Life Science Trends 2012

It's All About the Data: an exclusive interview with Dr. Antony J. Williams, p. 23

Carlyle & Conlan

Executive Search | Recruiting | Consulting

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Introduction

About this Report

Each year, Carlyle & Conlan provides an overview of trends and innovations in the life science industry, encompassing its drugs, biologics, devices and diagnostics sectors. Utilizing a number of in-depth, premium research reports available in the industry, Carlyle & Conlan's Life Science Trends summarizes and presents a variety of the most up-to-date industry news under several macro headers: *Research and Innovation*, *Fundamental Trends*, *Investing and Deal Making*, *Regulatory & Government,* and *Health Care*. The result is a meaningful, "quick-read" white paper into which topics our clients, partners and constituents can dig deeper based on their individual interests.

Life Science Trends 2012 captures significant advances in the industry from the past year and makes observations about developments of interest through the year ahead. Of central importance is the understanding that trends do not necessarily change on a yearly basis. For instance, the field of personalized medicine is expected to continue as a trend well into the foreseeable future.

Our report may differ from others in that an early version is sent to CEOs, venture capitalists, and other industry experts for review before its final release. This report was created using both primary and secondary data. Secondary data is highlighted with associated links to further information as available in the public domain or credited to the appropriate source.

We invite you to review the information contained in this report, which we trust you will find interesting and relevant to the sector.

About Carlyle & Conlan

Carlyle & Conlan, headquartered in the Research Triangle Park, is an executive and professional search firm focused on the life science and technology sectors. With a highly dedicated, experienced, and professional team of specialists, we work with small, mid-sized and large companies to secure their most important asset, human capital. Our placement focus is on highly experienced individual contributors through C-level search in a variety of functional position types throughout North America. More information about Carlyle & Conlan can be found at: http://www.ccesearch.com.

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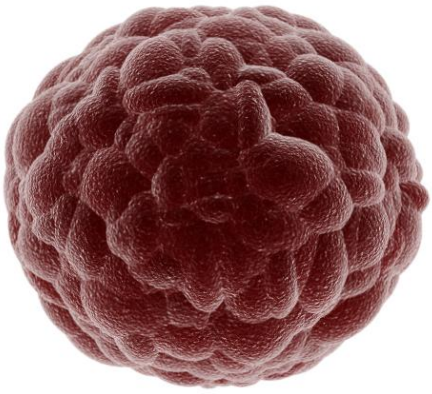
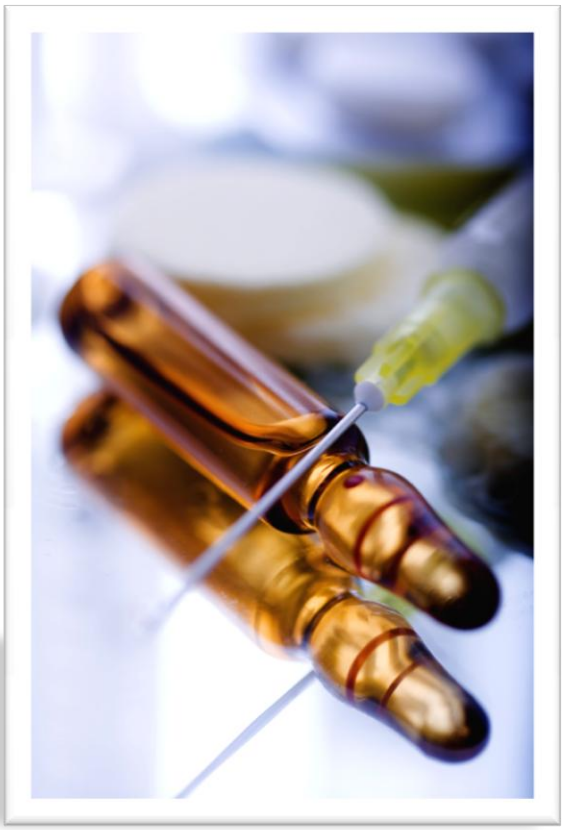
Research and Innovation

Cancer Treatment Reprograms Immune System

Scientists have been able to successfully target cancer cells by using cells from a patient's own immune system—creating a new way of treating cancer. Researchers engineered a patient's own immune cells to treat a type of blood cancer called Chronic Lymphocytic Leukemia, or CLL. CLL is a blood cancer; the only known cure currently is a bone marrow transplant, which is only effective in about half of the patients. In the approach, discovered by Dr. Carl June and his team at the University of Pennsylvania, scientists used the patient's own T-cells, white blood cells that help fight infections, and genetically reprogrammed them to attack leukemia cells in the patient. In two of the three patients treated by this method, the cancer cells were completely gone six months after the immune therapy. While there are serious side effects, such as a flu-like illness, all three of the patients are doing well after a year of treatment. The hope is that in the future, these T-cells can be used to help treat colon, breast, and lung cancer, and eventually kill all types of cancers.

Source: CBS News





Cancer Viral Therapy Attacks Tumors and Does Not Harm Healthy Tissue

Intravenous viral therapy has been shown to consistently infect tumors without damaging healthy human tissue, according to a clinical trial published in the journal *Nature*. The clinical study included 23 individuals with advanced cancer—cancer that had spread to several organs in the body, and standard treatments had not been effective. These patients were administered a single intravenous infusion of JX-594, an oncolytic virus that replicates naturally in cancer cells and has been genetically altered to enhance cancer-fighting properties. Patients were administered JX-594 at five different levels of dosage. The virus was tolerated well at all dosages by the patients, with the most adverse effect being flu -like symptoms that cleared within 24 hours. After ten days, biopsies were obtained and found that 87% of those who were given the two highest dosages of the virus had evidence in their tumor of viral replication, but none in surrounding healthy tissue. 75% of these participants within the two highest doses experienced stabilization or shrinkage of their tumor. While the purpose of the trial was to assess the safety and delivery of JX-594, scientists are excited about what these oncolytic viruses mean for the future of cancer treatment.

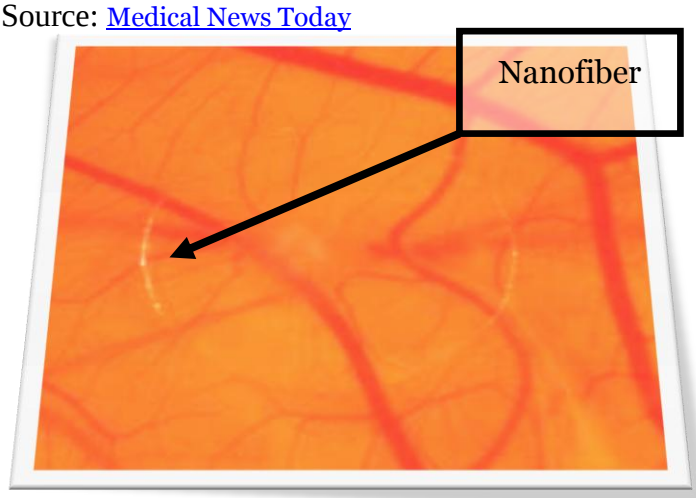
Source: Medical News Today

MicroRNA Has Potential for Cancer Blood Test, and Also for Other Diseases

MicroRNA has long been known to turn a cell's genes on and off; however in cancer cells these small bundles of genetic code become out of control. A team at MIT has begun using minute, hydrogel particles to measure microRNA levels, allowing microRNA profiles to be created. Since different types of cancer have different microRNA signatures, these profiles should be able to provide a method with which one can scan and diagnose cancer.

The problem with most microRNA detection methods is that the RNA must be isolated from the blood or tissue- a very expensive and time consuming process. However, with hydrogel particles, microRNA is more easily and efficiently detected. These hydrogels are a type of polymer chain network to which are attached millions of identical DNA strands. These strands are complimentary to specific microRNA sequences; therefore, any microRNA in a blood sample will be attracted to and attach to its respective DNA on the hydrogel particle. A scanner is used to detect how much, as well as what kind of, microRNA is present. The entire process takes less that three hours and is more accurate than previous diagnostic methods.

