RECOVERY STRATEGIES

Lessons Learned From Genzyme, Johnson & Johnson & Baxter

Part 1 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
The recession is dead, long live the recovery! But not so fast. Just because your company made it through the recession, doesn’t necessarily mean it will make it through the recovery. Yes, I’m dead serious. It is possible to screw this up.

Your company has just been through a savage economic battle. The pain of it is seared in your memory. But -hurray!- business is coming back. The risk now is that we will let our caution reign us in too much. After what we’ve been through, no one is actually turning away business, are they? But here’s the rub: if we don’t actively feed our companies as they grow - with quality hires and measured facilities growth - we risk major quality issues. In our industry, quality issues are death. At least, they should be.

Quality issues were a near-death experience for Genzyme. How does anyone get up in the morning with a whopping $175 million consent decree for a host of manufacturing shortcomings? The company closed one plant and ended fill/finish operations in another for products sold in the US. Fill/finish activities for Cerezyme® (imiglucerase for injection), Myozyme® (alglucosidase alfa), Fabrazyme® (agalsidase beta), and Thyrogen® (thyrotropin alfa for injection) for the US market now take place at Genzyme’s Waterford, Ireland, plant and at an external contract manufacturer.

On top of the corporate humiliation resulting from these quality issues is the human suffering - some patients were left with little or no supplies in the middle of their treatment. Investors too were angered, including Carl Icahn, who waged a proxy fight and prompted a board probe into insider stock sales.

As a manufacturer myself, for days I cringed to read the latest Genzyme news. I’ll confess I read of the warning letters and consent decrees with a measure of, “What were they thinking?” tempered by a dose of, “My God, could it ever happen to my company?” It’s a blending of two emotions; schadenfruede - that secret, guilty delight we take in other’s misfortunes - and plain old night terrors.

And yet, Genzyme lives on. Gone are the days when a consent decree rules out the possibility of growth or a merger. Genzyme soon found itself having to hold its nose and accept the advances of a suitor offering a price well below what it would’ve been worth without the quality issues. Even with this low bid, the acquisition remained uncertain. The suitor (Sanofi-Aventis) had to be sure it wasn’t paying too much. How do you fashion a merger with a company like Genzyme in which so many costs and risks are unknown?

I will give the dealmakers their due. They crafted a deal of incredible creativity. Sanofi originally offered $69/share - an offer that sounds at first blush very generous given the fact that Genzyme was trading at $56/share before the merger rumors started. But insiders know the company was worth much more. How do you fashion a merger with a company like Genzyme in which so many costs and risks are unknown?

Genzyme CEO Henri Termeer made the mistake of holding out in the hopes of creating a bidding war. Mr. Termeer was apparently a genius when it came to selling orphan drugs for awe-inspiring prices, but somewhat less adapt at selling a company.

But here’s the creative part: the deal requires Sanofi-Aventis to cough up more money depending on various factors, such as fixing manufacturing problems and whether the Campath leukemia med is approved for multiple sclerosis (MS). These are called contingent value rights (CVRs), and payouts could be as much as $4/share per CVR later. Or there could be no payouts. Or there could be payouts but only years down the road.

CVRs are not new to deal-making, only to deals like this. You might see them with a big pharma/small start-up merger, but you don’t see them in the merger of two large companies, like the Prizer-Wyeth deal or the Merck-SGP merger.

The implications of the structure of this deal go way beyond mere financial ingenuity. It means that regulatory actions - right up to the dreaded consent decree that was once considered a fatal blow to any company’s growth or merger prospects - are now merely part of the cost of doing business in our industry. Consent decrees as a cost of doing business. This is stomach-turning. And it gets worse.

“Pharma M&As have officially entered the high-risk world of derivatives trading,” writes Jim Prutow, a partner in the healthcare practice at the PRTM consulting firm.
“CVRAs are basically options in which the investor is betting for or against whether certain milestones will be achieved, eg, FDA approval, etc. These types of trades are not regulated or even posted on any type of public exchange.”

Welcome to our new industry. Quality issues are no longer a kiss of death, they’re just a higher risk level you can price into a deal. Will it be worth it for Sanofi, acquiring a tainted company? In truth, quite possibly yes. For one thing, the structure of the deal makes it so that if the MS drug is approved, it’s a win-win for both companies. More than that, Genzyme provides revenue streams and launches Sanofi into the rare disease business, where competition should be less. And there are fewer and fewer biologically focused biotechs out there, so it’s not like Sanofi had lots to choose from.

Rare disease meds also command a lucrative pricing segment, though that may not be a long-term reliable assumption. As with any high-price segment, other potential competitors will be attracted and attempt to compete on price. There are other risks out there as well, such as the possibility that Sanofi won’t integrate Genzyme well, particularly on the rare drug side, where the physician/patient/drug company dynamic can be quite different from other more mundane pharmaceutical products.

Most any acquisition leads to a shakedown amongst staff - both those who are laid off and those who choose to get out rather than face the coming uncertainty. Loss of key staff taxed with putting Genzyme back on track could further destabilize the situation.

I’m focussing on Genzyme here, but I could just as easily talk about the embarrassment of Baxter Healthcare, where CEO Bob Parkinson recently disclosed that he had received a warning letter from the FDA concerning problems at two plants in Puerto Rico. This comes just three years after the company was front and center in the contaminated Heparin scandal that led to deaths and a whole lot of intense FDA scrutiny.

