BY DENISE MYSHKO

Generics LOOMING LARGER Than Ever

A NEW GENERIC COMPANY MODEL IS EMERGING, ONE THAT IS BIGGER AND STRONGER AND MORE COMPETITIVE THAN EVER BEFORE.

The generic market is changing. IT HAS BECOME GLOBAL AND CROWDED, and as a result, generic companies have become even more formidable competitors for the branded pharmaceutical industry.

As generic companies continue to expand and consolidate, they are likely to step up their efforts to explore options for developing products beyond chemical equivalents, moving into specialty generics, biogenerics, and proprietary molecules. As a result, the generics market is fast becoming a worldwide phenomenon.

"There used to be four big generic markets: the United States, Germany, the United Kingdom, and Canada," says Doug Long, VP of industry relations at IMS Health. "Now generics are making inroads in most European markets. Japan and India are the next bastions in the emerging markets."

In Europe, generic sales have had double-digit growth, and the market is poised to increase in the next few years. In major markets, such as France, Spain, Italy, and the Netherlands generic growth of 12% to 15% has been reported, according to a recent report from Kalorama Information.

The world prescription generic drug market was valued at $36.18 billion in 2007, a compound annual growth rate of 12.6% from 2002, according to Kalorama. In 2007, cardiovascular drugs constituted the largest generic segment, accounting for 21.8% of revenue. (See box on page 22.)

According to the Kalorama report, there are generic versions for about 75% of existing drugs, and more than $60 billion in brand-name drugs will lose patent protection in the next decade. (See box on page 22.) Generics account for 50% to 60% of all prescription sales in the United States. Furthermore, during the past six years, applications for generic drugs have increased by 158%, from 307 applications in 2002 to 793 in 2006. In 2008, the Office of Generic Drugs estimates it will receive 857 generic applications.

Industry experts believe that the impact of generics is going to be much broader and deeper compared with the last 10 years.

John Doyle, Dr.P.H., M.P.H., managing director and practice leader, market access, at Quintiles Consulting, says the impact of generics is cascading down to all brands on the market.

"It is not just the branded market leader that has to defend its price or formulate a new pricing strategy," he says. "The increased focus on generic conversion by the healthcare insurance industry and the greater volume of generics available has now applied additional pressure on pharma companies to demonstrate value to defend price on multiple fronts."

Since branded companies are not going to win on price under market conditions of generic encroachment, he says, they have to try to win on safety or evidence of comparative effectiveness, meaning how the product compares in the real world after it has been in use for some time with a wide variety of patients.

"Pharma companies will start to lean on patient histories," he says. "They should have robust safety and effectiveness data. Although the generic may be a bioequivalent, it doesn't have that same mountain of real-world evidence. This is where pharmaceutical companies can demonstrate value."

The generic market is having an impact at a regulatory level as well, and Congress recently passed a $6 million increase in the budget for the FDA's Office of Generic Drugs. The FDA is requesting a 5.7% increase in its budget for fiscal year 2009, to $2.4 billion, partly to modernize drug safety and speed approval of generic drugs.

BIOGENERICS AND SUPER GENERICS

While pharma generics are growing rapidly, the picture is mixed regarding follow-on biologics. According to Kalorama, the worldwide biogenerics market has the potential to generate more than $16 billion in revenue by 2012, with an annual average growth rate of about 70% between 2008 and 2012.

IN 2012, the worldwide prescription generic market WILL LIKELY REACH $75.52 BILLION.

These products represent a shift in the biotech market, and in response, Kalorama researchers say, biotech companies are reformulating products or improving delivery methods to produce more efficient products that will be preferred by consumers.

Experts from IMS say biosimilars — or follow-on biologics produced by companies other than the originator — are expected to have an increasing impact on the biologic market over the next five to 10 years. The introduction of biosimilar epoetin alfa in European markets in 2007, for example, has started to have an impact on the market, to date holding around 6% of the market. On the other hand, the biosimilar omnitrope, introduced in 2006, has captured less than 1% of the somatropic human growth hormone market.

IMS experts believe that the generic impact on the biologic market will not be as great as what has been experienced by the oral solid market.

