PARTNERS

PARTICIPANTS:
CONFERENCE SPEAKERS AND ATTENDEES

Peter Young (Young & Partners): Depending on who wins the US presidential election, what do you see changing in the US with regard to healthcare and the drug industry specifically? What impact do you think it will have on pricing?

Doug Long (IMS Health): The thing that is likely to change the most is the Affordable Care Act. You have many issuers dropping out and a lot of places with only one payor. There is a tremendous difference between this and Medicare Part D. In talking with a person who worked on Medicare Part D, I learned that the difference is that with Medicare Part D, they focused on ensuring that there was enough profit in it for everyone. The issue with the Affordable Care Act is that they didn't want anyone to make more money. The question now that it is failing is what do you do? It didn't save money, it has increased the cost. Private-public partnership is a possible option.

Paris Panayiotopoulos (Ariad Pharmaceuticals, Inc.): It is difficult to balance having the right levels of innovation and having a sustainable healthcare system that people can afford to pay for. There are so many players and elements in the healthcare system. The one theme that I think about is transparency. Would all companies want all of their R&D costs for each product to be transparent? I'm not sure. Without significant transparency around things such as how much are you spending on R&D, how much innovation are you bringing to the marketplace, the reason for your current prices and the difference between the WACC and the net price, it is very difficult to find a solution. What I expect to see in the future is that the levels of transparency will increase, thus enabling us to come to a more informed way of looking at things.

Doug Long (IMS Health): Going back to the EpiPen situation. Everybody got caught up on the $680 list price. But the negotiated contract price is something like $280. Mylan was getting castigated on the $680, but the contract price is $280. Where's the difference going? Some of it is going to rebates back to the PBMs and a lot of it is in high deductible plans.

Peter Young (Young & Partners): I think you have the other problem which is that people are fixating on the wrong things and the wrong numbers. Let me give you a drug specific example. It's not visible to an average consumer what it costs to stay in the hospital, but because they have to go down to the drug store and pay for a prescription, the price of the drug becomes disproportionally magnified to the consumer. Yet, if you actually look at the costs of, providing healthcare through the system, the huge amounts such as those shown in Doug's slides, are in the hospitals escalating costs.

Samarth Kulkarni (CRISPR Therapeutics): I think there is another issue which is in shareholder returns. In the healthcare system, providers have probably the biggest waste. There is the place for the greatest opportunity for efficiency and it is also the biggest chunk of spending compared to pharma, which is small. If you look at the shareholder returns in the last 15 years, 90% of the value captured is pharma and everything else is 10%. When you have individuals making a lot of money on top of all the price increases that you have, it just creates a difficult situation.

Peter Young (Young & Partners): Guy Villax do you have any comments on the way in which people in Europe are dealing with the pricing and system issue compared to the U.S.?

Guy Villax (Hovione FarmaCiencia SA): I think in Europe the government budget is pretty much bankrupt, so when the budget that is available for hepatitis C is "X" and the drug costs all of that, if another drug comes along that costs half, it treats double the people. I think that when I have to tell my children what I do for a living, I don't feel so bad

because, although we still have obscene prices for the innovative drugs, within 8-10 years you get the best research for pennies. America probably has the highest generic penetration of any country.

Peter Young (Young & Partners): But do you think that things are working better in Europe than over here or is everyone having problems, but just a different mix?

Guy Villax (Hovione FarmaCiencia SA): I think everybody has problems, but I think certainly those countries outside of America free-ride on America. America pretty much funds R&D for the rest of the world and America pretty much invents most of the new drugs. To find biotech you go to Boston, San Francisco, and San Diego, and then quite a few levels of magnitude below you go to Basel. Additionally everyone else in Europe is remarkably earlier in clinical development.

John Glasspool (Shire): One of the key issues consistent around the world, particularly in the US, but everywhere where I've worked, is that the whole system is built on the costs of inputs not outputs. Systems are built for billing and not charging, and we know what we spend on people but we don't know what the benefit is and I think the key change that needs to take place in the system in the US and elsewhere is that the outcomes need to become more important. One reason drugs costs get called out is that they are easy to identify. No one knows the cost of a CT scanner or the true cost of a night at a hospital; these are basically made up numbers. The key is to look at outcomes in order to move towards rewarding innovation. I think in the future if you want to raise prices you will need to justify the price increase.

Peter Young (Young & Partners): Is the pricing issue going to have an effect on the demand for orphan drugs in terms of companies deciding to invest in orphan drug development?

Gayatri Rao, M.D., J.D. (Office of Orphan Products Development, FDA): We work closely with patient advocacy organizations and some large patient advocacy umbrellas. One of the challenges that I'm hearing from patient groups, particularly in the rare spaces, is that there is a challenge lumping orphan drugs into the specialty category. When orphan drugs are lumped into the specialty category, they are automatically grouped with the drugs with the high prices.

Doug Long (IMS Health): I have not heard any pricing backlash about orphan drugs.

Peter Young (Young & Partners): Are there any comparable orphan drug programs outside the U.S.?

Dr. Gayatri R. Rao, M.D., J.D. (Office of Orphan Products Development, FDA): Europe has orphan drug programs. They really modeled their program after ours; they do not have the fixed prevalence number of 200,000. Japan has a pretty well established orphan framework. Canada is trying to establish an orphan framework.