Or I could have turned the lens to the hundreds of millions of products that have been recalled by the once venerable Johnson & Johnson. There was Tylenol, Rolaid's, Benadryl, contacts lenses, and hip replacement devices. We’ve seen government probes, a factory closing, layoffs, bonus cuts, and then the story became about the company’s bungled attempts to manage the fallout from the their actual bungling.

I’m not going to say that all these industry catastrophes were the result of trying to take on new business in the recovery without the necessary investment in people and facilities. Only that in this environment, with sales coming back while everyone is still battered and shell-shocked and in a cost-cutting state of mind, the risk of more quality failures is high.

We need to quit worrying. The recession is over. Take measured risks to expand to meet demand. We don’t need anymore industry casualties. It should be us doing the hiring, not the FDA. We have a perfectly good recovery brewing, let’s not blow it.
RECOVERY STRATEGIES

Drug Pricing 101

Part 2 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
The biggest threat to our industry’s recovery may not be an economic double dip. It may, in fact, be my neighbor’s opinion on the cost of drug development. My neighbor will tell you, if you’ll just listen, that the rich drug companies gouge the common folk for ridiculous profits. He will complain about his diabetes treatment, which costs over $250/month, or his mother’s cancer treatment, which costs $17,000 for a 12-week course.

It’s hard not to sympathize, frankly. The nosebleed cost of those treatments is a cold hard fact. Congress and the President are listening. The drug industry’s defense of these costs, by comparison, is supported by wildly divergent estimates of the average cost of drug development, all of which rest on uncharacteristically questionable scientific methodology. If you’re looking for high-quality rigorous methodology, shouldn’t our industry represent the pinnacle of achievement? Yet on this crucial issue, even when the financial lifeblood of the industry is threatened, we can’t seem to come up with a handful of facts that stand up to examination.

The most-sited defense of high drug costs is the Tufts Center for the Study of Drug Development’s study from 2003 estimating costs upward of $800 million to bring a new drug to market, based on a sample of 68 drugs from 10 pharmaceutical companies. While the best known of the cost estimate studies, by no means does it define the high end. Figures from PhRMA in 2006 calculate the cost of each new drug at a whopping $1.32 billion.

For even higher numbers, you can choose the Pfizer evidence. Pfizer claims to have spent $8 to $9 billion a year on R&D for each of the past 3 years. If you go to the FDA website and look up drugs@fda.gov, you’ll see that Pfizer has shown being one-time drug approval per year. That’s $8 to $9 billion per drug. Looking back throughout the past decade, Pfizer spent $60 billion to get 12 drugs approved, averaging $5 billion per drug. Heady numbers, but hardly a representative sample of all the drugs out there.

On the other end of the spectrum, we have a new study that came out in March that pegs the “true” cost of developing a new drug at $55 to $59 million. The study, published in Biosciences by sociologist Donald Light of the University of New Jersey and economist Rebecca Warburton of the University of Victoria, attacks the Tufts study on almost every assumption.

Some parts of the Light and Warburton study are simply absurd. For example, they don’t accept the cost of a drug includes the cost of capital. How it is that in every other industry the cost of capital is part of how costs are calculated, but in our industry it’s somehow misleading, is beyond my understanding. The cost of capital needs to be included because when you commit to locking your capital up in the development of a drug, you’re giving up what you could have earned by putting it to some other use. Giving up the profits you would’ve made somewhere else is a cost.

The Tufts study, however, errs just as egregiously in the opposite direction. It inflates the cost of capital by assuming you would’ve earned 11% returns if your money was elsewhere. They must have a better financial advisor than I do.

But I have other problems with the Light and Warburton study as well. Their calculation of how much time it takes to conduct clinical trials and have them reviewed by the FDA is only 4 years. That would be amazing if it were true, but I would be greatly surprised if studies bore that out. Granted, it’s possible that the average length of time has been somewhat reduced because of an industry-wide shift toward therapeutic areas like anti-cancer drugs. Anti-cancer drugs require shorter times because of the nature of the disease - they need only demonstrate the ability to extend time to live by a matter of months. Clinical trials for a drug like Alzheimers could, by contrast, span years, much as the condition itself can.

But 4 years? Any drug that can get from trial to approval in 4 years is, in my experience, a wonderful anomaly. Phase III itself generally takes 3 years. My company enters the picture right before in-human testing, and I rarely see a drug that isn’t already a few years into development.

But I’m presenting you with personal experience, not scientific fact. How can we possibly come up with a true average development time? Maybe it’s impossible. I mean, what is an average development time? Do we measure every drug that has

**SIDEBAR**

**Industry Update:**

**The Python is Hungry**

While we have by no means returned to the heady demand of 2007 and 2008, the Society of Toxicologists (SOT) reported in their late February meeting that both demand and pricing were stable and improving after bottoming last year, and that there is a mood of cautious optimism. Unit demand is stable to improving and cancellations in recent months are down. Demand is strongest from midsize clients, though they do report optimism that improved capital flows to small biotech companies could help drive growth later this year. Major labs don’t reveal their utilization levels, but the SOT estimates toxicology CROs are operating at 60% of capacity compared to an ideal of 85%, but significantly better than the 50% of 2009. As capacity approaches 70%, the SOT expects wait times to increase and pricing to improve. The SOT issued a statement predicting that 2012 would bring a moderate recovery in IND-enabling study activity. The industry is showing “demonstrable improvement” in sentiment, as a result of improving RFP activity and conversion to sales.

