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Tectonic Transformations:

The Future of Biopharmaceuticals in Asia

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Executive Summary: Understanding Local, Thinking Local, Being Local

The biopharmaceutical industry stands at a crossroads with its very future in question. The problem is deep-seated, arising from serious structural flaws in the way the industry has been constructed. Incremental innovations are no longer sufficient. The industry needs a radical transformation, and Asia offers a unique opportunity for remodeling the system. The pre-requisite, however, is that biopharmaceutical companies truly comprehend the emergence—or re-emergence—of Asia, and meet the challenge of *understanding local, thinking local and being local.* Contract Research Organizations (CROs), with their cross-industry view of the landscape, must understand their pivotal role within the new "wheel-and-spoke" partnership model, and evolve from being pure service providers to becoming key enablers of healthcare transformation in Asia.

Introduction

As the world stands at a crossroads with respect to the global economy, geopolitical power shifts and climate change, so too is the biopharmaceutical industry approaching its own moment of truth. While the fundamental problems of low R&D productivity, rising R&D costs, price cuts and patent expiration remain, the pharmaceutical industry is actively, if somewhat desperately, trying to reinvent itself. It is using a variety of strategies ranging from branded generics and fixed-dose combinations in emerging markets, to global biosimilar programs that aspire to capture a piece of the US$ 50 billion opportunity arising from a handful of blockbuster biologics that come off patent in the next five years. There are almost daily announcements of mergers and acquisitions, of new partnerships and alliances. It is said that innovation is being stifled by ultra-conservative and bureaucratic approval processes, and there is discourse everywhere on different and often wondrous *in silico* and open innovation models of virtual drug development. The celebration that 2011—with its bumper crop of 35 NDA approvals in the US—heralds a turnaround for the industry is tempered by the observation that pipeline drugs in Phase I and II are at an all time low, leading at least one commentator to observe that the turnaround was perhaps in FDA regulations, rather than in R&D productivity[1].

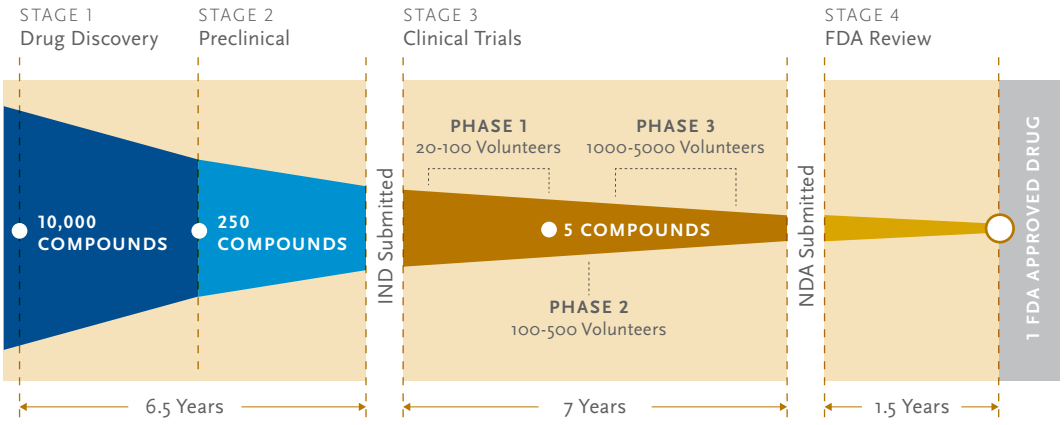
All this activity leads one to ask: "Is the industry breathing new life or experiencing agonal gasps?" The cacophony confuses rather than informs, and ultimately distracts from the fundamental challenges at hand. In this white paper, written as a follow up to last year's "Asia: A New Frontier in Strategic Drug Development"[2], we examine:

1. *The tectonic plates and fault lines upon which the biopharmaceutical industry currently rests*
2. *The importance of Asia and other emerging markets, and three fundamental truths to any successful emerging market strategy, and*
3. *The opportunities that the rise of Asia offer to the biopharmaceutical industry for a radical transformation.*

On Shaky Ground: The Case for Change

Those who dismiss the troubles of the biopharmaceutical industry fail to appreciate its complexity and the unique challenges of R&D in biopharma. To begin, the product development cycle from discovery to market launch for new drugs is much longer than the product development time in other complex industries such as aerospace and electronics. It takes eight to 12 years for biopharmaceuticals to

