McKinsey&Company

FEBRUARY 2010

McKinsey Quarterly

PHARMACEUTICALS & MEDICAL PRODUCTS PRACTICE

R&D in emerging markets: A new approach for a new era

Gone is the time when R&D in developed markets could meet the pharmaceutical needs of emerging ones. A local presence is required.

Michael Edwards

The pharmaceutical industry has long been driven by the demands of the North American and Western European markets, paying scant attention to emerging markets and the diseases more prevalent there.

Yet this pattern is changing. Emerging markets contributed 30 percent of the pharmaceutical industry's value in 2008,[1] and their pharma markets are forecast to grow by 14 percent a year to 2013.[2,3] By contrast, the US market—still representing 40 percent of the global one—is expected to expand more slowly, with annual growth of less than 3 percent over the next four years. Indeed, all developed markets tend to be characterized by low or negative growth, a stricter regulatory environment, and increasing levels of patent litigation.

Not surprisingly, many pharmaceutical companies now see some of the largest emerging markets as the keys to their growth ambitions. Over the past ten years, these companies have established low-cost research institutions in emerging markets, tapped into their talent pools in search of innovation, and set up corporate-social-responsibility programs to help tackle neglected diseases. But more must be done if companies are to capture the opportunity.

Most still tend to regard emerging markets mainly as a source of lower-cost R&D. Instead, they should consider how R&D can best serve these disparate and often poorly understood regions. The likely outcome is that these companies will eventually have a significant proportion of their scientists, chemistry, manufacturing, controls, and development groups there. Only in this way will they understand the needs and preferences of patients and physicians, develop products that meet those needs, and ensure that the products are introduced in a timely manner.

Medical needs and preferences

Patients in emerging markets and those in the West have different medical needs, and the former and their physicians have different treatment preferences. The result—demand for products that reflect these variations—affects decision making and resource allocation across the entire R&D pharmaceutical value chain, from basic research to investments in specific markets.

Choice of disease area

The prevalence of some diseases varies significantly among geographic regions and ethnic groups, as a result of genetic differences or environmental factors, such as diets and living conditions. Diseases that mainly affect developing countries have been largely ignored

[1] IMS World Review, 2009.

[2] IMS Health, Market Prognosis, March 2009.

[3] T. Anderson, I. Das, J. Olson, D. Sobelman, "Global pharmaceuticals: Emerging markets—infusing badly needed revenues for years to come," *BernsteinResearch*, May 1, 2009.

from a profit-making standpoint. However, as economies in emerging markets grow and governments begin paying for the treatment of the poor, certain hitherto neglected types of disease present revenue opportunities.

The better to understand these diseases, companies are realizing that they need R&D resources in emerging markets, since valuable insights from patients, physicians, and payers can be gained only through a local presence. Currently, oncology is the therapeutic area with the most significant commercial opportunities for drugs developed specifically for these regions. Hepatocellular carcinoma (HCC), often caused by hepatitis B and C virus (HBV/HCV) infection, is the most frequently cited example. HCC is the fourth most common cancer globally, and 75 percent of the one million people affected each year live in East Asia. Other cancers more prevalent in developing countries include Kaposi's sarcoma (seen less frequently in developed markets since the advent and use of the HIV "triple cocktail") and gastric/esophageal cancers, which have a much higher prevalence in East Asia. HBV represents another opportunity: of the 400 million people infected with it worldwide, roughly one-third are in China. Many pharmaceutical companies already focus on some of these opportunities. Novartis, for example, is investing in a Shanghai R&D center, which will initially focus its research on diseases particularly common in China (including hepatitis B and C).[4]

Other neglected ailments (including TB, malaria, roundworm, and Chagas' disease) are major health problems across large parts of the world—but not among the 20 most prevalent diseases in the largest emerging markets, with the exception of TB in India.[5] Their value, while growing, will remain small in the near term by the standards of developed markets, though some resources are being applied to TB (AstraZeneca, for example, has established a Bangalore R&D center dedicated to it). Research into these diseases is often conducted in conjunction with public and charitable bodies or in the context of access-to-medicine programs.

In the case of diseases of poverty, such as the dehydrating illness cholera, what's needed is not so much research as better basic living standards. For cholera sufferers, the treatment is simply having access to clean drinking water and rehydration powder.