The demand scenario these past few years represents a classic “pig in the python” scenario. The urgency of the recession led pharma companies to de-empasize early drug development, and shift funds to late-stage development, trying to get products to market faster to increase revenue in the shorter term. Early-stage development experienced a sharp decline in work, and late-stage development felt a boom. A colleague of someone we just hired jumped ship a couple of years ago and moved downstream to where the pig was. Now the boom is abating, and he’s looking at a drier pipeline at his new company. Time to move back upstream? Hopefully soon things will normalize throughout the pipeline. But after the past 2 years, it’s nice to feel the python is hungry again.
ever been developed? Do we measure just the recent ones? Even if we constrict ourselves to the recent only, it’s complicated. Thalidomide was first developed in the 60s and is now being used as an anti-cancer drug. Any average that pulls in Thalidomide or a similar compound is going to be skewed. An Alzheimer’s drug would do the same simply because the nature of the illness is long-lasting. Yet this question of average time is absolutely central to calculating cost because every additional year of study adds tremendously to the total cost.

This is just the beginning of the problems with the Light and Warburton study. I was surprised to see Light himself in his article “The Make-Believe Billion” published in Slate saying that the “estimate of pharmaceutical R&D costs consists of the unknown and highly variable costs of R (research) plus the net, median cost of a drug (development) of $59 million.” He has completely discounted the cost of discovery.

Even if we overlook this magically appearing molecular phenomenon, the math still doesn’t work. If discovery to approval costs $55 to $59 million, how do we account for the fact that Pharma companies typically pay $100 million for a Phase I and $500 million for a Phase II drug from a biotech company, with Phase III trials and all their inherent risks still looming ahead? The market has already determined what the expected cost of drug at each stage of development should be.

Here’s another way of looking at the Light and Warburton study against the cold hard light of day. If it really did cost only about $50 million to develop a drug, then pharmaceuticals would be the all-time best investment out there over any period of time. Think about it. Just $50 million to develop a product with sales between $20 million and $1 billion per year and a 10% cost of goods? Count me in!

I’m not going to defend the Tufts averages - or the Pfizer ones for that matter - don’t mesh with what I see coming through my plant either. If an average drug cost $1.3 billion for our sponsors to develop, I think few of them would ever get out of our sponsors’ labs. Just to recoup those kinds of costs, much less to make a profit, every single drug would have to have blockbuster status with deep market penetration and high costs per unit. One-third of my business is large Pharma, and I see those largely pursuing niche markets in which the costs have to be lower to pay off.

There are other ways of calculating average costs. Using PhRMA numbers, some people calculate how much money the Pharma and biotech industries claim to have spent on R&D throughout the past 10 years, and divide by the number of drugs approved. The results come to about $1.2 billion/drug, in line with the Tufts number. This method, however, also relies on accepting whatever the drug companies choose to label as R&D. In those instances in which it has been possible to examine the raw data, the results have included things that might be interpreted as marketing, such as conferences on a single drug where all attendees are doctors who have come at the manufacturer’s request with all expenses paid.

The true cost of development is probably somewhere in between. If you want a model you can believe in, go to Life Sci VC and search Bruce Booth’s “Choose Your Own Drug Model”. Here you can input your own assumptions, such as length of time per phase, size of market indications, cost per phase, choose whether or not to include the cost of failed molecules, and so forth, and come to your own average cost. Unfortunately, while you may arrive at a number you can believe in, it may not be a number that others will accept. Hence, our problem.

None of these methodologies stands up to the cold hard facts and personal tragedy of my neighbor’s drug cost woes. None will keep Congress from reviewing our sponsors’ labs. Just to recoup those kinds of costs, much less to make a profit, every single drug would have to have blockbuster status with deep market penetration and high costs per unit. One-third of my business is large Pharma, and I see those largely pursuing niche markets in which the costs have to be lower to pay off.

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None of these methodologies stands up to the cold hard facts and personal tragedy of my neighbor’s drug cost woes. None will keep Congress from reviewing our sponsors’ labs. Just to recoup those kinds of costs, much less to make a profit, every single drug would have to have blockbuster status with deep market penetration and high costs per unit. Until we can come up with a sound scientific argument to justify drug prices, our industry will remain under attack.
RECOVERY STRATEGIES

When Deals Work - & When They Don’t: Large Pharma Strategies for Off-Loading Shuttered Capacity

Part 3 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
As large pharma struggles with overcapacity, CROs are increasingly becoming part of the answer. But bagging large pharma as a partner can be as risky as it can be rewarding.

Sanofi’s strategic deal with Covance was a creative way of handing off excess capacity. Sanofi gives Covance between $1.2 and $2.2 billion in work, in exchange for which Covance buys two facilities in France and the UK for $25 million. Smooth.

When they work, these deals are a boon to contract research organizations (CROs). But CROs beware. Even the largest CROs are only worth $1.5 billion, compared to large pharma’s $100 to $150 billion. Large pharma has less incentive to move, and fulfillment of these strategic deals is more important to the CRO than to the pharma company. Such promises may be trivial to the mother ship, but can sink a smaller boat.

Parexel recently got tossed around in big pharma’s wake. This company experienced a huge run-up in hiring and expansion costs in anticipation of future large pharma deals - a 0.09 cent per share increase in overhead. Maybe they should never have run up those costs without booking the revenue. When the deals were delayed, Parexel was left with nothing but a handful of bills to show investors. The delays startled investors in May reports, and the stock suffered a precipitous 20% plunge the next day.