Figure 1: The Current Developent Model

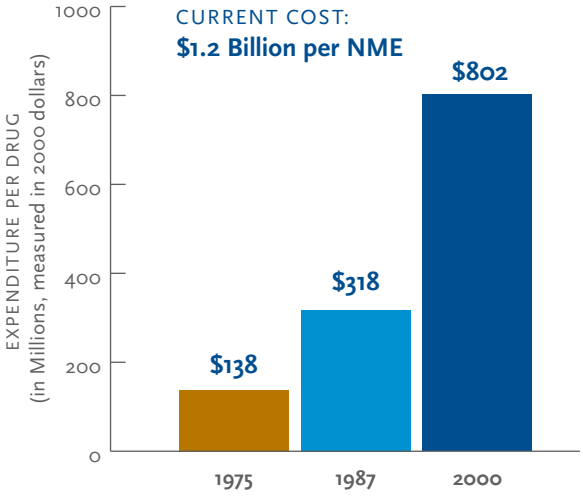


[1] Herper M. The Truth About 2011's New Drug Approvals. *Forbes.* 18 July 2011. Available from: http://www.forbes.com/sites/matthewherper/2011/07/18/the-truth-about-2011s-new-drug-approvals/

[2] Kureishi A. Asia: A New Frontier for Strategic Drug Development. Quintiles. 8 March 2011. Available from: http://www.quintiles.com/information-library/white-papers/asia-new-frontier-strategic-drug-development/

transition from discovery, through the clinical development stages to regulatory approval and launch. By contrast, the Airbus 380 took less than six years from drawing board to delivery of the first aircraft. The iPod took even less time, with launch of the product less than a year after Apple conceived the idea. The longer development times in biopharma add complexity, increase cost and compound the risk of future uncertainty. This protracted development timeline means pharma is forced to predict the market a decade or more into the future, which is virtually impossible. The world can and often does change radically in 10 years. For any one drug, management of the disease for which the drug is developed, the competitive landscape, the reimbursement and market dynamics and the regulatory expectation of the risk-benefit profile can shift tremendously in a decade (Figure 1).

Figure 2: Expenditures per Rx Drug



The net present value (NPV) is used in business to determine whether the current investment in a project is justified based on the projected future earnings. Defined as the present value of an investment's future net cash flows minus the initial investment, the NPV remains the only objective means of assessing which potential biopharmaceutical products are worthy of investment. However, as anyone having engaged in the exercise can attest, minimal objectivity and many unverifiable assumptions go into calculating the NPV. While this may work well in other industries with short product development timelines, the farther the assumptions are projected into the future, the more fraught with error they become. Unfortunately, the biopharmaceutical industry, having no clear alternatives to guide decision making, treats the results of these NPV calculations from its strategic planning departments as if they were hard science in prioritizing their product development pipelines.

Leaving aside the weakness inherent in the NPV, one might ask whether pharma R&D investments are successful even by the measure of the NPV. A 2011 report by Deutsche Bank looked at the seven largest European drug makers and asked this very question.[3] The report compared the total R&D investment with the total NPV of products launched between 2007 and 2011 by these companies and found that

Figure 3: R&D Expenditures and Yields

STRUGGLING TO GAIN RETURNS ON INVESTMENT (2007-11)

Roche	Sanofi	Novartis	GSK	AstraZeneca	Bayer	Novo Nordisk
R&D Spend						
$35.1B	$28.7B	$28.7B	$28.3B	$22.5B	$10.6B	$7.2B
Net Present Value of New Drug Approvals						
$6.0B	$10.2B	$37.7B	$19.6B	$7.1B	$6.6B	$3.4B
New Drug Approvals						
2	5	15	16	3	3	1