The next step in this research is testing to find out if microRNA can be used for detection of other diseases such as HIV or heart disease.
Source: Medical News Today



Capillary action: The transparent circle in the center of this image is a nanomaterial designed to mimic the protein VEGF. Here, it has enhanced the growth of blood vessels in the membrane from a chicken egg after three days. Source: Technology Review

Dendritic Cells in Liver Protect Against Acetaminophen Toxicity

High doses of acetaminophen can cause hepatotoxicity in the liver—inhibiting its ability to transform and filter chemicals through the body. In the US, acetaminophen overdoses are the most frequent cause of acute liver failure and, as a result, the FDA has mandated that drug manufacturers limit the amount of acetaminophen in combination drug products. Recently, researchers at the NYU School of Medicine have discovered that the dendritic cells in the liver play a protective role against the toxicity of acetaminophen. Dendritic cells are the main antigens in the liver that trigger an immune response and control the liver's tolerance to high doses of toxins, including acetaminophen. An abundance of these dendritic cells in the liver can protect it from acetaminophen damage, while lower levels of the dendritic cells are associated with exacerbated liver damage and acute liver failure due to acetaminophen. These studies were completed on mice, so further testing on humans will be necessary—but a whole new way to target liver failure prevention may be just over the horizon. Source: NYU

Nanofiber Regenerates Blood Vessels

When combating the after-effects of a heart attack or peripheral arterial disease, or ensuring that transplanted organs receive a sufficient supply of blood, regenerating blood vessels becomes very important. Researchers at Northwestern University have developed a liquid that forms a matrix of loosely tangled nanofibers when injected into patients. Each fiber is covered in microscopic protuberances that mimic vascular endothelial growth factor (VEGF). By mimicking VEGF, the fibers have the same biological effect of VEGF, the growth of new blood vessels. Tissue engineers have tried using VEGF itself to stimulate the growth of blood vessels, but the clinical trials were unsuccessful because VEGF tends to diffuse out of the target tissue before completing its job. The new nanomaterial lasts much longer, is much cheaper and less controversial than stem cells, and is completely biodegradable once its job is finished. There could be more uses for nanofibers that mimic proteins from the body, but more testing is needed to determine exactly where else these fibers will be effective.
Source: Technology Review

Epigenomics

Epigenetics, the study of DNA development and lineage specification of different cell types that have essentially the same genetic information but markedly different phenotypes, is central to human disease including cancer, metabolic, and other diseases. The study of epigenetics on a global level has been made possible only recently through the adaptation of genomic high-throughput assays. In sum, next-generation sequencing has transformed epigenomic research.

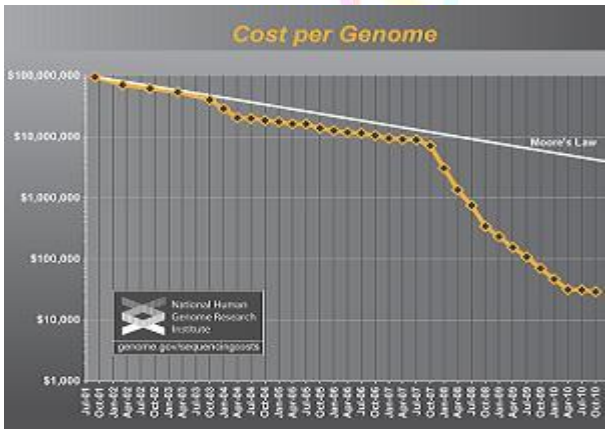
Epigenomic data sets have great value for annotating the genome and, in particular, non-coding genomes that have been rather inaccessible thus far. They can also provide insight into regulation across cell types, developmental stages, etc.

Epigenomics has garnered increased research interest as well as financing through programs like the NIH's Common Fund. According to industry analysts, the global market for epigenomics will reach nearly $4.1 billion by 2012. Drug applications for epigenetics are by far the largest sector of the market but diagnostics have the most potential for growth through 2012.

Sources: BCC Research : National Institute of Health Common Fund : VIZBI

The $1,000 Genome

Life Technologies recently announced a $1,000 genome, ushering in a new era of potential applications. Of interest is the rapid decline in cost per genome compared to Moore's Law for semi-conductors.



Source: National Human Genome Research Institute

IBM Nanomedicine Breakthrough to Aid Antibiotics

IBM researchers and scientists from the Institute of Bioengineering and Nanotechnology have unveiled biodegradable nanoparticles that make antibiotics physically attracted to infected cells. This nanomedicine breakthrough represents a new drug delivery method that could potentially fend off drug-resistant infections caused by MRSA and other bacteria. Hopefully this breakthrough will lead to a wide variety of uses, from healing wounds to emergency uses in a war. While the discovery holds promise in delivering medicines, one of its more striking features is how semiconductor manufacturing applies to producing organic material. For instance, chips require small wiring and cramming together ever-shrinking transistors in a precise way. Organic nanostructures require the same.

Source: ZDNET UK

New Generation Drug-Eluting Stents Offer Considerably Lower Risk of Stent Thrombosis and Restenosis

The results of a SCAAR study showed that Percutaneous Coronary Intervention (PCI) with a 'new generation' Drug Eluting Stents (DES) was associated with a 38% lower risk of clinically meaningful restenosis and a 50% lower risk of stent thrombosis—compared to old generation DES. These new generation stents have been developed to overcome the current limitations of the older stents, such as their long term safety—especially regarding the potential risk of late stent thrombosis or restenosis. In a Swedish study, the performance of the different types of DES was evaluated in a real-world population for two years. The main findings were that the 'new generation' DES was associated with a 38% lower risk of clinically meaningful restenosis and a 50% lower risk of stent thrombosis compared to old generation DES. Further studies are needed to determine whether one of the three components of the new generation DES (the polymer, the stent alloy, the eluted drug) is responsible for decreasing the incidence of stent thrombosis and restenosis.

Source: Medical News Today

Drug Shortages

Drug shortages are an ever escalating problem that endangers patients and raises the possibility of price gouging. President Barack Obama is directing the FDA to reduce said drug shortages- potentially saving lives in the process. Many patient deaths have been attributed to a lack of good quality drugs since hospitals are being forced to buy from secondary suppliers at high markups. The executive order, in effect, requires 1) drug shortages to be better reported, 2) the reviews of applications to change production of drugs facing shortages to be accelerated, and, 3) the Justice Department to obtain more information on possible price gouging and collusion. Legislation, for the first time, requires that drug makers notify the FDA six months ahead of a potential shortage, increasing supply side visibility. In 2010 the FDA reported 178 shortages and that number increased over one year. Since 2005, the frequency of drug shortages has nearly tripled. Most shortages are caused by quality or manufacturing problems, delays in receiving drug components, or simply because a company could make more money by discontinuing certain drugs in favor of newer, more expensive medication. Those hardest hit are the generic sterile injectable drugs, followed by oncology drugs (28%) and then antibiotics (13%). An inability to obtain adequate supplies of cancer drugs for research has resulted in suspended clinical trials, a halt in patient enrollment, and trials delayed to find an alternative treatment regimen.

Sources: Yahoo News : Burrill Report

Pharmaceutical Industry Outlook

According to IMS Health, global pharmaceutical market growth will be restricted to the mid-single digits (5-8%) through 2014 because of the significant imbalance between new product introductions and patent losses. In addition, Pharma has continued to witness major merger and acquisition (M&A) deals since 2010. With all the patent challenges for blockbuster products, most companies have been looking towards M&As to makeup for the loss of revenues. Major deals in this area include Johnson & Johnson's acquisition of Micrus Endovascular Corp—with their next step looking to buy out the rest of Crucell NV, Merck KGaA's acquisition of Millipore Corporation and Pfizer's acquisition of King Pharmaceuticals, along with others. Elsewhere, companies have been looking towards biotech firms to build their product portfolios. Looking ahead, M&A is expected to continue and it is also expected that there will be a significant pickup in in-licensing activities and collaborations for the development of promising pipeline candidates. Another recent trend of the pharmaceutical sector is the focus on emerging markets. Until recently, most of the commercialization efforts of companies were focused on the US market, along with Europe and Japan. There is an increasing demand to expand market presence in BRIC countries and other large, emerging markets. These emerging markets should see strong sales thanks to a higher medicine demand, as well as initiatives for healthcare, a new patient population and an increased use of generics. Emerging markets growth could help stabilize core business during the 2010-15 patent cliffs. IMS Health estimates that these emerging markets will grow 14-17% through 2014. Although the US will retain its position as the single largest market, China's pharmaceutical market is expected to grow three to five times more than the US and contribute to 21% of global growth through 2013.

Source: Zacks Commentary

Shining a Spotlight on Non-communicable Diseases (NCDs)

Two out of every three deaths are attributable to NCDs, principally cardiovascular disease, diabetes, cancer and chronic respiratory disease, costing trillions of dollars over the next few decades. Eighty percent of these deaths occur in countries with developing economies or economies in transition, representing untold pain and suffering for millions of people. For each 10 percent rise in mortality from NCDs, annual economic growth is reduced by .5 percent.

According to this trend, if things do not change, major NCDs will cost the global economy some $35 trillion from 2005 to 2030, making these diseases one of the top threats to global economic security. September's UN High-lever Meeting on Non-Communicable Diseases provided a worldwide focus on the surge in NCDs. However, with previous focus on HIV/AIDS and infectious diseases, most developing countries have little expertise in NCDs.

Source: National Institute of Health

The 5 Biggest-Selling Drugs that are about to Lose Their Patent

The 'patent cliff' that has been haunting the pharmaceutical industry for years is finally here. With patents on many blockbuster drugs about to expire, an estimated $250 billion in sales is at risk from now until 2015. Once patent protection of drugs is lost, generics quickly siphon off as much as 90% of their sales. This cut results in substantial savings for the consumer but unfortunate cuts for the pharma companies. While these cuts will benefit the generic industry in the short term, said companies will also see a slowdown in revenue growth after 2015 since fewer blockbusters will be coming off patent.