CROs chasing these big deals need to be sure to have cancellation fees if large pharma doesn’t meet its obligations. No matter how friendly things are when the deal is cut, situations evolve. What’s a large pharma to do if some juicy biotech happens by later offering cheaper late-stage assets that offer the potential to bypass the CRO completely? Even cancellation fees don’t cover risk of delays, and a CRO can find itself sitting nervously with increasing costs and an empty plant.

Things look exceptionally bright for CROs right now with an industry book-to-bill ratio that’s up well over 1.10. That means CROs are signing a lot of contracts. But declared cancellation rates are rising too, and it’s safe to assume there are even more cancellations that never actually get declared, because it’s easier to just push them indefinitely into the future to avoid having to declare a material event to shareholders.

When companies fail to find the right strategic deal, the consequences can be dire. AstraZeneca made headlines when, after announcing a 3-year plan cutting 10,400 jobs, they also reported they would be demolishing a 2.2 million-square-foot facility in Wilmington, NC.

It’s bad enough they had to let go of those jobs, but why, bloggers and columnists throughout the industry demanded, would they then proceed to raz the building to the ground? Surely this was unnecessarily dramatic? Obviously a built out facility has more commercial value than a lot of grass and butterflies.

Actually, in the world of financial accounting, such a thing is not obvious at all. As we work through this tepid recovery, difficult (sometimes unpopular) decisions have to be made along the way. The reasoning behind these decisions is often not transparent. AstraZeneca’s decision may be a perfect example.

There are a number of reasons why an empty lot can be worth more than a built-out one. Consider depreciation, for one. Generally, when large pharma renovates a lab, the concerned division sets up a very very long depreciation schedule on the investment. The longer the schedule, the more they can boost short-term profits. But such a schedule has a nasty side-effect of attracting higher state property taxes. There is only one way to get that tax removed, and that is to physically demolish the building. Perverse, but true.

That’s only the first point. Consider insurance. Insurance runs almost 50% higher on an unoccupied building. This makes sense - with no one around to spot leaks and fire hazards and monitor security systems, more stuff happens. Insurance companies know this.

The real estate market itself is a factor. I know of at least six pharma or small contract development and manufacturing organizations (CDMOs) that have been on the market for more than 3 years. And those are smaller, more adaptable facilities. AstraZeneca had a purpose-specific 2.2 million-square-foot 30-year-old facility connected with walkways. Even Home Depot couldn’t be expected to make something of that.

As for repurposing, well, there are just too many empty pharma plants in the US to make them all bio-incubators.

Adding to this problem is the perception that a bio-incubator has to look state-of-the-art, and therefore must have been built within the past 8 years. I can’t say I completely agree with this - on a recent milk run through the Cambridge area last week, I saw several bio-incubators, and the one that stands out in my mind is a well-funded virtual company housed in
an aging building beside the Boston Medical Center. It really looked to me like the investor’s money was going to clinical trials, not glass and chrome. But perception plays a large role in investing, and most investors are looking for state-of-the-art facilities.

There are also the less-tangible factors implicit whenever a large company is managing a facility - empty or not. Internal costs are generally higher in a large company. Let me give you an example. In 2001, I worked for a large company that charged $300 per month for every internet connection. How did the manager in charge of the unit react to this cost? He reduced the number of people with access to the internet. Yes, really.

Then there is the simple fact that no one in a large company makes a career for themselves by selling or repurposing an empty facility. It’s more glamorous and more visible to be working to develop new business or products than to deal with the waste products of previous businesses.

By far, the better solution in AstraZeneca’s case would’ve been a creative deal to offload their excess capacity, but in this case, it wasn’t to be.

It’s a risky business, but the trend toward more strategic partnerships between CROs and large pharma is growing, and I fully expect it will continue to grow. I suspect part of the reason is that many CROs fear if they don’t make such partnerships, someone else will, and they’ll be left out in the cold.

The good news is that these partnerships are driving business toward outsourcing. The bad news is the deals of large volumes of business in exchange for lower prices and margin. For those companies willing and able to engineer their processes to produce high volume and lower prices per unit, it’s all good. Still, others will find opportunity in specialty projects or solutions-driven work. Only those incapable of carving out either niche is the outlook glum. One thing is for sure: the CRO landscape is about to get a lot more interesting as firms differentiate on what it means to serve different client segments well.

For large pharma, working strategically with a single CRO has numerous advantages. You can bring them into the process earlier, ensure a smoother transition, achieve the efficiencies that come with working with the same partner repeatedly, and lower costs by negotiating volume deals.

Over the long run, these alliances will change the CRO landscape, but they will also drive innovation. Trials are becoming bigger, more complex, and more global. Global CRO players have a better shot at long-term growth and profitability, particularly as production levels normalize.

As economic conditions improve and drug makers begin to untie pipelines - and the CRO book-bill ratios of at least 1.0 during the fourth quarter show that this is happening - we can expect this trend of drug makers outsourcing more and more of their R&D budgets to CROs to continue.

Tough decisions are being made by large pharma in this economic environment, and agile dealmakers in the CRO world stand to benefit. But as always in a relationship in which both partners don’t come into it on an equal footing - consider a good pre-nup.