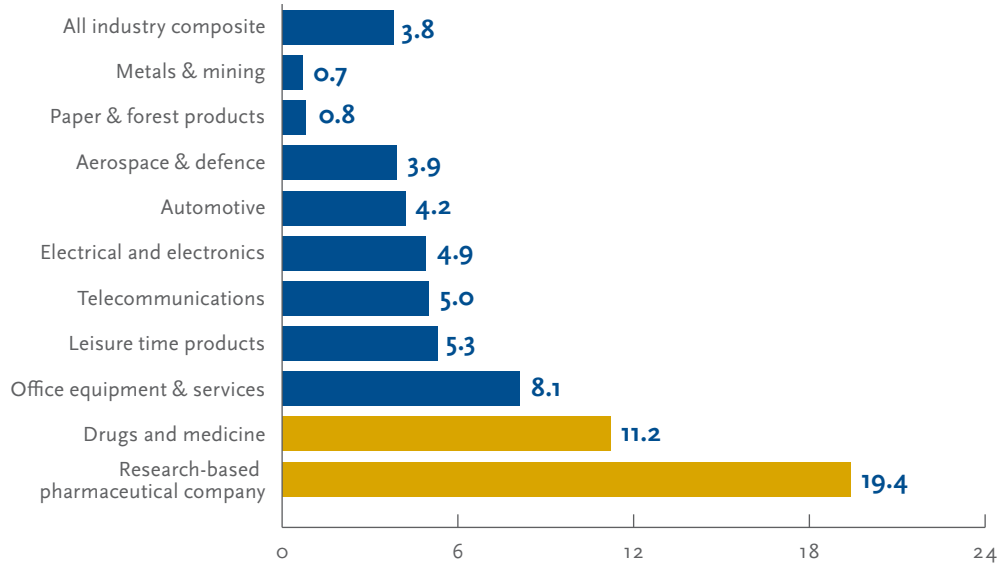
From The Financial Times, 17 Oct. 2011

[3] Parkes R, Race T, Clark M. R&D productivity: Delivering sufficient value to support post-cliff growth. Deutsche Bank. 1 September 2011.www.quintiles.com/information-library/white-papers/asia-new-frontier-strategic-drug-development/

while the total R&D investment was US $161 billion, the cumulative NPV was just US $86 billion. In fact, only one of the seven drugmakers had a higher NPV for the products they launched than the amount they spent on R&D during this period (Figure 3).

Compounding the challenges of a long product development cycle and the uncertainty of future returns on investment is the fact that R&D in biopharma is extremely expensive. The typical R&D budget of a multinational biopharmaceutical company consumes 15-20% of gross revenues. By comparison, the R&D budget of the aerospace and electronics industries utilizes 4-5% of gross revenues (Figure 4). Moreover, the activities that consume the highest proportion of the R&D budget in biopharma are clinical trials that generate the safety and efficacy data required for regulatory approval. These late development activities consume 80-90% of the R&D budget, but add little or nothing to new scientific or technological advances. Consider the situation if 80-90% of the Airbus 380 development budget was invested not in designing the aircraft—in advances in metallurgy, electronics and aeronautical engineering—but burned in test flights. Thus, only a small fraction of the biopharma R&D expenditure is actually fed back into the pure and applied scientific research activities which determine the future of the industry.

Figure 4: R&D Percent of Sales



'Research-based pharmaceutical companies' based on ethical pharmaceutical sales and ethical pharmaceutical R&D only, as tabulated by PhRMA. 'Drugs and medicine' category based on total R&D and sales for all products of companies within the drugs and medicine sector, tabulated by Standard & Poor's Compustat, a McGraw-Hill Division.

A corollary of this asymmetrical, late-stage R&D spending pattern is that when a drug fails in late stage development, there is little to be salvaged from the failure. Drugs, with rare exceptions such as thalidomide, do not make a comeback. In contrast, when the Boeing 787 developed cracks during tests flights in its carbon fiber fuselage, the design was adapted and the test flights resumed. Similarly, an exploding engine on the Airbus 380 led to redesign of the engine and technological improvements, not to full market withdrawal of the aircraft.

And once a biopharmaceutical product makes it to market after surviving the discovery to registration attrition rate of 10,000:1, the medicine enjoys a relatively short shelf-life of seven to 10 years before patent expiration. While the Boeing 737 still flies the skies almost 35 years after launch, with several line

extensions and only the Airbus competing for market share, a typical drug will lose 80-90% of its sales to generic competition within six months of patent expiration in the US.

With such long development times, the cost of bringing a new drug to market is extraordinarily high. Various estimates place this cost between US $500 million and more than US $1 billion. However, a more accurate estimate is undoubtedly the total R&D expenditure of a company divided by the successful number of products launched. Using this measure over the time period 1997 – 2011, the cost of each new drug brought to market for the top 12 pharma companies is staggering, ranging from a low of US $3.7 billion to a high of US $11.8 billion per molecule developed.[4]