Experts interviewed by PharmaVOICE concur, saying the impact of biosimilars is not expected to be felt immediately.

"With the FDA focusing on safety, I expect that there will be a delay in approvals for follow-on biologics," Dr. Doyle says. "There are so many additional manufacturing hurdles for a biologic to overcome that there is the potential for a negative impact on the quality of the product or the proposed profile. For follow-on biologics to come to pass, there will have to be clear and unequivocal demonstration of their risk-benefit profile to ensure that they are truly equivalent or better than the primary product."

Additionally, a regulatory pathway for biosimilars in the United States has yet to be determined.

"Follow-on biologics will likely be similar and not interchangeable, following what's going on in Europe," Mr. Long says. "The challenges of interchangeability and equivalence will not be overcome overnight. I think the likelihood is that these follow-on biologics will be similar in nature and not equivalent."

According to FDA officials, the proposal for the agency's fiscal year 2009 budget will seek new statutory authority to allow FDA to approve abbreviated applications for certain biologic products licensed under the Public Health Service (PHS) Act. Currently, no abbreviated pathway for these products, commonly referred to as follow-on protein products, exists in the PHS Act.

FDA officials say the agency has not submitted a formal proposal or legislative language to Congress regarding follow-on protein products, but regulators are interested in moving forward with the review of such products.

The agency's suggestions in the proposed budget include provisions to ensure the safety and effectiveness of these biologic products for patients. The proposal will include a predictable and public guidance process for licensing follow-on protein products under the PHS Act. The proposal will prescribe the type of data required for the FDA to review applications for follow-on protein products and will require labeling for safety concerns related to the interchangeability of these products. In

addition, the proposal will include adequate intellectual property protections to preserve continued robust research into new and innovative life-saving medications.

A MARKET IN FLUX

Generic companies are extending their reach into specialty products and developing reformulations. Teva Pharmaceutical Industries and Barr Pharmaceuticals are two such companies, and they will now likely present even stronger competition for pharma after the July 2008 announcement by Teva that it would acquire Barr for about $7.46 billion.

The fastest-growing generic segment will be cardiovascular drugs, WITH CAGR OF 19.8% BETWEEN 2007 AND 2012.

The combined company will have more than 500 currently marketed products; more than 200 ANDAs pending with the FDA with annual brand sales of greater than $120 billion; and about 3,700 product registrations pending with various regulatory authorities worldwide, primarily in Europe.

Teva executives say the acquisition bolsters the company's specialty pharmaceutical platform, bringing together Barr's women's health portfolio with Teva's respiratory franchise, as well as augmenting Teva's biologics capabilities.

Consolidation among major generic companies is going to continue, says Kay Morgan, senior VP, drug products and industry standards research and compliance, at Gold Standard.

"There is not enough room in that market for all the players, particularly with the consolidation that is happening at the chain pharmacy level," she says. "Generic companies sell to the retail pharmacies. Two years ago, generic companies could go to one of the top 10 retail chains and get part of that market. Today, the number of chains is shrinking, and when there are fewer chains, there is less opportunity to participate in this space."

The Barr-Teva merger move comes on the heels of two other deals: the June announcement of Sanofi-Aventis' intention to acquire Zentiva, a Czech generics company, for about $2 billion (1,655 million), and Daiichi Sankyo's announcement that it would acquire India's Ranbaxy Laboratories for about $8.5 billion.