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**BIOGRAPHY**

Derek G. Hennecke
President & CEO
Xcelience

Derek G. Hennecke is a founding member, CEO and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner. Having launched a management buy-out from MSD Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted 2008 Ernst & Young Florida Entrepreneur of the Year award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and perpetual growth. Mr. Hennecke was also recognized as a finalist for the Ultimate CEO awards by the Tampa Business Journal and Small Business of the Year by the Greater Tampa Bay Chamber of Commerce, in 2008. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250 staff Biologics plant for more than two years. In Cairo, Egypt, as GM, he oversaw a radical turn around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.
Recovery Strategies

The New Phase I Entrepreneur

Part 4 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
It's not just the recession. The structure of the drug development pipeline is changing. We have been used to a certain rate of flow through preclinical, Phase I, II, and III. The recession pushed investment into Phase III, and investment in Phases I and II slowed to a trickle. Today, the flow is normalizing, but not yet back to normal. Phase I remains anemic. So what's going on?

For a clue on early clinical research, we need only look as far as Parexel, one of the largest CROs in the country. Even with investment clearly returning to the early stages of drug development, Parexel is shutting down 30% of its Phase I capacity, letting 300 people or about 3% of its workforce go. Parexel wouldn't close down this portion of its business if demand was robust.

This is just one case, and it could be unique to Parexel. It could be a strategic decision, or it could be linked to its recent strategic deal with Pfizer. Indeed the CRO acknowledged the delay in the start of some Phase I investment, which seems to support the idea that the recovery is still tepid. But what I find interesting is that the company defended its decision by saying that there has been a shift among drug makers toward using existing patients rather than healthy volunteers, eliminating a large portion of their business if demand was robust.

More and more drug makers are choosing to conduct Phase I studies in affected populations, as opposed to the traditional path of healthy normals. Obviously, Parexel’s CEO is not arguing that drug makers are skipping Phase I, what he’s saying is that the target population for Phase I tests has significantly shifted. Phase I is still being done, but maybe there are fewer tests being carried out in this phase. So, maybe product development strategy has shifted. Until a few years ago, company spend on Phase I studies was increasing; companies approached each Phase I compound as if that compound would succeed, and therefore conducted every possible test.

Now, companies are delaying studies where possible, choosing instead to conduct the bare minimum Phase I studies in accordance with agency guidelines and move more quickly into Phase II. Phase II spend is increasing its slice of the drug development pie, at the expense of Phase I.

So Phase II must be the place to be, right? Not if you're looking for success, anyway. A recent study showed that achieving success in mid-stage development is getting harder than ever. The Centre for Medicines Research analyzed the results of 16 companies with 60% of the global drug R&D budget and found that the success rate of Phase II compounds plummeted from 28% in 2006-2007 to a mere 18% in 2008-2009. To some extent, we shouldn't be surprised. It makes sense that as time goes on, it will get harder and harder to find new drugs. We've been discovering drugs for the past century. The easy ones have all been discovered. Now, to get a new drug developed, it has to be either completely original or better than anything already out there. It's like we've been farming in the valley for decades, and we're now planting on the mountainside. The investment is higher, and in many cases, the number of successes per attempt are lower. To keep producing at the same rate, we're going to need a lot more investment. But the opposite is happening - companies are reducing R&D to increase returns for shareholders. So success rates are falling.

Taking a closer look at the failures of the past couple of years bears this out. Thomas Reuters Life Science Consulting analyzed the 108 reported Phase II failures from 2008-2010 for new drugs and major new indications of existing drugs (Drug News Perspect. 22, 39-51; 2009; Drug News Perspect. 23, 48-63; 2010; Drugs Today, 47, 27-51; 2012).

Of the 108 Phase II failures, just over half failed outright because of insufficient efficacy, meaning that for purely scientific reasons, they were no better than what was already out there. Analyzing the failures by therapeutic indication, we find that 68% fell into four high-risk disease areas: alimentary/metabolism, cancer, cardiovascular, and neuroscience, according to Thomas Reuters Life Science data. Yet, despite therapeutic area risk, I have to wonder to what extent these fatal weaknesses could have been identified with additional predictive Phase I testing. Early identification avoids a whole lot of unnecessary and expensive Phase II testing.

The next biggest chunk at 29% failed for strategic reasons. They pass the scientific test, but just don't cut it for business reasons. Maybe the product is a little bit better than what's already out there, but not enough better to justify the cost of development; or it's in an area that's no longer a strategic market for the
The fact is that adding Phase I testing that could predict Phase II failure adds costs to Phase I, and slows down progress, increasing the possibility that a competitor will reach the market first. In this economy, companies focus on near-term success just to live another day, and we don’t have the luxury of taking the long view. And so the market shifted toward delayed Phase I testing.

Already though, the market is adapting, as our free market system is supposed to do. Though Phase I remains underinvested, there is opportunity here. Right now, no one is in Phase I. When all the molecules have moved through the system, big pharma will be shopping for more early stage drugs. The few players that have established themselves here will be like the first lasses on the dock when the sailors return from their years on the recessionary seas.

"What I foresee is not just the re-emergence of mini-biotechs in Phase I, it’s a new type of entrepreneurs – scientifically trained entrepreneurs with a business model that is perfectly suited to the new pipeline and takes advantage of the new lower entry barriers to Phase I trials.

It starts with one biologist and one chemist. Quite often, these will be senior executives made redundant by big Pharma. One plays the role of CEO, and they bootstrap together some capital to take one or preferably two compounds (one lead, one back-up) through the newly simplified Phase I process. The compounds themselves may even be sourced from their former company - many companies would be happy to offload a few compounds for, say, a small cut of profits if it succeeds. They martial the compound(s) through Phase I, where risks have effectively been reduced, then sell it before Phase II, passing it like a hot potato into a phase where odds are it will fail.