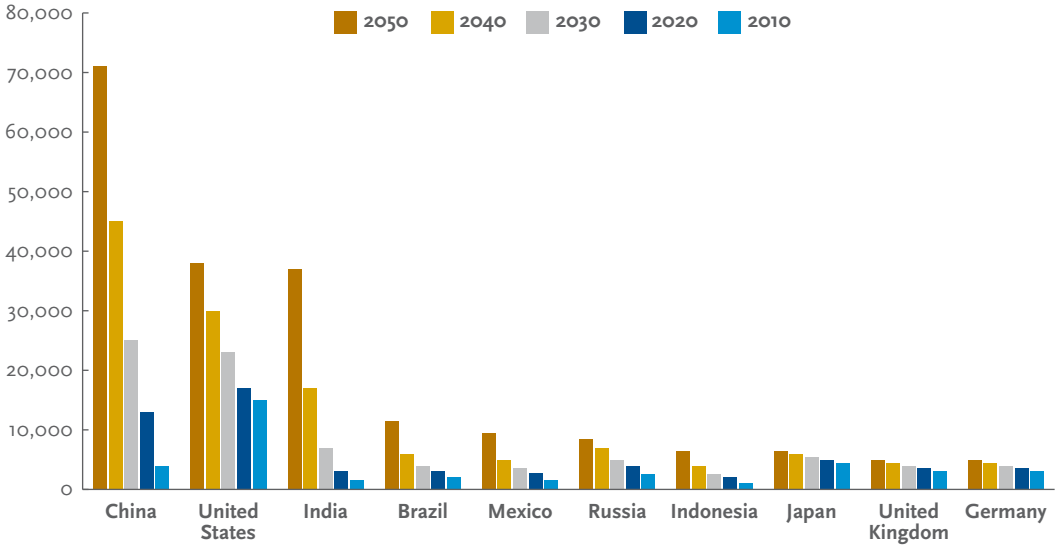
Finally, there are overwhelming marketing ambiguities as well. When a drug is launched, who is the customer? Is it the physician who decides on the one drug among many to prescribe? Or is it the insurance company or public provider that pays for the drug? Or is it the patient, for whom the drug was ostensibly developed, but is the passive recipient of the product? Whichever way one views these dilemmas, the existential pressures to commercialize biopharmaceutical products successfully are enormous and often lead to aggressive marketing practices that damage the reputation of the industry and result in massive fines from the regulators.

Suffice it to say, with the biopharmaceutical industry undergoing rocky times, one cannot ignore the shaky ground on which the industry stands.

Asia Rising – Again

In the words of former US Secretary of the Treasury Larry Summers, "The dramatic modernization of the Asian economies ranks alongside the Renaissance and the Industrial Revolution as one of the most important developments in economic history." Indeed, the rise of Asia in a single generation has been nothing short of spectacular. While the Industrial Revolution doubled the standard of living during a generation in Asia, a single generation has witnessed their per capita GDP rise 10 to 100-fold. Over the past three decades, the percentage of people living below the poverty line in East Asia has dropped from 78% in 1981 to 17% in 2005.[5]

Figure 5: The World's 10 Largest Economies (GDP in US $ Billions)



Goldman Sachs – *BRICS and Beyond*, 2007

[4] Herper M. The Truly Staggering Cost of Inventing New Drugs. *Forbes*. 22 February 2012. Available from: http://www.forbes.com/sites/matthewherper/2012/02/22/the-truly-staggering-cost-ofinventing-new-drugs-the-print-version/

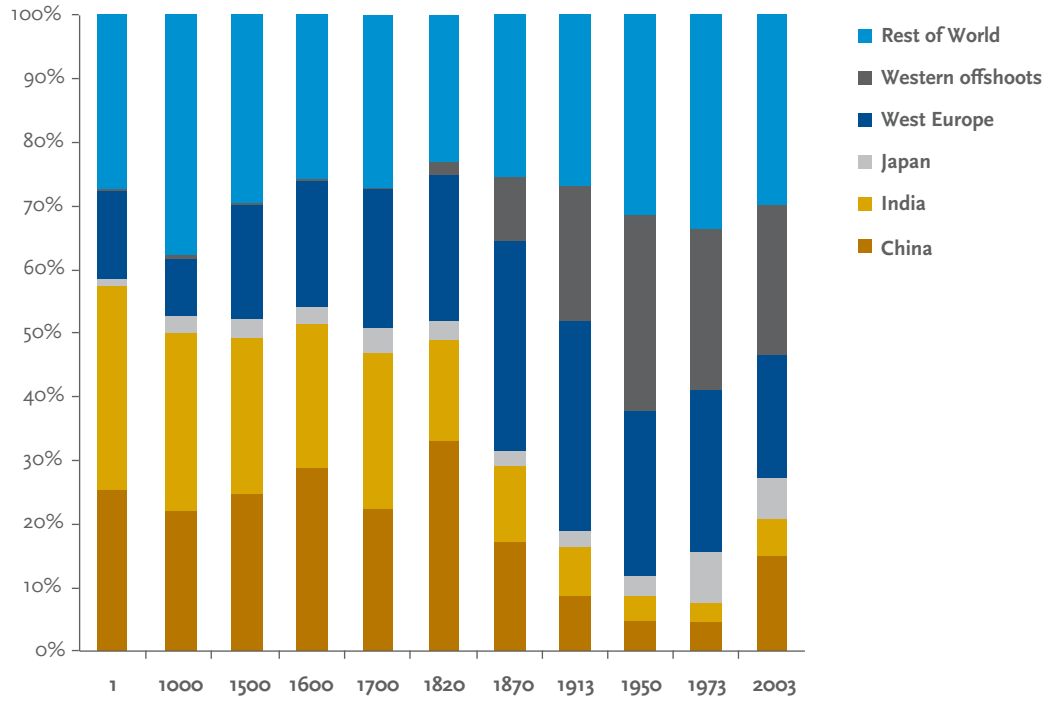
[5] The World Bank (Internet Page). Poverty & Equity: East Asia & Pacific. Available from: http://povertydata.worldbank.org/poverty/region/EAP