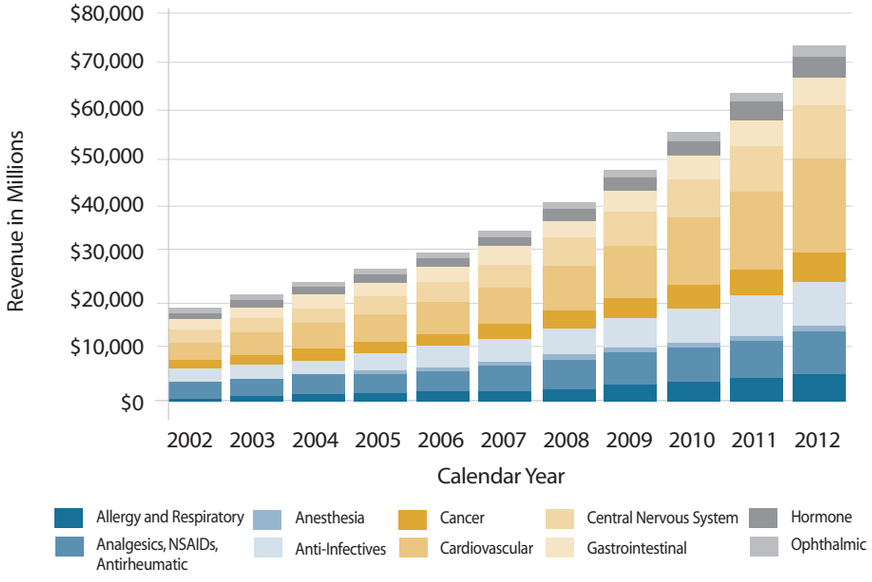
Acquiring a generic company is not a new trend; for example, Pfizer acquired the generic company Greenstone in 2003. But some industry experts have called into question these acquisitions, saying generic companies

BEST-SELLING PRESCRIPTION DRUGS WITH EXPECTED PATENT EXPIRATIONS — 2006-2012

EXPIRATION YEAR	BRAND NAME	BRAND MANUFACTURER	DISEASE OR INDICATION	2007 REVENUE ($ IN MILLIONS)
2009	Arimidex	AstraZeneca	Breast cancer	$1,730
2009	Valtrex	GSK	Viral infections	$1,370
2009	Tricor	Abbott	Antilipidemic	$1,218
2010	Taxotere	Sanofi-Aventis	Breast cancer	$2,743
2010	Protonix	Wyeth	GI disorders	$1,911
2010	Levaquin	J&J	Bacterial infections	$1,646
2010	Gemzar	Eli Lilly	Pancreatic cancer	$1,592
2010	Aricept	Eisai and Pfizer	Alzheimer's disease	$401
2011	Zyprexa	Eli Lilly	Schizophrenia	$4,761
2011	Seroquel	AstraZeneca	Schizophrenia	$4,027
2011	Plavix	BMS	Atherosclerosis	$3,550
2011	Actos	Takeda	Diabetes	$3,329
2011	Actonel	P&G	Osteoporosis	$1,620
2011	Avapro	BMS	Hypertension	$1,584
2011	Atacand	AstraZeneca	Hypertension	$1,287
2011	Lescol	Novartis	Cholesterol	N/A
2011	Xeloda	Roche	Cancer	N/A
2012	Diovan	Novartis	Hypertension	$5,012
2012	Singular	Merck	Asthma	$4,300
2012	Lovenox	Sanofi-Aventis	DVT	$3,829
2012	Crestor	AstraZeneca	Antilipidemic	$2,800
2012	Viagra	Pfizer	ED	$1,760
2012	Detrol	Pfizer	Overactive bladder	$1,190
2012	Premarin	Wyeth	Menopause	$1,055
2012	Allegra	Sanofi-Aventis	Rhinitis	$1,035
2012	Evista	Eli Lilly	Osteoporosis	$1,009
2012	Kaletra	Abbott	Viral infections	$538
2012	Sustiva	BMS	HIV infection	N/A

Source: Kalorama Information, New York. For more information, visit kaloramainformation.com.

THE WORLD MARKET FOR PRESCRIPTION GENERIC DRUGS REVENUE BY SEGMENT 2002-2012



Source: Kalorama Information, New York. For more information, visit kaloramainformation.com.

BRAND-NAME COMPANIES WITH GENERIC SUBSIDIARIES

GENERIC COMPANY	PARENT COMPANY
American Pharmaceutical Partners	American Bioscience Inc.
Bedford Labs	Boehringer Ingelheim
ESI Lederle	Wyeth
Ethex Corp.	KV Pharmaceuticals
Falcon Pharmaceuticals	Alcon
E. Fougera	Nycomed
Genpharm	Merck KGaA
Glades Pharmaceuticals	Stiefel Labs
Inwood Labs	Forest Labs
Kremers Urban Development	Schwarz Pharma
Mova Labs	Alara Healthcare
Roxane Labs	Boehringer Ingelheim
Sandoz	Novartis
Sidmak Labs	Sobel NV
Technilab Pharma	Merckle
Warrick	Schering-Plough
West Ward Pharmaceuticals	Hikma Pharmaceuticals

Source: Kalorama Information, New York. For more information, visit kaloramainformation.com.

are separate businesses and are outside pharmaceutical companies' core competencies.