The top five best-sellers to lose patent protection over the next year are:

- 2011/Quarter 4
  - Lipitor- Pfizer. $5,329,000,000
- 2012
  - Plavix- Bristol-Myers Squibb/Sanofi-Aventis. $6,154,000,000
  - Seroquel- AstraZeneca. $3,747,000,000
  - Singulair- Merck. $3,224,000,000
  - Actos- Takeda. $3,351,000,000

For 2012, this patent cliff will affect around $22,804,000,000 worth of retail sales of major drugs, approximately 37.8% of the retail affected for the 2010-2015 'patent cliff' ($60,346,000,000).

Sources: Daily Finance : Securews

No Outcomes, No Income

Life-sciences companies need to learn how to become outcomes-based. Ed Bennett, web operations manager at the University of Maryland Medical Center, recently stated that the entire health care reform law can be simplified into four words: no outcomes, no income. While there is no one-size-fits-all business model, most experts agree that the future road to success in the life sciences sector is paved with research that demonstrates improved patient outcomes.

David Ormesher, CEO of closerlook inc, a strategic marketing agency that brings healthcare clients closer to their customers, says that "Outcomes are not the same as efficacy. Soon CMS will be paying providers based on outcomes, and physicians will insist that the pharmaceutical company is able to deliver measurable improvements. Whether pharmaceutical companies evolve from strictly delivering products to healthcare solutions or whether they learn how to partner with diagnostics, medical device, food, and exercise companies, marketers will need to learn some new moves."

According to Carolyn Buck Luce, Pharmaceutical Sector Leader of Ernst & Young, this "prove it or lose it" environment will force pharmaceutical companies to take such steps as pharmacoeconomic analysis, comparative effectiveness research, and data mining using digital health records to demonstrate the superiority of their products. Ms. Luce states that "companies may also need to take on more risk that a treatment may not work by agreeing to outcomes-based pricing approaches".

Source: Excerpts from PharmaVOICE's Crystal Ball Report, page 34, Carolyn Buck Luce and David Ormesher

Biologics Growth and Impact

According to the Green Shield 2010 Drug Trends Study of more than 56 million drug claims from 2005 to 2010, the use and impact of biologic medications on drug plans continues to be significant.

Among its findings:

- The total market share of biologics has grown from 8.3 per cent of drug spending in 2005-06 to 11.3 per cent in 2009-10, an annual growth rate of 12.1 percent;
- The most expensive five percent of drug claimants account for 40 percent of drug plan costs, and almost half of those costs are now derived from biologic drugs; and
- People aged 35 to 44 have the highest annual growth rate in drug costs, due in large to the use of biologic medications.

While biologic drugs have higher success rates than traditional chemical-based medications, their costs far exceed those of older pharmaceuticals. For example, the newly developed vaccine Provenge, used to treat prostate cancer, costs nearly $100,000. To date, many of the newly developed biologic drugs are immunomodulators and anti-neoplastics, used to treat illnesses such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and certain cancers. However, their expansion into other treatment modalities is just a matter of time. According to a Thompson Reuters-Newport study of US drug trends, 6,000 biologic drugs were in clinical trials in 2009. That compares to 1,200 in 2005. The study predicts that by 2014, six of the top 10 drugs on the market will be biologics. Already, the top 12 biologic drugs account for $30 billion in US drug spending, the study says. Source: Benefits Canada

The Next Big Thing in Biotech: Sangamo

Sangamo Biosciences may be on their way to providing a drug that will act as a functional cure for HIV/AIDS. The company is striving to determine a way to replicate a rare/naturally occurring mutation that can make some people impervious to HIV infection. The drug they are developing is called SD-728 and it works by genetically altering T cells in a patient's immune system by removing a protein from the surface of the cell. The protein removed is one that HIV commonly uses as a front door for infection, and by taking it away, the HIV cannot infect the cell. And if the HIV can't infect the cell, it can't replicate or do any damage.

The SD-728 drug is still in phase 1 of clinical trials, so there's a long way to go before a verdict can be reached in terms of the quality and effectiveness of this drug. So far, in the early phases of testing on a handful of patients, SB-728 is safe and well tolerated in the patient population, with only mild, reversible symptoms typical of infusion reactions. The team at Sangamo hopes that the drug will eventually be able to achieve a functional cure for people already infected with HIV, and they will hopefully be able to stop taking their daily medication. However, the answers are a long way off and more research will be needed to discover just how effective SD-728 actually is.

Sources:
Yahoo Finance : Sangamo Investor

Trending Toward Personalized Medicine

David de Graaf, President and CEO of Selventa, a personalized healthcare company that analyzes molecular patient data, says, "We are where mainframe computers were in the 1980s. The new healthcare industry needs to diversify, find smaller, better-defined markets, and lead by innovation. This all starts with a deep understanding of molecular disease in individual patients. I perceive much bigger emphasis on patient data and the need for the identification of individual and combinations of molecular disease drivers in each patient, giving us the ability to manage disease over its lifetime from a molecular perspective. Ultimately, this will lead to therapeutic approaches led by diagnostics, rather than drugs. These therapeutic diagnostics will determine whether or not to treat, which drugs in the formulary can or should be given, and aid in the identification of potential adverse events."

According to Dr. Severin Schwan, CEO of Roche Group, a drug and diagnostic development company, "Demand for innovative medicines and diagnostics will be tested against ongoing pressures on public healthcare budgets. Society's resources will be allocated to those solutions that provide treatment of benefit for the individual patient. To this end, patient stratification before treatment by means of molecular diagnostic technologies will get increasingly important."

Source: Excerpts from the PharmaVOICE Crystal Ball Report, p 22, David De Graaf & p 27, Dr, Severin Schwan.

Unlocking Shareholder Value

Faced with patent expirations, big Pharma sought methods of increasing shareholder value in 2011, including spinning off business units and raising dividends. Pfizer announced the disposition of its $1.9 billion nutritionals unit and $3.6 billion animal health business. It also sold off its Capsugel business for $2.4 billion. Abbott announced that it would split into two companies: A diversified medical products firm under the Abbott name and an as-yet-unnamed drug maker. Also, Abbott decided to split its dividend between the two businesses.

Meanwhile, AstraZeneca and GlaxoSmithKline continued with their multibillion-dollar stock repurchasing plans. Amgen announced a $5 billion buyback plan and Teva Pharmaceutical Industries recently announced a $3 billion plan. Pfizer raised its payout 10% and announced a $10 billion buyback plan while Merck raised its dividend 11%. Share repurchases and dividend increases are expected to continue in 2012. Source: Fierce Pharma

Investing & Deal-Making:

Foundation Funding

Too often not-for-profits are not on the radar screen of entrepreneurs seeking funding for their companies. Specialized foundation funding, however, may be just what those entrepreneurs need, especially in heath care discoveries.

As traditional venture capital investment in biotech firms has flattened (see chart at right) and tightened even more for earlier-stage companies, foundation funding opportunities are believed to be growing, both in number and size.

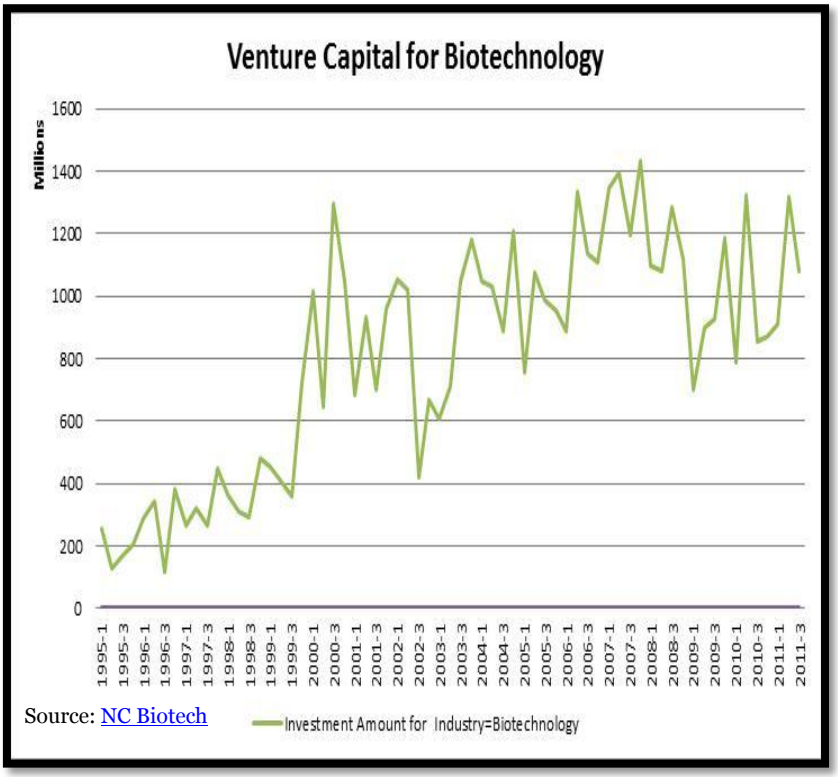
For companies, the benefits of foundation funding go beyond getting the needed cash. The vetting process leading to a foundation grant lends valuable credibility to the technology and the company from the recognized experts.