Despite the global economic crisis, with double-dip recession in the US and a currency crisis in Europe, the economies of Asia continue to grow steadily. While GDP growth of countries such as India and China may have slowed to the 6-8% range, these numbers are many fold higher than the forecasted growth rates for the US and EU, and are bringing transformative change to a continent that covers 30% of the earth's landmass and is home to 60% of its people. Although news of China and India dominates the headlines, other countries in Asia are also rapidly emerging. Indonesia, the fourth most populous country in the world after China, India and the United States, is projected to become the seventh largest economy by year 2050, eclipsing the UK, Germany and Japan (Figure 5). Vietnam, with a population rivaling that of Germany with 85 million people, has a growth rate equivalent to that of China.

Although Asia is indeed modernizing, it would be a mistake to think the continent is Westernizing. Asians may have acquired a taste for Western food, culture and lifestyle, but there is unmistakably a reassertion of local culture and identity. This is a fundamental point that global multinationals need to understand. It is no longer sufficient for companies to "think global, act local." Rather, companies must "think global, be local" and to "be local," companies must understand what "local" truly means.

For example, to understand the Indian government's point of view on patient participation in clinical trials conducted by multinational pharmaceutical companies, one needs to appreciate the role foreign companies and governments have historically played in the country. While many believe China and India have only recently risen to global economic prominence, their histories can be traced back five thousand years—and this is not the first time they have held sway over the world economy.

Figure 6: Percentage of Total World GDP – a two thousand year view



Data extracted from: Contours of the World Economy, Angus Maddison (2007)

During the first eighteen hundred years of the last two millennia, Asia dominated the total world economy, with India and China together accounting for over 50% of total world output[6] (Figure 6). Colonization of Asia by the West accompanied by the Industrial Revolution in the late eighteenth century brought affluence in Europe and poverty for Asia. An understanding of how this came to be provides an insight into how Asia perceives the West.

The initial territorial control of portions of India in 1757 was not by the British Empire, but by the East India Company—a joint-stock company which arrived in India a century earlier ostensibly to trade. Within a decade of the East India Company taking control of Bengal, the area witnessed a great famine that lasted three years, caused 10 million deaths and reduced the population of Bengal by a third. The cause of the famine is attributed to taxes being raised from 10 to 50% (revenues that flowed out of the country), crop failures and the forcible abandonment of agricultural crops in favor of poppies to supply the nascent opium trade in China.

Even with this small historical context, current issues such the concerns of Indian activists regarding multinational biopharmaceutical companies conducting clinical trials in India, or opposition to the US-Indian Nuclear Agreement can be better understood and viewed with deeper sensitivity. Given the indisputable importance of Asia to the revival of global biopharmaceutical companies, any successful emerging market strategy needs to navigate by three fundamental truths:

First, Asia is not a single entity, just as Africa is not a single country. Asia is not only the most populous continent with the largest land mass, but it is also richly diverse. Compared to the relatively continental homogeneity of the Americas and Europe, Asia is highly heterogeneous with respect to language, culture, religion, ethnicity and politics. Nor is Asia merely a sum of India and China. Many Asian economies are rapidly *re-emerging*, and should be recognized for the important growth opportunities they offer. It is not a story of rags to riches—a narrative that resonates with the American dream—but of an Asia returning. This is not a romantic notion, but an extremely important distinction because it will guide the behavior of companies with a mid- and long-term view of establishing themselves in Asia. And for companies wishing to build significant inroads and establish relationships with these emerging nations, the most sensible time to enter is when they are still pre-emerging and need the support of Western companies to make important investments into their emerging infrastructure.