"It is extraordinarily difficult for pharmaceutical acquisitions of generics to be successful," says Jeffrey Yordon, founder, president, and CEO of Sagent Pharmaceuticals. "The cost structure is wrong. The culture is wrong. Their ability to empower their people to make deals doesn't go along with the detailing mentality that proprietary multinational companies have."

Ms. Morgan says the larger branded pharmaceutical companies aren't flexible enough for the decision-making required to sell generic products.

"Most brand companies are very large and have many layers of decision-making," she says. "When they need to lower a price, they have to go through several layers. At generic companies, there are only one or two layers."

Still, executives at Daiichi Sankyo are undeterred and say the transaction is fully in line with the company's goal to be a global pharma innovator as outlined in its vision for 2015.

According to a media representative from Daiichi Sankyo, the company has competencies in R&D, quality control, regulatory, and so on that are common between proprietary and generic businesses, and Ranbaxy knows the generic market. The two companies have opportunities to learn from each other and leverage one another's competencies.

Analysts at Deutsche Bank say the acquisition of generic companies can provide larger drug firms with a hedge against a branded drug market in which more than $70 billion in revenue is set to expire through 2012. Such acquisitions could also give larger drug companies wider market access and help boost

THE GENERICS MARKET IS BECOMING MORE GLOBAL, AND THE PLAYERS ARE BIGGER THAN EVER.

brand awareness. Worldwide, the generic sector looks likely to deliver between 9% and 12% growth from 2007 to 2012, more than the 4% to 7% expected growth among branded products.

According to Dr. Doyle, the approach companies are taking has changed, and generic units are now considered to be strategic business organizations.

"There is a concerted effort to build these businesses," he says. "This goes hand-in-hand with the industry theme of targeted medicine: treating the right patient at the right time with the right medicine. There is more integration now with the branded business model; in the past, a generics unit represented a diversified profit center."

PAYER INFLUENCES

Also driving the increased use of generics has been the implementation of Medicare Part D. A recent study by Wolters Kluwer Health, a division of Wolters Kluwer, shows a large increase in the use of generics amid the introduction of Medicare Part D.

Before January 2006 when the Medicare Part D program commenced, the generic-to-brand ratio was even, with 50% of Medicare Part D patients overall using generics and 50% using brands. By the end of 2006, within the Medicare Part D population, that split increased to 56% for generics versus 43% for brands.

TIPS FOR MARKETING FOLLOW-ON BIOLOGICS

FOLLOW-ON BIOLOGICS ARE A FOREGONE CONCLUSION IN THE UNITED STATES. TOO MUCH MONEY IS AT STAKE. THE MORE DIFFICULT DISCUSSION STARTS WITH HOW BRANDED COMPANIES CAN COMPETE.

The financial pull on reimbursement organizations and the constituent push on Congress for less expensive biotechnology treatments will inevitably lead to a regulatory approval pathway for so-called follow-on or generic biologics.

Traditionally, biologics could count on long marketplace exclusivity to make up for the high cost of development, a cost that typically took 10 to 13 years to recoup. This is all about to change.

Generic biologics will force investors and executives alike to reassess return on investment. The most conservative analysts estimate that follow-on biologics will cut biopharmaceutical revenue by 25%. The sales of many biologics will not be enough to justify the cost of their creation.

Rather than looking to cut margins in manufacturing, biopharmaceutical executives can gain more marketplace leadership by taking a page from other industries and differentiating themselves in the eyes of patients, healthcare providers, and reimbursement agencies. This starts in product development by figuring out what the customer wants, not just what the patient needs.

TIP NO. 1: Focus on the Customer

To incorporate the voice of the customer, focus on gathering and analyzing the medical needs and desires of prospective patients. Assign sales and marketing personnel to learn the desires of healthcare providers and patients through interviews and surveys.