Foundation funding is typically non-dilutive to a company's shareholders and foundations can bring to companies their expertise in a particular therapeutic area.

Foundations can also help with clinical trial recruitment – one of the biggest hurdles for testing investigational drugs for rare diseases. The Cystic Fibrosis Foundation, for example, maintains a clinical trial network of 80 care centers around the country.

Sources: NC Biotech Entrepreneurship.org

Vintage '07 and '08 Venture funds are raising money, but only those with strong prior exits are attracting Limited Partner attention.



Source: NC Biotech

Biopharma Venture Funds Stepping Up Where VC Firms are Stepping Out

Nearly all major biotech, Pharma, and combination drug-device companies have pursued an alternative to in-house research spending, creating corporate venture funds that invest in early-stage companies whose technologies are believed to hold promise. One attraction that Big Pharma or biotech companies can offer private investors is the access to technologies from their lab, in addition to dollars from a venture fund.

As sizeable as these companies' funds are, they have a long way to go before they fill the gap created by declines in traditional venture capital financing. With traditional VCs' interest in longer-term biotech investments waning, corporate venture funds will more frequently play a tag-team role with traditional VCs in industry financings.

Source: Gene News

Match.com for Entrepreneurs & Investors

AngelList is turning Silicon Valley upside down. The Match.com for startups and business angels, AngelList is helping startups to raise millions from angels on the site almost every day, challenging VCs for deal flow and with valuations. AngelList co-founder Naval Ravikant, a serial entrepreneur and angel investor, and his partner, Babak Nivi, gained a huge following among entrepreneurs with their blog, Venture Hacks, which explains to founders how to "hack" the venture capital fundraising process. AngelList, according to Ravikant, is the continuation of that vision – the "product version" of Venture Hacks.

Screenshots of the AngelList dashboard show early stage funding activity going on in Silicon Valley. Here's the summary:

- Over 200 companies have received funding so far; one or two are raising money almost every day.
- It's not just web and Silicon Valley startups anymore: plenty of sectors and plenty of locations.
- There is a bubble in seed-stage investing, but it's a small bubble.
- AngelList is threatening to VCs who don't have proper differentiation, but it's awesome for entrepreneurs and investors who know how to use it.
- According to Ravikant, *"almost 1,300 investors – about 60% angels and 40% VCs who do seed and series A – are on the list. Dozens of companies apply every day. Usually the top one or two companies every day raise some money from the list. We can't accurately track how much money is raised because we aren't in the financing, we simply introduce them."*

While AngelList represents an excellent, alternate funding source for technology companies, the large amounts of financing and substantial risks inherent in the life sciences sector might curtail the effectiveness of this type of investment resource for companies in our industry. Time will tell…

Source: Business Insider

Crowdfunding for Startups

During 2011 the US House of Representatives signaled that legislators in the US recognize the power of Crowdfunding becoming an equity finance source for technology startups in the US. The Entrepreneur Access to Capital Act requires approval from both the Senate and President before becoming a reality, but if it passes, the Crowdfunding for technology startups could soon be a reality.

Crowdfunding is the collective cooperation, attention and trust by people who network and pool their money and other resources together, via the internet usually, to support efforts initiated by other people and organizations. The emergence of the web as a distribution platform has increased the number of potential donors exponentially which has lead to the expansion and divergence of crowdfunding.

Using crowdfunding as a source of equity finance for businesses could break new grounds because government regulations often restrict the financing options for small, private, for-profit enterprises. Here in the US, the three main obstacles that prevent crowdfunding as a mechanism for equity investment are: a limit of 499 investors before a private company has to disclose ifs finances, an investment is restricted to investors with substantial personal funds, and a concern that removing said restrictions will expose unsuspecting investors to fraud. The Entrepreneur Access to Capital Act wants to enable for-profit companies to raise up to $2 million dollars, provided that the company informs the potential investors of the associated risk of the venture, and only allowing individual investments of $10,000, maximum, per investor.

Crowdfunding has two distinct constituents: investors focused on financial return, and investors looking for social return. Either way, crowdfunding potential promises to be a benefit to start-ups if it passes through Congress.

Source: BioTech Start

The 2011 Dealmakers' Intentions Survey

The third annual Campbell Alliance Dealmakers' Intentions Survey is a forward-looking measure of deal-making activity in the pharmaceutical and biotech industries and offers a prospective view of the partnering and licensing landscape for the year ahead.

This year's survey results represent input from all the major pharmaceutical markets including:

- 61.1% of respondents from the United States
- 17.5% from Europe
- 11.1% from Canada
- 8.7% from Japan
- 1.6% from other regions

The results of the Dealmakers' Intentions Survey are grouped into four categories:

Expectations and Intentions

Overall, active dealmakers anticipate licensing activity will remain steady or grow; respondents suggested modest expectations for increasing phase II deal levels, and the majority expects phase III deal activity to remain the same.

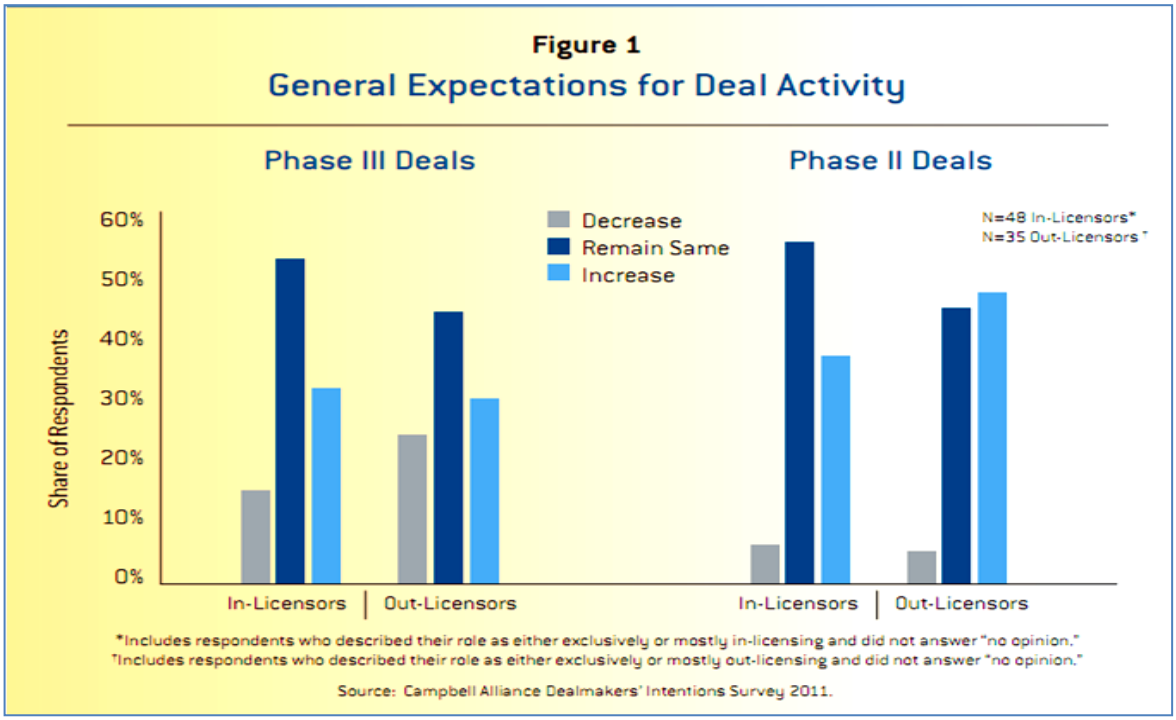
The greatest number of respondents anticipates an increasing level of deal making activity to occur in early-stage products. Half of all respondents expect an increase in deal activity for phase I and preclinical products compared with 44% for phase II and 33% for phase III. According to the survey, phase II pipelines are more robust, and a shift in interest to early-stage products is to be expected. This trend may continue for the next several years as products at all stages progress through the pipeline.

The anticipation of early-stage deal-making shows companies are betting on science when mechanisms are well described. Expect to see more deals at this level as early-stage companies demonstrate the promise of newly-defined mechanisms, newly-established means of interacting with targets, and innovative means of modifying disease.

Valuation

Although some dealmakers anticipate an increasing number of deals, they also recognize several forces driving down valuations. These forces include price, share of patients, discount rates, and the cost of clinical trials.

Overall, expectations are most aggressive for pricing in the US with an average expectation among all respondents of 2% annual price increases. For Europe, the average expectation is for pricing to remain flat, while for Japan, the average expectation is for prices to decline almost 1% annually.