Typically, these entrepreneurs would target a small niche (no blockbusters here) and form an LLC structured around a single compound or two. Usually a company like this would involve an investment of about $2 million; more than is considered seed capital, but less than a Series A financing structure, which is the first major round of financing.

The key is to get the compounds for as little investment as possible. That way, the venture capital companies can focus on driving the value of the asset, not the company. A few of these companies will later become Fully-Integrated Pharmaceutical Companies (FIPCos), but not many because of high failure rates.

The business case presented to venture capitalists is a strong one. There is little or no money required for equipment, management teams facilities, and stationary - all the accoutrements that come with a new biotech. The business case can be based almost exclusively on the risk-benefit analysis of the compound itself, and only through Phase I.

This new model is all about the compound, and the early scientific and commercial decision-making process that supports it. Not a penny or a moment is wasted on filling out work orders, supply requisitions, performance reviews, marketing meetings, or corporate strategizing. For scientists themselves, it’s a great opportunity to do what they love to do, working in small elite teams of people they like and respect.

For the industry, there is the potential to rejuvenate the very seeds of scientific discovery, providing a new and vibrant source of Phase I drug development to fuel the pipeline, and increase the rate of success in Phase II and beyond.◆

**BIOGRAPHY**

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Beyond the Headlines: AstraZeneca, Pfizer, Asia & Strategic Alliances

Part 5 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
Most people see and react to the headlines. Others probe further, searching for deeper understanding before forming opinions. Below are four industry headlines you’ve probably already seen. A glance beyond the headlines may reveal a different take on the same old story.

**FAT MARGINS FOR A NEW BLOOD THINNER?**

Astrazeneca's new blood thinner Brilinta will cost about 19% more than the current price of Plavix, the leading blood thinner. It's a pricing decision many believe is outrageous given that Plavix will face generic competition in May, effectively reducing the average price of a generic blood thinner to pennies a pill.

Adding to this seemingly inflated pricing strategy is the fact that Brilinta will enter the market handicapped by a black box warning that may give physicians pause. The warning requires doctors use only low-dose aspirin with Brilinta. This could be a problem given that most American doctors prefer high-dose aspirin, and other blood thinners carry no such caveat.

So why the the fat margins for the new blood thinner? Is AstraZeneca really just throwing a price at the wall and hoping it will stick? Are they afraid that because they might sell less, they will have to increase their pricing to make up the difference?

**Beyond the Headline**

Companies don't make pricing decisions that way. It's Business 101: raising prices in the face of lack of demand gives you even fewer customers. You can bet AstraZeneca has a different angle.

Ideally, AstraZeneca would like to tackle the blood thinner market head on without the black box warning, but you go to war with the armor you have on. Instead, AstraZeneca is going after a lower volume, higher-priced niche market.

They're banking on the possibility that Plavix may be contraindicated for some patients. Several studies have shown that the use of Proton Pump Inhibitors (PPIs) for acid reflux, such as Prilosec and Nexium, actually reduce the effectiveness of clopidogrel, the active ingredient in Plavix, and increase the chance of cardiovascular events.

The data has yet to be proven clinically significant, but the FDA released an early communication about the ongoing safety review of clopidogrel in January 2009. AstraZeneca is looking seriously at potential overlap of these and other drugs to determine the actual market for Brilinta, and price it accordingly.

**INSIDE PFIZER: THE DECLINE & FALL OF JEFF KINDLER**

Pfizer's ex-CEO Jeff Kindler made blistering headlines as the Captain who steered the Wall Street icon into the iceberg. His departure capped a decade of declines that saw Pfizer's share price collapse from $49 to $17, and the company's drug pipeline went down with the ship.

**Beyond the Headline**

August's Fortune magazine features a provocative and gossipy story called What Happened at Pfizer, which goes inside the corporate boardrooms under his leadership. Not all is bad; positive lessons abound in this story, including how to build a good team, delegate, work hard without micromanaging, and his experience that trial prosecutors can be good compliance officers but are not necessarily CEO material.

The article also delves deeply into the less-fortunate legacy of what a leader should not do, accusing him of an indecisive approach that created an atmosphere of confusion and chaos:

*After more than a year of on-and-off debate, Kindler just couldn't make up his mind. 'Jeff was really afraid of making a mistake,' says one person who worked on the deal (buying Wyeth). 'Everything had to be analyzed and re-analyzed. You'd close a meeting and he'd say, 'Okay, here's what we're going to do.' You'd sharpen your swords. And the next morning, it'd be off.'*

In another example, he split the research operation in two - setting up a separate unit for biologic drugs and launching a new facility in San Francisco - only to reverse the decision 30 months later after taking on Wyeth's big biotech operation.

What I learned from Pfizer: plan, load your gun, and don't forget to fire. Once your shot is discharged, you're done. Above all, don't say anything you wouldn't want to see on the cover of Fortune magazine. Even a boardroom with the door closed and only one person in it is not a private place.

**GO EAST YOUNG MAN /WOMAN**

The drive to outsource development and production to Asia has been a headline for the past decade.
Beyond the Headline

According to Mangesh Sai at PharmExecBlog, a routine inspection carried out by the FDA in the state of Maharashtra, India, noted an increase in the number of sub-standard drug samples. Officials found 26 samples that were not what they purported to be. This followed a finding of 16 sub-standard quality samples in May and 20 in April. According to the report, some ampicillin and amoxycillin formulations contained no active ingredients whatsoever. Others contained between 6% and 30%. Thiamine tablets with vitamin B1 and diclofenac sodium, paracetamol, and magnesium trisilicate tablets were also found to be below standard.