With this information in hand, product development teams can incorporate these as differential characteristics. Customer information can lead to a redesign of packaging, a preferential set of dosing parameters to target, or even a list of drugs typically taken by the proposed patient population — and thus a list of drug interactions to avoid.

This information is powerful on two fronts. First, customer information like this has historically been seen as proprietary by the courts, and thus not open to review by a generic competitor; and second, this information can let the company accentuate patient lifestyle improvements or healthcare provider margins, providing an edge over generics.

TIP NO. 2: Changing the Role of Sales

Sales and marketing executives need to learn how to ask the right questions to diagnose what the provider and the patient would prefer in terms of lifestyle, ideal dosing, labeling, and so on. This requires building trust with providers and not simply pitching product or providing samples.

This also requires a cross-functional team. Regulatory affairs needs to review the survey material and anticipate questions to ensure no promotion of products in development. Legal needs to ensure that intellectual property and trade secret information are not accidentally shared in conversation.

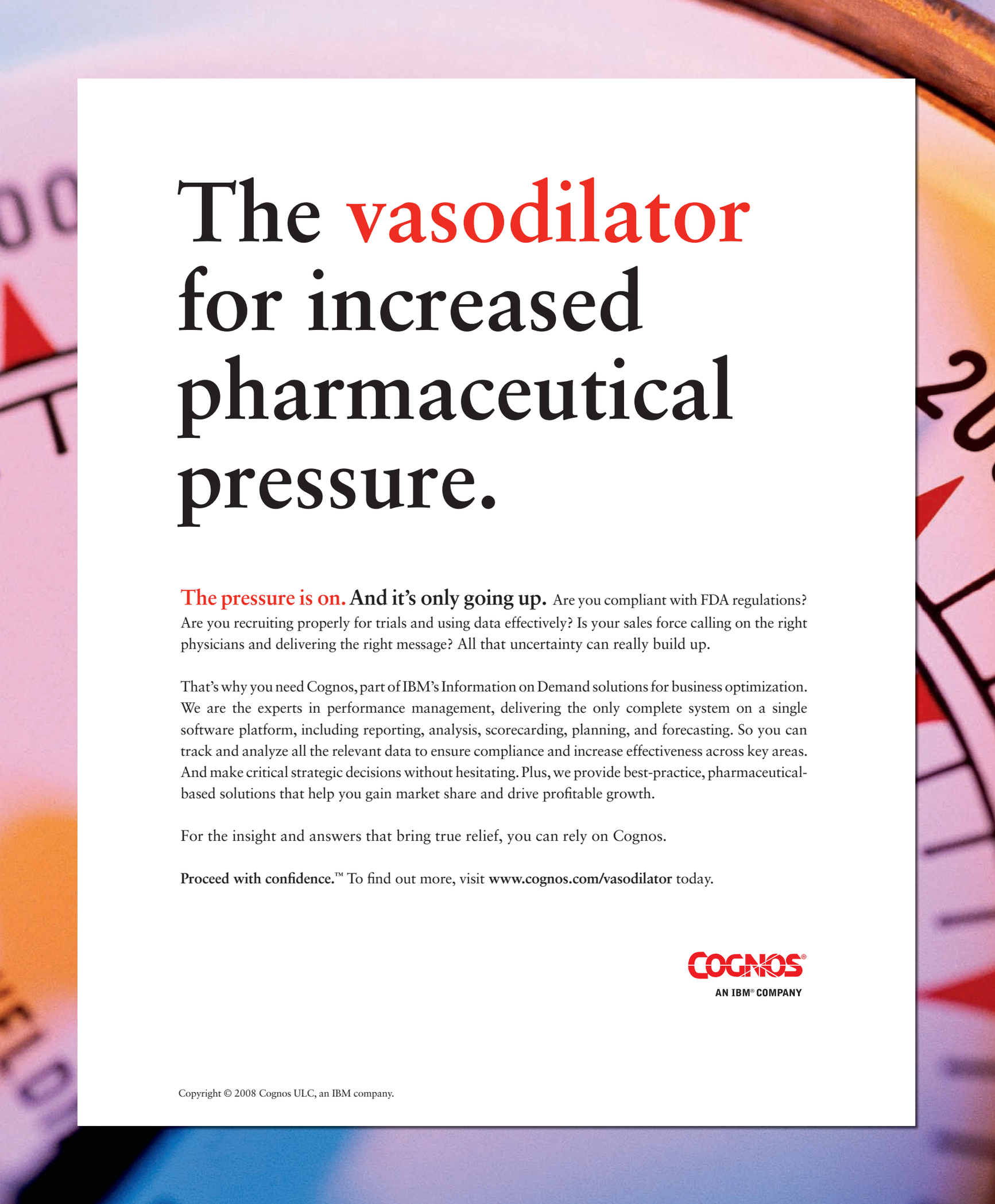
TIP NO. 3: Observation as a Technique

Harvard Business School's Dorothy Leonard has cited the example of a medical device firm whose representatives watched a surgical operation to get new ideas to bring back to product development.

During the operation, the medical device representatives noticed that the surgeon's ability to see the micro tools inside the patient was interrupted every time a nurse walked between the surgeon and the video screen display. This information was taken back to product development engineers who developed a small screen that could be worn by the surgeon.

Once the salesforce has added information gathering to its repertoire, it's time to examine all the other functions within the company for their contribution to product development and competitive capabilities.

Source: Cerulean Associates LLC, Williamsburg, Va. For more information, visit ceruleanllc.com.



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THE GENERICS MARKET IS CROWDED, AND MANY COMPANIES ARE MAKING THE DECISION TO EXIT THE MARKET QUICKLY ONCE THEY REALIZE WHAT THEIR SHARE OF THE MARKET COULD BE.

DR. JOHN DOYLE
Quintiles Consulting

THE GREATER FOCUS ON GENERIC UTILIZATION BY THE HEALTHCARE INSURANCE INDUSTRY AND THE GREATER VOLUME OF GENERICS AVAILABLE HAVE NOW APPLIED ADDITIONAL PRESSURE ON PHARMA COMPANIES TO DEMONSTRATE VALUE TO DEFEND PRICE ON MULTIPLE FRONTS.