Source: Campbell Alliance

Organization and Process

The survey participants were polled about therapeutic areas in which their organizations were likely to conduct a phase II or phase III deal in the current year. Two countervailing trends seem to emerge: First, with so many forces driving down asset valuations, companies are coping with this trend by turning to market segments that are more resilient in the face of this assault. They are looking for areas where payers are not as powerful to limit pricing and access or where the clinical trial investment has not become so large. At the same time, companies seem to be responding to the high level of competition in the areas that are most obviously resistant to these trends.

Oncology is still the most popular area of focus. Oncology's share of anticipated deals is 20%, but the level of competition in oncology may finally be driving companies to look elsewhere. With oncology as an example that applies across the industry, a steady migration is expected away from the currently most competitive areas along with a renewed willingness to take a risk on new mechanisms.

Areas with notable increases in interest include cardiovascular, metabolics, and dermatology, but this does not foretell a returning trend to primary care conditions. Instead, deals in these therapeutic areas will be centered on the places that resist valuation erosion—areas where there is a well-defined patient group, high levels of unmet need, and prescribing primarily by specialists.

Strategic Implications

Large Pharma in-licensors face an important challenge in focusing only on those areas that are most resistant to the valuation challenges. Namely, those are the exact areas where an ambitious biotech management team can envision pursuing an independent commercialization strategy. By nature, products facing little competition tend to have niche patient populations. These areas typically require limited clinical studies, less nuanced management of the regulatory process, and a small commercial force. As a result, large Pharma has less to bring to the table. Many emerging companies are determining that a large Pharma partner is not necessarily required for success in the US market.

These small companies are choosing to raise the money necessary to retain North American rights and are putting the operations in place to present independent commercialization as a credible alternative to a global partnering deal.

Large Pharma needs to recognize these trends and adjust its priorities:

- It can choose to ride the wave of ex-US licensing and demonstrate to companies with attractive assets that it will partner in a manner that lets those companies achieve their strategic goals.
- It can encourage its partners to recognize the value of global rights and increase the offers they are willing to make for those rights.
- It can step up acquisitions, recognizing the value of de-risked assets where global or North American rights are retained.
- It can recognize the risks associated with these strategies and return to an emphasis on navigating technical risks. They can choose to move into new areas faster or encourage identifying areas where contrarian views on emerging technologies and potential mechanisms are warranted.

Conclusion

How is the Pharma industry going to deal with increased competition in the most promising areas, low expectations for increasing pricing, a lower likelihood of market share, increasing discount rates, and rising costs of clinical trials? There are signs that the industry is returning to its roots in innovation. This starts with embracing the increasingly exquisite molecular understanding of disease and the associated variety of potential targets. It extends to a renewed focus on emerging technological frontiers. All of this is having a profound effect on when, how, and if licensing deals are done. Big Pharma is turning to earlier stage deal making and designing mechanisms to mitigate the risk of participating in such nascent areas.

Meanwhile, emerging companies are seeing an opportunity to retain control over the products they have worked hard to develop, pursuing independent commercialization strategies. Large Pharma is being forced to reassess its approach to acquiring new products, whether that means paying more, taking risks on earlier stage products, or exploring new technologies on its own.

Summarized from the Campbell Alliance 2011 Dealmakers' Intentions Survey prepared by Ben Bonifant and Jeff Stewart. Source: Campbell Alliance

Strategic Deals, Biotech Return to Boost CROs' Business in 2012

CRO performance across late stage, Phase I and central laboratories should improve in 2012 as strategic deals develop and smaller clients return, according to financial services firm RW Baird, which heard from leading contract research organisations (CRO) at its recent conference. Broadly speaking, the outlook is positive.

- **Icon hoping for an improvement in its ancillary offerings.** The central laboratory unit at Icon posted a $5.5m (€4.0m) loss in 2011, but it's predicted that it will make a small profit in the coming fiscal year. Icon has also entered into a preferred provider relationship with Bristol-Myers Squibb (B-MS) which should generate the steady feed of work the CRO management has said the unit needs.
- **Pfizer ramping up.** Improvement at the central laboratory unit and Phase I should coincide with an increase in sales from the Pfizer deal, which gives Icon and Parexel the edge over PPD in the eyes of investors. Draper downgraded PPD in response to shares reaching his target value and other factors.
- **Tox up, tox down.** The toxicology sector, despite encouraging signs, is still recovering. Reports on the health of the sector have varied from quarter-to-quarter but Eric Coldwell, equity analyst at RW Baird, believes this variation can be explained: "Ostensibly conflicting commentary on recent preclinical market trends likely reflects nuances of business mix and study duration among players in this space. Despite recent softness detected by one player, we sense that the broad preclinical market remains relatively stable."

Excerpted from an article by Nick Taylor in Outsourcing-Pharma.com, September 13, 2011
Source: Mobile

Venture Firms Reduce Biotechnology Investment on FDA Risk

Venture capital firms are investing less in experimental drug makers and medical device makers because of what they say are regulatory hurdles, a survey found.

Almost 40 percent of 150 venture capital firms that responded to the survey have decreased their investment in life sciences during the past three years, according to the National Venture Capital Association. The same proportion expects to continue to reduce their spending on these companies over the next three years, a potential $500 million loss, the association said.

It is becoming more difficult to generate venture-type returns because the process is so long and the capital required is so deep. Venture firms have shifted their investments overseas, where regulatory approvals come quicker. More than one-third of survey respondents said they would increase their spending in Europe and 44 percent in Asia, compared with 13 percent saying the same for North America.

The U.S. Food and Drug Administration is taking steps to address some of the industry's concerns; the agency plans to streamline regulations and speed up the approval process for some drugs, among other changes. The agency approved 25 new drugs as of September 15, 2011 and at that pace, by year's end, would clear the most new drugs since 2004.

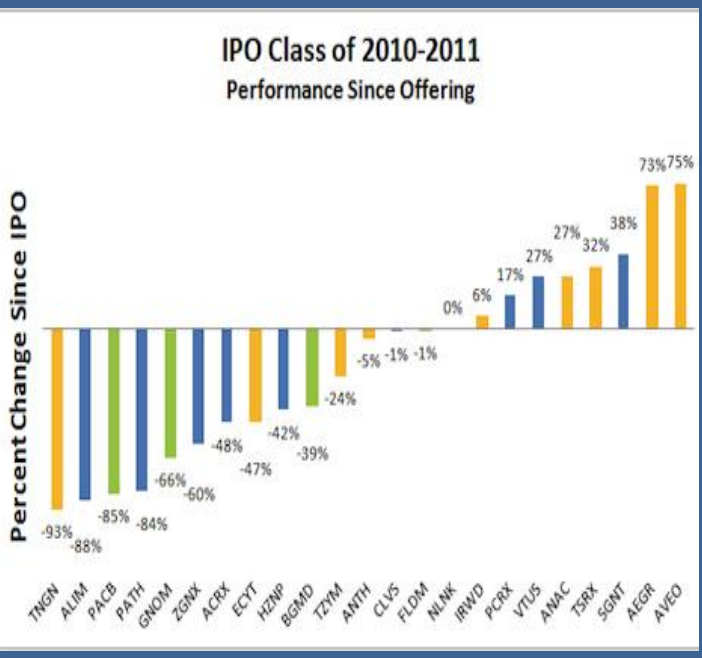
Excerpted from an article by Ryan Flinn on Bloomberg.com, Oct 6, 2011.
Source: Bloomberg News

IPO Update

It has been a very challenging few years for new Biotech IPOs. Although the recent Clovis and NewLink IPOs and rumors of other IPOs planned for early 2012 show signs of life, the current Biotech IPO market is still suspect. The 23 US Biotech IPOs of 2010 are down on average 17% since their offerings, with 14 of them (61%) below their IPO price. Interestingly, this parallels IPOs in the hot social media space.

A few specific observations on the biotech performance:

1. **Although the average is negative, there is a wide dispersion of outcomes.** An additional sign of life is that there have been a few strong performers such as AVEO and Aegerion, each of which remains up about 75% above its offer price. These have been offset by Tengion, Alimera, Pacific Biosciences, and NuPathe all off over 80%.
2. **Companies working on innovative new molecular entities have, in general, outperformed those with late-stage reformulation/low tech strategies.** The colors in the above right chart attempt to characterizing these companies, largely based on their lead programs: **orange means their primary program is a new molecular entity or new active ingredient; blue are Specialty Pharma approaches (reformulations or new uses of known actives or generics); and green are Life Science tools and diagnostics.** In this group of 23 IPOs, those companies working on innovative NMEs have gone up on average 4% vs. significant negative average performance of others. It may be that the markets are rewarding innovation, but it may have more to do with the regulatory and market challenges of some of the Spec Pharma companies in this group.