BIG PHARMA BUOYS BELEAGUERED CROS

Eli Lilly set off a wave of 3- to 5-year strategic partnerships when it linked with Covance in 2008 in the depths of the recession. Such deals were touted as salvation for CROs providing a much-needed revenue stream in the face of economic adversity.

Beyond the Headline

2011 marks the beginning of a first wave of strategic partnership contract renewals. The result is that some CROs who have spent much of the past 3 years revamping their business around the demands of a major partner and are just starting to see the first projects come down the pipeline, must now realize that these contracts will be re-negotiated.

“We expect pharma to turn the pricing screws another revolution, either explicitly or implicitly via higher resource utilization targets or additional investments,” David Windley, Equity Analyst at Jefferies & Company told Nick Taylor of Outsourcing-Pharm.com. Given that this renewal period overlaps with the patent cliff, Windley says CROs can expect pharma to “extract a fresh pound of flesh” from CROs in the renewal process.

Windley argues that a standard 3-year strategic deal is “borderline unreasonable.” He argues that getting the deals up and running is in some cases challenging and costly and raises the question of their ultimate value. He recommends CROs push for longer contracts to be sure they receive some payback from their up-front commitment.

For most companies, Windley predicts the renewals will come, albeit at a cost, if only because there are enough joint projects in the works that it would be costly to start over.

In cases of outright incompetence or unsatisfactory performance, the alliances will end, and that in turn will present opportunities for other CROs. Should the CROs be lining up? Not necessarily. Windley argues that for those who believe the good old days are on their way back, CROs should take them. Too many CROs have reported that the trials of these deals outweigh the triumphs.

PAREXEL might be one such CRO. PAREXEL shares suffered after Icon reduced it’s 2011 financial guidance citing weighty up-front investments to support a deal with Pfizer. Pfizer has a deal with PAREXEL as well, and some analysts claim to be growing increasingly uncomfortable with the level of risk involved.

It’s easy to jump to a conclusion with only a cursory look at the headlines. The information we need to make informed decisions is rarely found in the initial reporting of events. The Roman Emperor Marcus Aurelius advised his subjects: “To read with diligence; not to rest satisfied with a light and superficial knowledge, nor quickly to assent to things commonly spoken of.” Then again, if you’ve read this far, you already knew that!

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Recovery Strategies
Karma in Clinical Trials: India Versus America

Part 6 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC
In 2006, 2.5 million people participated in clinical trials across the US. The last reported death I can find was in 2008. The odds of dying as a result of a clinical trial then are abysmally small; less than 1 in 2.5 million, assuming the average trial of 1 year (Phase Is are shorter; Phase IIIs are longer).

By comparison, the odds of dying in a plane crash in a given year are 1 in 400,000. The 1-year odds of dying while walking across the street are 1 in 48,500. The odds of dying in a car crash are 1 in 6,500 (Don't Be Terrorized. reason.com; August 2006).

Volunteering for a clinical trial is therefore considerably safer than the trip to and from the lab, whether you fly, drive, or walk.

So why aren't people signing up to participate? A recent study in Annals of Surgery (September 2011;254(3):438-443), for example, said only 6 in every 1,000 patients who had cancer surgery in a California registry of cancer patients participated in a clinical trial. This is significant—cancer drugs account for 40% of all INDs.

Are American patients unwilling to take part? Or is it just easier and cheaper for companies to launch studies abroad? These are two of the reasons clinical trials have been moving to places like India, where the government facilitates clinical research with little or no oversight, participants are easily come by, and the cost of the clinical trial is about half of what it would be in the US.

In India, clinical trials are a booming industry, and while the monetary costs are minimal, the costs are of a different kind. In 2007, 132 deaths were attributed to clinical trials in India. The following year, that figure rose to 288; then 637. In 2009, 668 Indians died in clinical trials, according to the India Tribune, August 8, 2011.

Even these shocking numbers are probably far below the actual number of deaths. The system is designed to minimize reporting. In India, the trial investigator - hired by the firm conducting the trial - is solely responsible for determining the subjects’ cause of death. That's like having a cop stumble in on his own son in a crime scene and expecting him to impartially report his findings. No trial investigator wants the clinical trial drug to be the blame. It's much easier to assume the subject died of a prior disease. To make matters worse, there's no system of independent auditors to investigate the cause of death and very little recourse even when the trial is found to be at fault. The government deemed only 22 of the 668 deaths this past year worthy of compensation. Compensation for five of those families was $300 to $600.

Dr. Chandra Gulhati, a medical practitioner who led several UK clinical trials, told the India Tribune he investigated a case in which 800 pages of protocol were submitted to the Drug Controller in India for approval, and

SIDEBAR

The Explosion in Outsourcing

While biking down the Tampa Bay Trail in August, a jogger swerved into my lane and sent me flying over the handlebars. The ambulance attendants peeled me off the pavement and took me to the hospital, where I learned I’d broken my collarbone in four places.

When I followed up with my orthopedic surgeon the next business day, he informed me that I needed a plate and a dozen screws to line the fragments back up. He had operated the previous year on my wrist after a hockey accident, so I was surprised when he told me he couldn't do the operation. He does wrists. He could give me the name of a doctor who does collarbones. A few days later, I lay on that other doctor’s operating table.

I felt a great deal of confidence going under on the table of that doctor. He does nothing but operations like mine from dawn till dusk. That's the kind of confidence I want my customers to have when they come to see me. It reinforced a decision I made earlier this year.