> As Asia develops and modernizes, the countries of Asia will manifest more clearly their distinct cultural identities. Multinational companies in all industries that wish to succeed in Asia will need to learn to "be local" in order to recognize and leverage value-creating local opportunities.

Second, there is a tendency to consider "country" synonymous with "market." Hence we use the term "emerging markets" as a narrow synecdoche for nations and entire societies that are undergoing rapid development. This leads to the more serious mistake of viewing Asia superficially as a simple extension or expansion of the Western market, without taking into consideration the historical and cultural differences. As Asia develops and modernizes, the countries of Asia will manifest more clearly their

6 Maddison A. *Contours of the World Economy* 1-2030 AD: *Essays in Macro-Economic History.* Oxford University Press, USA. 2007

distinct cultural identities. Multinational companies in all industries that wish to succeed in Asia will need to learn to "be local" in order to recognize and leverage value-creating local opportunities.

Finally, while the initial growth of Asia has been fueled by a cost-arbitrage of low-skilled products and labor, there is now a reverse flow of intellectual capital back to China and India, and the science and technological skills acquired at MIT and Stanford are being firmly planted in Wuhan and Bangalore. Those who think China and India will not be able to compete with quality biopharmaceutical products must consider how Korean cars were scoffed at in the 1990s, or Japanese electronics were ridiculed a generation before that. Asia's rise will not only be as a market, but also as diverse group of economically developed and technologically advanced nations taking their place in a multi-polar world.

Reality is much larger than the human mind can comprehend; history more complex than the simple narratives we have been taught at school. The tired, crumbling model of an industry that seeks to help mankind and alleviate suffering could well seek inspiration in Asia by *understanding local, being local and thinking local*, and not seeing Asia with tired old eyes as an extension of the West.

The Way Forward: Transformation, Not Incremental Innovation

Innovation and change occur at two levels. First-order change refers to solutions that restore equilibrium without altering the underlying state; the systems and structures from which the problems arose remain unchanged. Second-order change, on the other hand, is a change of the state itself—a shifting or transformation of the entire framework. Consider the analogy of a person experiencing a nightmare, in which the dreamer is being pursued by a monster. The dreamer may run, hide or turn to confront the monster, but in each case the change is first-order and the framework remains unchanged in that the person is still dreaming and the monster still present. However, if the person awakes from the dream, the monster ceases to exist. This awakening is second-order change.

It has been stated with increasing frequency that the salvation of the biopharmaceutical industry lies in innovation. Indeed, one can argue that while new medicines have been discovered and developed with regular—if diminishing—frequency, there has been very little innovation in the industry itself over the last few decades. Moreover, given the catalog of challenges detailed earlier, one wonders whether any incremental innovation can be sufficient to overcome the fundamental structural flaws in the existing biopharmaceutical model, and whether a complete transformation of our thinking and approach to developing new medicines is needed. As Einstein observed, "the significant problems we face today cannot be solved at the same level of thinking we were at when we created them."

The biopharmaceutical model currently stands at the threshold of transformational change. The old model cannot and will not persist in its present form, and those recognizing and seizing upon this fact will shape the new model. What this transformation will look like is open to speculation. For the biopharmaceutical industry to be successful, there are several circles of interest that must become confluent: innovation must alleviate illness and suffering; those that are ill and suffering must have

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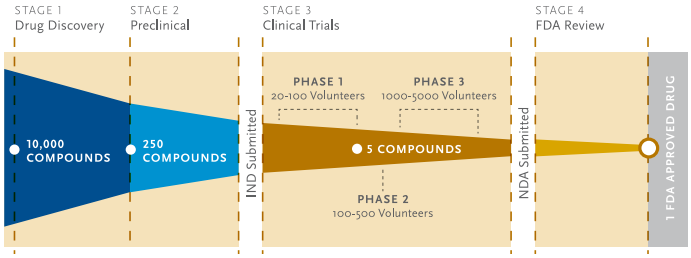
access to these innovations; and the use of these innovations must in turn create rewards for the innovators to stimulate further innovation. These circles of interest must in turn be confluent with a much larger circle, that of society at large—the realm of the greater good which encompasses regulators, medical ethics and public health.