3. Being highly capitalized over time hasn't correlated with post-IPO performance. The three companies that have raised the most span the spectrum: Pacific Biosciences has raised over $600M and has suffered by >80%, Ironwood is near its IPO price after raising >$500M, and AVEO is up 75% on an invested capital base of >$400M.

4. Even the top returning companies are barely above 2x on their total invested capital. Just over half of the group have valuations below their paid-in capital levels. Adding them all up, this group has a combined APIC of $5.56B relative to a combined market cap of $5.2B. Even AVEO and Aegerion, despite great post-IPO performance, are below 2x in aggregate. The best two companies, Ironwood and Sagent, are just above 2x.

In summary, the IPO Classes of 2010-2011 have seen mediocre to poor performance to date, although a couple of outliers have some promise. When compared to the very attractive performance of M&A deals with returns >4x in 2011 and 2010 (e.g., Amira, Calistoga, CGI Pharma, Arresto, etc...), it is curious why these companies go public at all. Quite possibly IPO was the chosen option for many of these companies because they'd tapped the private markets to the limit and had to move on to new funding sources. Or perhaps it's because none of them could get acquired as private companies. Unlike the "winners" of the IPO vintages of the 1990s, it seems likely that IPOs are selected simply because no buyers stepped up.

Source: Forbes

Regulatory and Government:

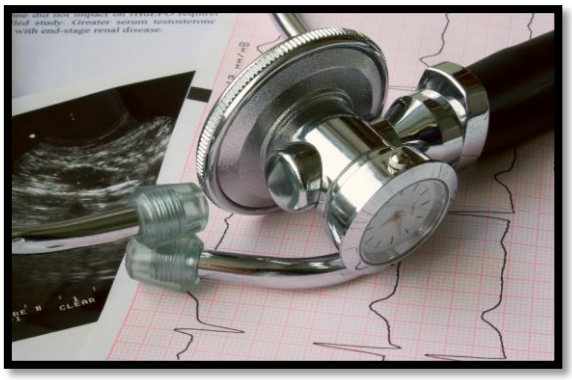
The FDA 510(k) Process at 35 Years

The Federal Food, Drug, and Cosmetic Act requires reasonable assurance of safety and effectiveness before a medical device can be marketed in the US. Traditionally, the FDA has separated the regulatory approval pathway for medical devices from those for pharmaceutical and biological therapeutics, reflecting the logic that complications with a purely mechanical device can be identified fairly easily, and removed if necessary.

Medical devices make substantial contributions to human health. For example, a report in the New England Journal of Medicine says that new drugs and devices approved in the US yielded a 40% reduction in mortality from coronary artery disease – the number one killer in the US. During this era, innovation in medical devices flourished, making the US the undisputed world leader in medical technology.

More recently, the FDA has become inclined to treat devices as if they were pharmaceuticals, while simultaneously expanding regulatory requirements for drugs and biologics. Such actions have had a crippling effect on medical innovation in the US, and have led medical technology companies and entrepreneurs to abandon the US market in favor of a more reasonable regulatory process overseas.

Since the enactment of the *Medical Device Amendments of 1976 (MDA)*, the use of the 510(k) regulatory approval process has historically provided faster reviews and less-stringent clinical-data requirements for devices that are substantially similar to predicate devices previously approved by the FDA.



A 2011 review of the 510(k) process by a committee of the Institute of Medicine (IOM) found the current 510(k) process flawed based on its legislative foundation. Since substantial equivalence of a device, generally, does not require evidence of safety or effectiveness; and when there is a substantially equivalent predicate device, the new device is assumed to be as safe and effective. Devices that were on the market before the MDA were never systematically assessed for safety and effectiveness – but are being used as predicate devices. The IOM found, therefore, that 510(k) clearance is not a determination that the cleared device is safe or effective. While not suggesting that devices cleared through the 510(k) process are unsafe or ineffective, the IOM concluded that the 510(k) process lacks the legal basis to be a reliable premarket screen of the safety and effectiveness of moderate-risk devices.

Sources: Institute of Medicine
Science Translational Medicine

Obama's 2012 NIH Budget Request

US President Barack Obama asked Congress to increase funding for the National Institutes of Health (NIH) by $1 billion in his 2012 budget request—the amount he promised in his State of the Union address. The proposal also calls for a 12% increase for the National Science Foundation and a 9% increase for the US Department of Energy's Office of Science. In the coming months, the House and Senate will draft their own budgets, making adjustments for the President's requests. However, in an effort to reduce overall federal spending, the Republican-led House appears to be poised to reduce scientific research and development funding. The Obama administration remains hopeful that investments in science and innovation will prevail. This 2012 budget debate may be delayed due to a reconciling of the 2011 budget, so the outcome of the NIH budget has yet to be determined.

Source: BioTechniques

FDA Officials, Hoping to Stave off Critics, Point to Increased Drug Approvals

The FDA approved 35 new drugs in the year that ended in September 2011, a number that was surpassed only once in the past decade. Of these 35, 24 of the drugs were approved in the US before they were approved in any other country. The FDA commissioner, Dr. Margaret Hamburg, believes "we approved a set of drugs that are truly medically important, and in fact did so in a way that made these drugs available to Americans before other places around the world." These drug advances include; the first new drug for lupus in the past 50 years, the first new drug for Hodgkin's lymphoma in the past 30 years and the first drugs for late-stage melanoma. Since the biotech and Pharma industries have been struggling in recent years to produce new drugs, this increase in drug approvals is great news. The difference appears to be a lowering in some approval standards, particularly for cancer drugs, and a speeding up of reviews which has helped to get the drugs through.

On the flip side, some of the more complex medical devices are first approved in Europe before they make their way to the US. This change is due to a different set of regulatory standards in Europe and the fact that the medical device industry in the US doesn't pay as much to support the FDA as the drug industry does. Not to mention that several safety scandals have occurred in the past because there was too little testing on devices before they were approved for sale. The friction caused between the device industry and FDA because of these issues will continue as legislation, including industry fees critical to the FDA, passes through Congress.

Source: NY Times

FTC to Super Committee: Ban Pay-for-Delay Deals

In order to bring down the federal deficit, the Federal Trade Commission (FTC) called on the US Congressional super committee to ban 'pay-for-delay' deals between brand-name and generic drug companies. New data released suggests that the practice of brand-name pharmaceutical companies paying generic competitors to hold off their lower-priced generic version does not show signs of slowing down. These collusive deals are costing taxpayers $3.5 billion a year in higher drug prices. The industry is seeing nearly ten times as many pay-for-delay deals than it did in 2005.

Generic prices are typically 20% to 30% cheaper than brand-name drugs, but can be as much as 90% cheaper. The FTC argues that the pay-for-delay deals, that keep these cheaper brands off the market, are anti-competitive, violate antitrust laws, and result in the generic drug hitting the market 17 months later than generic drugs with no such agreement. Brand-name drug companies defend their deals and point out that the FTC and Department of Justice have the authority to review any settlement on a case-by-case basis.

The FTC called on the super committee, tasked with identifying $1.2 trillion to $1.5 trillion in cuts from government spending, to focus on banning the deals to save money.

Source: Med Page Today

FDA Releases REMS Guidance

In November 2011 the FDA released its guidance for industry titled "Medication Guides—Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)."

This guidance was released to address two topics pertaining to Medication Guides for drug and biological products. First, the guidance addresses when FDA intends to exercise enforcement discretion regarding when a Medication Guide must be provided with a drug or biological product that is dispensed 1) in an inpatient setting, 2) in an outpatient setting when the drug or biological agent is dispensed to a health care professional for administration to a patient, or 3) in an outpatient setting when the drug or biological product is dispensed directly to a patient or caregiver. The guidance also discusses the requirements for a Medication Guide as it relates to a Risk Evaluation and Mitigation Strategy.

Link to Guidance:
Drug Safety

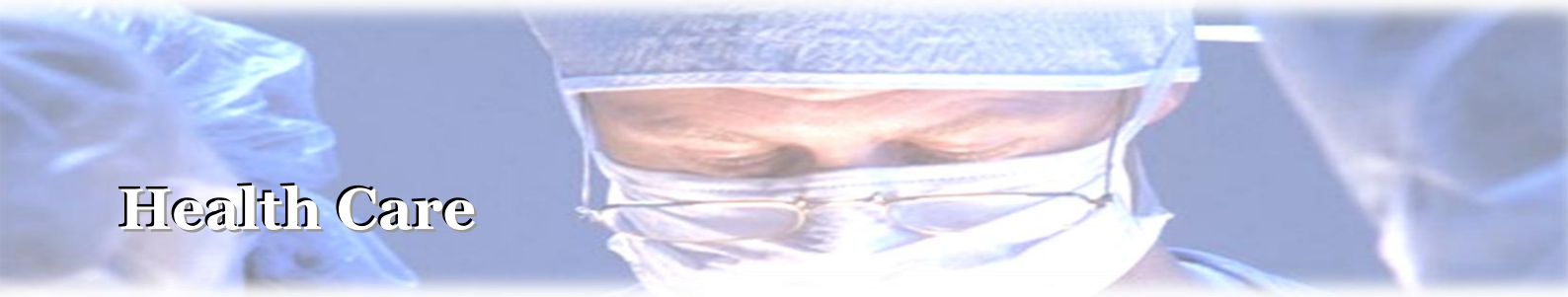
Biosimilars Guidelines Imminent for Congressional Approval in US

The generics industry will likely receive a boost in 2012, as the FDA concluded the public consultation phase of the biosimilars regulatory pathway in early January 2012. Since the basic structure of the biosimilar authorization is expected to gain industry and patients' support, the US Congress is expected to approve the legislative recommendations set for implementation as of October 1, 2012.