Xcelience does formulation and manufacturing of clinical trial materials. Like my doctor, we're specialized. We take pride in being the best at what we do and going the extra mile. Like my orthopedic surgeon, I often get happy customers asking me if I could do one more thing for them. Lately I've received several requests for spray-drying and hot-melt extrusion.

I could've purchased some equipment and announced that Xcelience now does spray-drying and hot-melt extrusion. But that wouldn't have been akin to my orthopedic surgeon announcing that he now does collarbones as well as wrists. I'm not sure I want the generalist. I have more confidence in the specialist.

In August, we announced a partnership with Bend Research, an established industry leader in solubilization technologies, such as spray-dried dispersions and hot-melt extrusion formulations. Bend Research has been working with these technologies for over a decade, though their history includes more than 30 years of application engineering and physical chemistry in non-pharmaceutical industries.

Xcelience will continue to oversee the project through that phase if the customer asks us to, but Bend Research consistently delivers a level of spray-drying and HME expertise we could only aspire to. Through this partnership, we can now deliver that same level of science.

But it's not just about Xcelience. We are one small part of a much larger trend. Outsourcing in general is exploding. In fact, a recent report from Visiongain forecasts revenue from contract manufacturing will hit $64 billion by 2016, more than doubling between now and 2021.

Manufacturing of finished dosage forms will be leading this growth with compounded annual growth of 8.7% between now and 2016. Production of APIs accounted for 71% of the total contract manufacturing industry worldwide last year.

The US was responsible for 42% of contract manufacturing and demand for CMOs is expected to continue to come from drug makers in developed countries as they ramp up their R&D, but also increasingly from biotech.

Industry employment statistics are also ticking up, albeit modestly. We may rejoice that our industry no longer tops the list of industries laying off. The most recent study by Challenger Gray and Christmas showed a 50% drop in layoffs through August. Just 122 positions were eliminated that month, while drug makers said they planned to add another 433 jobs.
the green light was given four days later. If the same project had been submitted to him, he says it would've taken him a month to understand it. Dr. Gulhati is now investigating the cause of 81 deaths due to recent clinical trials.

Do participants willingly consent to such massive risks? The evidence suggests that at least in some cases they do not. In addition to using poor and illiterate trial volunteers, the concept of achieving consent forms is loosely interpreted. An HPV vaccine trial, which was later cleared in the case of six deaths, highlighted a number of deficiencies. Consent forms were signed by the wardens of the hostels where the participants lived, rather than by the participants themselves. There was no proper procedure to monitor the health of the participants for adverse effects, no uniform system for reporting Adverse Events, and no follow-on health insurance for treatment in case they fell ill during the trial.

The study also found more than 20% of study participants were from India's small tribal groups even though the law specifically bars the use of people from tribes unless the drug is of specific benefit to them. The report called these "minor deficiencies" but here in the US and Europe, we would take them more seriously.

This is a situation that will change as India becomes a developed country. At India's current rate of growth, it will have a real GDP per capita of $15,000 in 2030. That might not sound like much (in the US it was $46,000 in 2009), but it will move most of the population above the poverty line. It's just a matter of time until either the Indian people or international humanitarian organizations start moving ahead of the curve.

So far, stirrings of discontent come mostly from NGOs, rather than the Indian citizens themselves, and the focus of concern is not the humanitarian issue, but whether or not the trial drugs themselves are beneficial enough to Indians to justify the trials. The NGO PATH says India should only conduct tests for medical conditions like diarrhea and malaria, which are Indian-specific. Cancer is not specifically an Indian disease, so foreign researchers should conduct their research at home, it says.

**FDA LOOKING TO ADD TWO MORE MONTHS TO APPROVAL PROCESS**

One way to improve the quality of trials in India would be it equips the FDA with the capability of reviewing the torrents of data coming out of trials in that country. Instead, we have an over-worked under-funded agency struggling to meet its 10-month PDUFAs deadlines.

But this too may soon change if the FDA is granted the wish it brought to Congress this summer - an additional 60-day filing period to the drug approval process and a fee increase.

The FDA's goal is to shorten the approval process by lengthening it. It's not as counter-intuitive as it sounds. Right now, the average Prescription Drug User Fee Act (PDUFAs) process takes 10 months, which many say isn't long enough for a thorough review. The response that comes out of that 10-month pipeline indicates whether or not the drug is likely to be approved, and requires the company to take specific actions toward approval. Some companies argue the FDA is under too much strain to produce an outcome in that time-frame, and the result is a response that really isn't predictive of whether or not the drug will actually be approved.

The combination of the extra time with the FDA's request for increased funding may be the right prescription. The FDA collects one third of its funds, or $922 million of a $3.28-billion 2010 budget, from the companies seeking FDA approval. The agency wants to raise this user fee another 6% over 2012 levels to bring in an additional $713 million in 2013. The fee in 2012 for applications requiring clinical data are currently $1,841,500.

Right now, funds generated go directly into the reviews with nothing left over. The new money is destined for drug safety, rare diseases, and training in new technologies and science. The agency contends that by increasing the science, it'll be able to approve drugs faster in the long run.

I agree with the FDA that rushing to judgment to meet a department goal is foolhardy; and I can't argue against investing in more training for any organization. The question is, how do we know that the extra two months and the additional fees will result in better drugs delivered quicker? Tell me on LinkedIn what you think.

**BIOGRAPHY**

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