Thus, a key element of the new model will be a renewed focus on healthcare, both in alleviating individual suffering and in addressing the healthcare needs of society. No longer will it suffice to develop an expensive new medicine which is accessible to only a small minority of patients, at a cost that siphons resources and leaves even larger healthcare issues unaddressed. The guiding question at the heart of the new model will be: *How can science and technology create innovative solutions for patients that lead to healthier societies?*

We have previously asserted that fundamental to this new model will be partnerships[7]. A single person or entity can neither hope to comprehend the problem of healthcare in its entirety, nor possess all the pieces to the solution. In the old model of drug development, a biopharmaceutical company retained the entire drug discovery and clinical development process. This linear, monolithic "go-it-alone" model is giving way to the "wheel-and-spoke" model of multiple partnerships and strategic alliances. The new model lends itself to the principle of "how can we work to win together?" and away from "how can I win before you do?" This in itself is a paradigm shift. (Figure 7).

Figure 7: Shifting Paradigms in R&D: from Linear to Wheel and Spoke



> *"Go at it alone"*
> *Large commitment of resources*
> *Diffuse focus*
> *Long PD cycle*
> *Competitive*

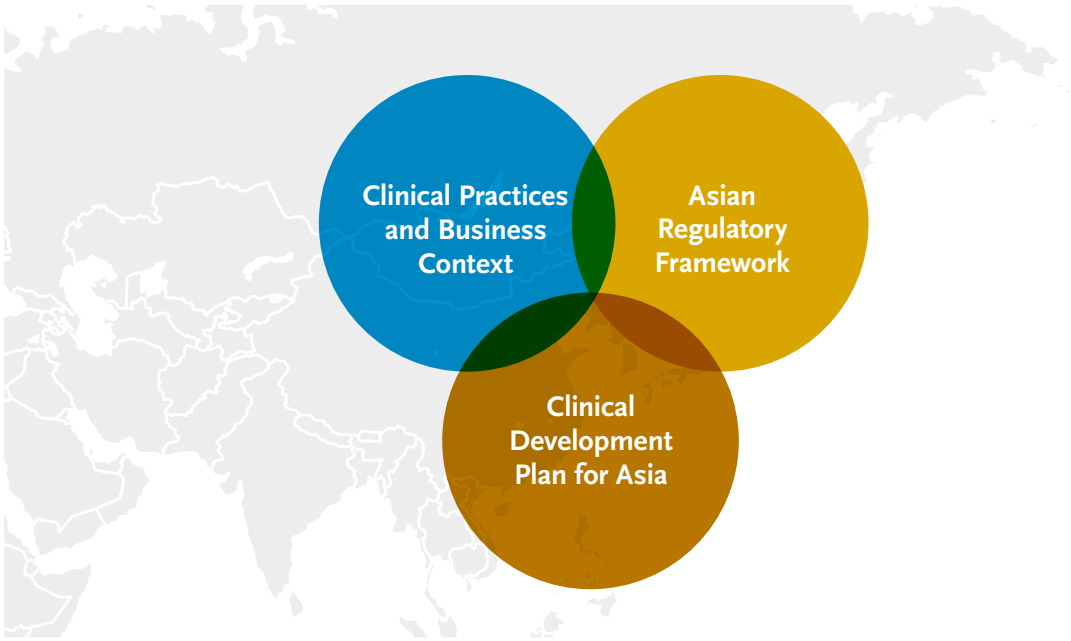
WHEEL & SPOKE MODEL

> *Partnership & alliances*
> *Flexibility in allocating resources*
> *Focus on strengths*
> *Shorter "pay back" cycle*
> *Collaborative*

7 Kureishi A. *Asia: A New Frontier for Strategic Drug Development*. Quintiles. 8 March 2011. Available from: http://www.quintiles.com/information-library/white-papers/asia-new-frontier-strategic-drug-development/

Inherent in this wheel-and-spoke model is a transformation of the relationship between biopharmaceutical companies and their traditional service providers, the CROs. As pharma companies focus their resources to excel at their key competencies, they will need to rely increasingly on stable alliances with reliable partners for successful drug discovery and development. Traditional CROs are widening their capabilities and transitioning from service providers to creators of innovative solutions, leveraging their unique cross-sectional industry perspective across the drug development horizon. An example of this transition is Quintiles' Strategic Drug Development Unit Asia based in Singapore, which provides clinical development and regulatory strategy for biopharmaceutical companies seeking to develop their drugs in Asia (Figure 8). Clients are provided a bottom-up medical context for where their drug would fit into the medical landscape in Asia, followed by evaluation of various regulatory scenarios, culminating in a clinical development strategy unique to that drug.