The FDA recently published a set of draft recommendations in Biosimilar Biological Product Authorization Performance Goals and Procedures, Fiscal Year 2013-2017. Some of the more pertinent features of this draft are:

- The draft assumes an inflation-adjusted value of $20 million in non-user fee funds and an unspecified quantity of biosimilar user fee collections allocated toward the review process for biosimilar applications during the five year period.
- 70% of reviews of new and resubmitted applications will be carried out within 10 months and 6 months of receipts, respectively, during fiscal years 2013 and 2014. These percentages increase to 80% in FY 2015, 85% in FY 2016, and 90% in FY 2017.
- The FDA has pledged to review and act on 90% of manufacturing supplements within 6 months of receipt.
- The FDA is to provide in-depth notification including target dates for communication feedback on areas such as labeling and post-marketing requirements, and a notification within 74 calendar days from the date of FDA receipt of original submission on issues identified.

Source: IHS



Germany: Agog over AMNOG

In September 2011, the Pharmaceutical Executive Global Digest released a report on the structure of Germany's new pricing system, AMNOG. In this report, industry experts speculate on how the system's ambiguity may bring a halt to new drug launches.

In January of 2011, Germany introduced price controls through AMNOG legislation intending to generate substantial savings in the national healthcare budget. Politically inspired and hastily enacted, AMNOG has created uncertainty for regulators and the industry. Its ambiguous nature severely complicates planning for drug company investments in Germany, and several companies have already announced delays of new drug launches.

What is AMNOG?
AMNOG marks the end of free pricing of new pharmaceuticals in Germany. For any new drug, the pharmaceutical company has to submit a dossier to The Common Health Board (Gemeinsamer Bundesausschuss, G-BA), which conducts a benefit assessment to qualify the additional benefit of the drug over existing therapies. If the G-BA concludes that the drug does not offer additional benefit, the drug is transferred into reference pricing or subjected to reimbursement negotiations; the price for the drug would not be allowed to exceed the cost of comparable drugs. If the G-BA decides the drug offers additional benefit, the manufacturer can sell the product at a freely set price for one year.

Rebates
AMNOG seems to be focused on the negotiation of rebates as a means of net price reduction. There is no indication that AMNOG rebates will be treated differently from existing rebates, but no one seems to be certain of this.

Waivers
Exceptions to the price approval process can be granted to orphan drugs, which will automatically be rated as drugs with additional benefit. Low-volume drugs can also qualify for a waiver.

Reaction to AMNOG
Depending on perspective, opinions vary greatly. Some believe that AMNOG is a learning process and that it is long overdue. Others note that new substances will have a hard time receiving the additional benefit rating, and HIV specialists are worried that AMNOG has blind spots that will leave some people with specific needs out in the cold.

Conclusion
The drug industry is struggling to understand AMNOG's impact on the German market. Most agree that the uncertainty with regard to getting a feasible price in Germany means that the industry will not be able to plan efficiently for a German launch of a new drug.

It will take about five years before AMNOG sees dossier submissions that have taken the new requirements into consideration – and by that time the government may well make changes to those requirements. But today, legislators have reason to be happy – AMNOG generated more than one billion Euros of savings through compulsory rebates in its first four months. These savings occurred before negotiation on prices for new drugs had even started.

Excerpted from Pharmaceutical Executive Global Digest, September 2011. Find Pharma

Health Care Reform and the 2012 Election

The future prospects of the Affordable Care Act hinges on the 2012 US presidential elections—if President Obama wins, the act will continue to move forward. If not, there are some major implications for the future of health reform law. So far, the Republican effort to repeal or defund the Affordable Care Act has been entirely symbolic; without the control of the Senate or the White House, there's not much they can actually do. But with Democrats on the defense and President Obama's poll numbers falling, Republicans are starting to think about repeal strategies. There are several different scenarios that could occur in the 2012 election:

- If President Obama loses, and Republicans take the Senate by a lot, more than likely the health reform law is history. All Republican presidential candidates have committed to signing repeal into law.
- If Obama loses, and Republicans take the Senate by a little, the health reform law will lose large chunks of its legislation. At this point, it would cost money to repeal the bill, so Republicans would have to figure out how to pay for it and edit it to their liking.
- If President Obama wins, but the Republicans take the Senate, the health reform law may be stuck in even more of a stalemate than it already is. President Obama will have a tough time securing the money he needs to make the law work as Republicans will battle him at every opportunity.
- If President Obama wins and Democrats keep the Senate, the health reform bill will remain as is, and continue to move forward, despite constant political bickering.

With all these possibilities, nothing can be for certain except the fact that this election will result in some major changes for the future of healthcare.

Source: Politico

New Data Shows Drug Delivery has Positive Impact on Patient Compliance

With costs around $290 billion a year, patient non-compliance is one of the biggest medical problems facing America today. Non-compliance is the failure to conform to medical recommendations in day-to-day treatments, such as timing, dosage, and frequency. A recent study done by Catalent Pharma Solution reports that drug delivery methods can greatly improve patient medication compliance. Between a standard pill and an orally-disintegrating tablet (ODT), there was a much higher compliance rate for the ODT, around 98.5%, than for the standard oral treatment, which was around 81%. This difference in percentage stems from several factors, one of which is that more than 40% of adults in the US report problems swallowing pills.

According to the Harris Interactive study of 679 adults, age 18 and up, nearly 1 in 5 who have taken oral medication have hesitated because they thought they might have trouble swallowing them due to the pill's size or shape. Once the pill has actually been swallowed, it must disintegrate in the stomach and be absorbed through the small intestine. An ODT on the other hand, disintegrates quickly once in the mouth, causing a quick entry to the bloodstream and no problem with swallowing.

A study done by SDI Health has shown that Zelapar, a Zydis fast-dissolve ODT, resulted in higher patient compliance rates than alternative pills, capsules, and other ODT formulations. Zelapar is faster and safer than other drugs due to transmucosal adsorption—bypassing the stomach and liver—in order to avoid metabolism and improve bioavailability. By applying this Zydis fast-dissolve technology, Zelapar has created a positive market impact and outperformed other branded, generic oral formulations in sale growth rates. Patient medication non-compliance is one of the most expensive, under-addressed problems in healthcare and the pharmaceutical industry is doing what it can to facilitate convenience and ease of dosage. As proved by the case study, Zydis fast-dissolve is patient preferred, easy to swallow, effective and a fantastic treatment option for those who suffer from dysphagia (i.e., difficulty swallowing).
Source: Drug Delivery Tech

Sunshine Act to Discourage Clinical Investigators?

The Patient Protection and Affordable Care Act of 2009 went into effect January 1, 2012, including the Physician Payment Sunshine provisions of this Act requiring drug and medical device manufacturers to publicly report all gifts and payments made to physicians and teaching hospitals. These provisions of the Act required the manufacturers to invest heavily in compliance, as well as perform more arduous evaluations of their industry partners to best ensure compliance.

However, the greatest concern may be that the implementation of these provisions may negatively impact health care in the long run. Physicians and teaching hospitals will realize that every transfer of value to them from the manufacturers will be publicly disclosed, along with the names of the physicians receiving the transfers. There could be a strong disincentive for physicians to take such transfers from industry. Early reports indicate that many teaching hospitals have already announced prohibitions of such transfers in the future.