Efficacy and dosing

Dosing levels may need to be adjusted in emerging markets to reflect variations in a drug's efficacy and toxicity among different geographical or ethnic populations. For example, some subpopulations or ethnic groups have lower levels of critical P450 enzymes, which affect drug metabolism and therefore dosing requirements.

[4] See http://www.novartis.com/research/pharmaceutical.shtml.

[5] "Mortality and burden of disease estimates for WHO member states in 2004," World Health Organization, February 2009.

Body mass (which on average tends to be lower in emerging markets than in the United States or Europe), also affects dosing levels. In Japan, local regulators increasingly approve lower doses than their counterparts in the United States do. Approved doses for Bayer's ciprofloxacin, for instance, vary by region—600 mg in Japan, up to 800 mg in the United Kingdom, and up to 1,200 mg in the United States.

Although personalized medicine—the tailoring of doses to genetic differences among individuals—is still some way off, genetic differences among certain ethnic groups are a further factor in dosing levels. Thirty percent of Asians, for example, have a cytochrome P4502C19 gene variation that limits their ability to metabolize up to 15 percent of all clinically useful drugs,[6] compared with 6 percent of Caucasians. This difference influences clinical practice. Physicians in Hong Kong commonly prescribe lower doses of certain drugs, such as diazepam (Valium), for Chinese patients than for Caucasians because individuals carrying this variant are at higher risk of toxicity when taking these drugs. In addition, the efficacy of some drugs is limited to genetically defined populations or ethnicities, so regulators might approve a drug only for particular ethnic groups. BiDil, a fixed-dose combination of isosorbide dinitrate and hydralazine, is used to treat heart failure. The medication was dismissed when it failed to demonstrate efficacy in a heterogeneous-population trial but revived when efficacy was shown in patients with significant African ancestry.[7]

Real insight into the nuances of dosing can be gained only through local experience and close interaction with local experts.

Patient and prescriber preferences

Understanding physicians' and patients' preferences and responding to them effectively is important to success in emerging markets. Fixed-dose combination medicines—drug therapies with two or more active pharmaceutical ingredients combined in one tablet—are preferred in many markets, but their popularity varies greatly from one to the other. Of course, they can be more convenient for prescribing physicians and patients alike and may improve compliance.

One of the most extreme examples of a fixed-dose combination, the polypill, manufactured by India's Cadila Pharma, includes five active pharmaceutical ingredients.[8] Now in Phase III, it will be targeted at patients with elevated blood pressure or high cholesterol.[9] The polypill includes active pharmaceutical ingredients (all now available as generics)

[6] A. Chung, "Racial differences in response to pharmacological treatment," 2004.

[7] Abdallah S. Daar and Peter A. Singer, "Pharmacogenetics and geographical ancestry: implications for drug development and global health," *Nature Reviews*, Volume 6, 2005.

[8] Hydrochlorthiazide, atenolol, ramipril, and simvastatin, as well as low-dose aspirin and folic acid.

[9] "Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): A Phase II, double-blind, randomized trial," *The Lancet*, Volume 373, 2009.

originally made by AstraZeneca, Sanofi-Aventis, and Merck. The CV Pill,[10] made by Torrent, is already on the market. In some places, such combinations can be priced at a premium and win patent protection.

Formulations represent another opportunity to meet local needs while also potentially extending a product's lifecycle. Many can be considered, including extended-release pills, soluble powders, inhalers, nasal sprays, injectables, and long-acting patches. In each case, the benefits of meeting an emerging-market need or preference must be weighed against the cost of developing a novel formulation. Companies must also decide whether a formulation can be developed in time to extend the lifecycle adequately.

The logistics of delivering products to hospitals and pharmacies is another important area that pharmaceutical companies will need to understand. Heat and humidity can destroy medications, for example, and there may not be a reliable cold-chain supply system to deliver them from factory to hospital. In 2007, Abbott launched Aluvia (a heat-stable tablet formulation of the protease inhibitors lopinavir and ritonavir) in Uganda. The soft-gel capsules and oral solution previously available were not appropriate, given the scarcity of refrigeration equipment. The tablet version has now been filed for registration in more than 150 countries, and nearly 75,000 patients were treated with it in 2008.