Figure 8: Strategic Drug Development Asia: Our Offerings



Growth in Asia is central to the survival of the biopharmaceutical industry. Indeed, it is difficult to find a biopharmaceutical company in the US or Europe that does not have an emerging market strategy, or one that is not staking its survival by forecasting a large part of its future earnings as coming from emerging markets. Even so, the opportunity in Asia is still being viewed too narrowly—the current tendency of global biopharmaceutical companies to see emerging countries as extensions or expansions of Western markets, rather than the unique and phenomenal transformations that they are. More so in Asia than in other parts of the world, the biopharmaceutical industry should be seeking a paradigm shift—a rebirth—rather than incremental innovations.

Asia contains all the seeds of transformation that the biopharmaceutical industry seeks. It has massive economic growth, huge burdens of disease and societies that are in the process of rebuilding and remodeling themselves. With economic growth and the reverse brain drain bringing intellectual capital back into Asia, local science and technology is establishing a firm foothold. However, with rapid growth and affluence, the question that remains at the forefront in Asia is sustainability. And at the heart of sustainability is social justice and stability, with better living conditions in the cities and rural areas, and healthcare that is accessible and affordable. In short, the need, the know-how, the resources and the will for innovation are all present in Asia. We must now have the courage for a second-order change, a new awakening that refocuses the biopharmaceutical industry on the healthcare needs of the re-emerging societies of Asia.

The wheel-and-spoke model can likewise be viewed in a much broader context. Historically CROs have functioned as pure fee-for-service providers, situated external to the biopharmaceutical industry. However, in Asia the service industry has a much larger role in the rescue and transformation of the biopharmaceutical industry. With its broad, cross-sectional industry view, and its deep relationship with hospitals and investigator sites in Asia, the service industry can be viewed as a non-partisan player that advocates better healthcare and regulatory processes in a re-emerging Asia. For this, the biggest challenge for the service sector is to transform its self-perception – to no longer see itself as the hand-maiden of the biopharmaceutical industry, but as an advocate for better processes in a re-emerging Asia, investing in training people and building infrastructure. For the CRO industry to see themselves as solution providers rather than service providers is a mere first-order change. The second-order transformational change is for CROs to see themselves as the midwives of a *New Health* in Asia, bringing clinical research expertise and investments to tertiary care hospitals, crafting clinical development plans that address Asian medical needs, and nudging the evolving regulatory landscape in Asia in a direction that benefits those most in need of healthcare. For this, the service industry itself must think Asia and be Asia, and in doing so, restore patients to the center of the healthcare system.

Viewed through this prism, absorbed through a mantra of "understand local, think local, be local," the sliding tectonic plates upon which pharma sits become less foreboding. And perhaps, it's no coincidence that the Chinese term for crisis—(危机) *weiji*—is the juxtaposed characters for danger and opportunity.

About the Author

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Dr. Amar Kureishi joined Quintiles in August 2010 to establish the Strategic Drug Development Unit (SDD Asia). With a mission to help biopharmaceutical companies formulate clinical development and regulatory strategies for their products, SDD Asia rapidly gained an international following, helping ten clients devise Asian strategies for 15 different compounds in its start-up year.

Prior to joining Quintiles, Dr. Kureishi was Global Head of Medical Affairs for Bayer, responsible for all therapeutic areas within the worldwide Bayer Healthcare organization. During his 11-year career with Bayer, Dr. Kureishi held progressively senior leadership positions across different geographies, including posting in the USA, Germany, China and Singapore. In 2005, he was assigned to China as Vice President and Head of Clinical Development & Medical Affairs for Asia-Pacific with a remit to build Bayer's clinical development capabilities and infrastructure in China and Asia-Pacific, resulting in the accelerated development of products such as Nexavar and Xaralto.

Dr. Kureishi is a physician and infectious disease specialist, having received his medical degree from the University of Alberta in Edmonton, Canada. He is a fellow of the Royal College of Physicians and Surgeons of Canada, and an alumnus of INSEAD. Prior to joining industry, he was Associate Professor at the University of Calgary, Canada, and has authored more than 60 articles and abstracts. He has established thought leadership with his previous white paper, *Asia: A New Frontier in Strategic Drug Development*, in which he set forth a collaborative, multiple alliance "wheel-and-spoke" model for drug development in Asia, an example set by SDD Asia.

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