Judith Beach, Ph.D., Associate General Counsel Regulatory and Government Affairs, Global Chief Privacy Officer, at Quintiles, stated that the original intent of the provisions of the Act was to promote transparency of payments to physicians for the purpose of discouraging conflicts of interest of approved drugs, "but an unintended affect has been that clinical research has been lumped in with all other transfers of value to doctors. We believe these provisions will have a negative effect on physicians' willingness to serve as clinical investigators because the raw data on payments will be release with no explanation and no context. This, in turn, will make it very likely that organizations, patients, regulators and media will draw negative and uninformed conclusions from this raw data."
Source: PharmaVOICE

Comparative Effectiveness Update

Papers in the December 2011 issue of *Health Affairs* examine priorities for the comparative effectiveness research in which the Patient-Centered Outcomes Research Institute (PCORI) will engage. These articles offer recommendations for PCORI's research priorities and outline challenges facing the institute and comparative effectiveness research in general, as follows:

- To have the most influence on real-world health care decision making, Harvard University's Alan Garber recommends that PCORI compare interventions on the bases of their clinical risks and benefits, their economic considerations, and the insights they might offer into medical care.
- AS PCORI begins putting together a research agenda, the National Pharmaceutical Council's Robert Dubois and Jennifer Graff propose an eight-step framework to guide the setting of research priorities. Critical components of their proposal include assessing the public health benefits of various treatments and ensuring transparency throughout the priority-setting process.
- Katherine Cooper Wulff of the Johns Hopkins Bloomberg School of Public Health and colleagues illustrate why it will be an uphill climb to translate the results of comparative effectiveness research into practice, especially if the research raises questions about established procedures.
- "Personalized" cancer treatment – using biomarker tests to identify certain genes, proteins, or other indicators that can enable the use of highly tailored therapies –offers tremendous potential for improved outcomes and lower treatment costs. However, the lack of available evidence to support the effectiveness of these tests and the high costs of needed research will require better data collection and creative funding sources, say Scott Ramsey of the Fred Hutchison Cancer Research Center and colleagues. Source: Health Affairs

It's All About the Data

Thousands of professionals in the life sciences and other industries rely on external chemical data in their decision matrices. Just how reliable is publicly available data? Don Alexander of Carlyle & Conlan interviewed Dr. Antony J. Williams for perspective on this issue.

Antony J. Williams graduated with a Ph.D. in Chemistry as an NMR Spectroscopist before becoming a Cheminformatician and Chief Science Officer for Advanced Chemistry Development, ACD/Labs. He started ChemSpider as a hobby project, with a couple of friends, before it was acquired by the Royal Society of Chemistry where he is currently VP, Strategic Development. Dr. Williams has written chapters for many books and authored more than 140 peer reviewed papers and book chapters on NMR, predictive ADME methods, internet-based tools, crowd sourcing, and database curation. He is an active blogger and participant in the internet chemistry network.

Don: Tony, thanks for your time today. Please tell me about how well the idea of crowd sourcing (i.e. the Wikipedia model) has worked with chemistry databases?

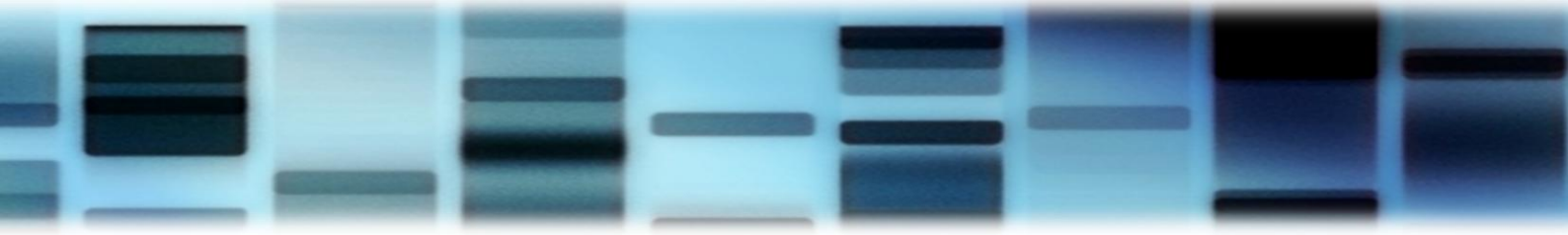
Tony: The world's online encyclopedia, Wikipedia, has a few thousand "chemical records" and, for that platform, crowd sourcing is working very well. Dozens of people have contributed articles and, about three years ago, a group of us dedicated ourselves to validate all chemicals (to the level of each atom and bond) and ensure that every chemical structure representation is correct. This work continues, after the three years of initial investment, to clean up the chemicals and associated data in these records. Just last week, I made an edit to the Wikipedia article on Zantac where the scientist who discovered the compound was incorrectly identified.
Crowd sourcing does not necessarily mean a large number of people. One of the biggest issues in our domain is that a number of databases don't allow for crowd sourcing and even when errors are noticed there is no easy way to flag them, so they persist. At multiple conferences I've asked "Who in the room uses Wikipedia or reads Amazon book reviews?" Almost everyone raises their hand. Then I would ask, "How many of you have ever written an article on Wikipedia or an Amazon book review?" Maybe 1%-2% have ever commented or written on something like Wikipedia. This is neither good nor bad, it just is. It is not only about the technology… we prefer to take rather than to give for a variety of reasons. This is certainly true of the free resources available online.

Don: How pervasive do you feel the faulty data may be?

Tony: It really depends on the databases in question. There are a number of small databases that claim to be manually curated and, based on direct evidence, this is simply not true. An estimate would be 5-25% faulty data for manually curated databases. I have seen far worse though! It wouldn't be surprising to see up to half of the aggregation databases, hosting millions of records, containing erroneous data. This estimate stems from hundreds of thousands of curations and deletions from (their own) systems that were incorrect.

Don: Have you witnessed instances of this same issue with privately held databases?

Tony: Right now, there is an ongoing project called Open PHACTS that is a European Innovative Medicines Initiative (IMI). Open PHACTS is a consortium-based approach to meshing together, in a semantic manner, pathways, proteins, and targets. There are 22 organizations, (including 9 pharmaceutical companies and 3 biotechs) that are part of the project and it will host both public and private data.



Previously, life science organizations were downloading public domain data and processing, cleaning, mapping and linking all of this pre-competitive data themselves and it was extremely wasteful in terms of time, manpower and, of course, money. The various members of the consortium can no longer afford to rehash all the public domain data that continues to grow at a very impressive rate so one of the major outcomes of the project will hopefully be much cleaner data that finds its way back into the public domain and is enhanced in ways that are directly beneficial to the drug discovery process.

Don: What do you suspect is the level of reliance on this faulty data?

Tony: There are qualitative observations and peer reviewed publications where people have downloaded public domain assay data with a series of hits against targets and assays. They repeated all measurements to find many false positives. When they did computational analysis, there were a number of compounds that should have shown responses against the assays but didn't. They measured the data and found responses… these were false negatives. At this point, it is simply a measure of data quality. This has nothing to do with data mapping or incorrect chemicals. The measurements simply didn't measure the response. What does it mean if you measure a chemical in a particular assay twice and it is binary? Such observations are rather common.

Don: Are there any publicly available instances, so far, of significant adverse impact based on faulty data reliance?

Tony: Significant adverse impacts in terms of drugs making it to market are unlikely as, fortunately, we have a lot of checks in place for any compound making it into the clinic. The most derogatory impact to date may be at the level of model quality regarding the computational models that can be derived. However, incorrect data-mappings and re-measurement of data can have significant costs.

Don: Any thoughts as to parallel issues with biological databases?

Tony: There are already existing reports of errors of 5-10% in biochemical databases, sometimes even higher. There are errors in all databases. There are even fraudulent submittals in chemistry into crystallographic databases. Presently, we are analyzing a number of online public domain databases for data accuracy in regards to accurate chemical representations of the world's best-selling drugs (over 150 molecules). Based on our early work, none are perfect, as expected, and some are absolute disasters.

Don: Do you have any general ideas around how to best fix these issues?

Tony: Two approaches that I am encouraging right now are, first, adopting an agreed upon standardization process for chemical compounds across all databases. The result is that the chemicals data will run through a standardization system. It may be open source and, therefore, developed and hosted by multiple parties to get best-in-class pre-competitive sharing of standardization routines. Then, one would implement a set of standard processing filters that are collaboratively agreed on. The FDA already has documented their preferred standards and, so, this can be the initial basis of this work.
The second most important remediation is that all of these databases should have the ability to leave comments and annotations on a per record basis. In the blogosphere we are used to leaving comments. Why not on individual records in a database? The database hosts should allow for commenting and annotation and users of the system should actually be doing it. Anonymity should be an option.

Don: Is anyone actively funding curation of data for these databases?

Tony: In my opinion there is more of a focus on the development of platforms and sites to host data rather than on the data and its quality. There is no lack of new, highly funded, data repositories but how much money is being allocated to the sourcing of high quality data? There is recognition for building a new platform but no one gets celebrated for cleaning up a data point. Hopefully this will change when alternative metrics are available for capturing contributions to online resources.

Don: What is the status on geographical borders with respect to data management?

Tony: Other than some of the more obvious commentaries made about Chinese barriers to freedom of the internet there are few obvious borders with respect to online data for Life Sciences. It is easy to download data from many online resources. The internet is an increasingly open environment but confusion ensues as both data hosts and data-consumers are unsure of the licenses associated with the data. Also, while data is presently shared across boundaries, we haven't witnessed too many efforts, yet, to fund much global collaboration in the life sciences.

For More Information:

All That Glitters is Not Gold: Quality of Public Domain Chemistry Databases

A Quality Alert and Call for Improved Curation of Public Chemistry Databases

Internet-Based Tools for Communication and Collaboration in Chemistry

The Long Term Cost of Inferior Database Quality

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