But by 2007, that trend became even more pronounced, with 63% of all Medicare Part D prescriptions going to generics versus 37% for brands, a split of more than 26 percentage points.

Among those in the coverage gap who discontinued their brands, only 6% returned to their branded medication after leaving the gap.

Cardiovasculars will account for 26.2% OF THE GENERIC MARKET, while analgesics, NSAIDs, and anti-rheumatic drugs WILL BE 12.2%.

Industry experts say payers are driving fundamental changes in the pharmaceutical industry.

"Payers are increasing their use of utilization management strategies," Dr. Doyle says. "They are coming up with new ways to channel utilization in their healthcare plans toward generic use. For instance, they are adding a coinsurance-based tier to their formularies or coming up with additional ways to limit dispensing of branding therapeutics, such as a step-therapy formula that mandates generics first, or simply raising the branded tier's copay even further to encourage their members to use generics. This makes for a more competitive market."

He says the large number of generics on the market now has an impact beyond the brand leader, and this is forcing the pharmaceutical industry to demonstrate the value of their products in a broader context.

A better strategy for some pharma companies, according to some industry experts interviewed, is authorized generics.

Dr. Doyle says the use of discounts and rebates as a way for branded companies to try to regain market share from generic products is on its way out.

"The days of linking rebates to the volume of the medicine used or the market share of the drug are numbered," he says. "This is a crude and reactive way of trying to hold onto market share in the face of generic encroachment. A better approach would be to endorse and support the use of generics and target a particular subpopulation in which it would make sense to continue to be targeted by a branded drug."

Dr. Doyle says a proactive pay-for-performance model could better position companies and would provide payers with an understanding of a product's value in the marketplace.

"Manufacturers and payers would have a better understanding of the utilization patterns of a drug and the outcomes that are achieved," he says.

"Branded manufacturers could create a pay-for-performance contract based on a measurable and mutually agreed upon health outcome," he continues. "The process will require feasibility testing and retrospective data mining to calibrate the outcome measurement. The generic companies are not going to be in a position to do that as well as the branded companies."✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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