Coming to market

After a company has studied the needs and preferences of consumers and physicians in emerging markets, decided which drugs to develop for them, and determined the appropriate dosages and formulations, it must bring its products to market. At this stage, the company faces a whole new set of challenges.

Regulatory requirements and the move toward global trials

Establishing R&D activities in emerging countries will help pharmaceutical companies obtain market access in a timely way. To a certain extent, some local presence is already a prerequisite: China, India, South Korea, and Taiwan all require trials with local patients for local product registrations. Some pharmaceutical companies use contract research organizations to meet these requirements, but others have established their own development centers to run the trials. In 2008, Sanofi-Aventis, for example, established a Biometrics Research Center in Beijing to support global and local clinical trials, from the initial design of studies through data management and statistical analysis.

The inclusion of emerging markets in trials for new drugs has other benefits as well. Development cycles can be reduced thanks to the faster recruitment of subjects from a larger pool of patients. The costs of recruiting patients and paying investigators are lower

[10] Combining atorvastatin, ramipril, metoprolol, and aspirin.

too. That can benefit the development of drugs targeted at either emerging or developed markets, as patients recruited for trials in the former can count toward the total number of patients that US and European regulators require.

By including relevant populations from emerging markets in trials, companies might also reduce the current time delay, which can mean the loss of significant revenues, between launching their drugs in the West and in emerging markets. Some companies are beginning to tackle this issue. Merck, for example, has made a public commitment to launch its drugs simultaneously in both spheres—no small undertaking, since some of its previous launches in emerging markets were up to ten years behind those in the West. Other companies also appear to be moving toward this goal. Bayer was selling the multitargeted kinase inhibitor sorafenib (Nexavar) for HCC in China less than a year after its US launch. Bristol-Myers Squibb launched the antiviral HBV therapy entecavir (Baraclude) in China with only a six-month delay.

Market shaping through local R&D

R&D in emerging economies provides a number of market access benefits to pharmaceutical companies by engaging local stakeholders early in drug development. Working with leading physicians at this stage, for example, can help build a product's reputation and, most important, give companies insights into how they could tailor products to local needs. Working with local physicians in East Asia to develop new oncologic drugs (such as tyrosine kinase inhibitors) could help pharmaceutical companies learn how the region's oncologists approach cancers such as GI stromal tumors, which are rare in developed countries.

A local R&D presence also helps build a company's reputation for innovation and attentiveness to specific needs. In countries that do not require the inclusion of local patients for regulatory approval, local Phase IV postlaunch trials or epidemiological studies can help demonstrate efficacy in the immediate patient population. (The number of Phase IV trials in emerging markets has grown at an annual rate of more than 50 percent in the past five years.) Postlaunch activities such as a Phase IV trial in new indications might expand them, even on a local basis. That could give a company's sales force and medical– scientific liaison staff additional data for discussions with local doctors and reinforce the message that the company aims to meet the regional market's needs. Local R&D activities also help build relationships with governments and regulatory agencies. In some places, a local presence is already a prerequisite for market access, as is increasingly the case in Russia. Elsewhere, it helps to establish relationships with authorities who might accelerate approval for a drug and authorize higher levels of reimbursement.

Related thinking

"Why drugs fall short in late-stage trials"

"The microeconomics of personalized medicine"

"The road to positive R&D returns"

"New frontiers in pharma R&D investment"

By building significant R&D resources in emerging markets, pharmaceutical companies will revolutionize their global R&D groups. The result will be a shift in focus, so that the entire development pathway—from the early stages to life cycle management—includes both developed and developing markets.

For the pharmaceutical industry, these changes will mark the end of an era when companies assumed that the needs of the world's pharmaceutical market were largely those of developed countries. The new era will require considerable organizational change. R&D departments will need new resources. Funding may have to be ring-fenced, since revenues in emerging markets will probably be less than half those in the United States and European Union in the medium term. But perhaps the most important change of all, given the speed of the market's development, will be a rapid change in mind-set. Companies already recognize the need to tailor their product portfolios for emerging markets. To be real leaders in the future, they must tailor their R&D activities too.

Michael Edwards is an associate principal in McKinsey's London office. This article also appeared in *Invention reinvented*, a compendium of articles setting out McKinsey's perspectives on pharmaceutical R&D. To read other articles from the collection, please visit the pharmaceutical and medical products section of mckinsey.com.