BY CYNTHIA BORDA

ODA
THE ORPHAN DRUG ACT

25 YEARS
1,800 DESIGNATIONS
319 PRODUCT APPROVALS
AND COUNTING

THE ORPHAN DRUG INDUSTRY HAS COME A LONG WAY. Since the implementation of the U.S. Orphan Drug Act in 1983, this groundbreaking legislation has POSITIVELY IMPACTED AS MANY AS 12 MILLION AMERICANS WITH RARE DISEASES.

There have been many clinical and marketing achievements since Jan. 4, 1983, when the Orphan Drug Act (ODA) was passed. In the past two and half decades more than 1,800 treatments have been designated with Orphan Drug status, and 319 products have been approved by the Food and Drug Administration compared with a mere 10 products developed before 1983.

The ODA provides development incentives to companies through tax credits for the cost of clinical research, grant funding to defray the costs of clinical testing, assistance in clinical research design, seven-year exclusivity for marketing the orphan drug, and a waiver of the Prescription Drug User Fee Act filing fees.

An orphan drug is designated by the FDA as a treatment for a rare disease, which is a disease or condition affecting less than 200,000 Americans. The National Institutes of Health estimates that there are 6,000 rare diseases affecting 25 million Americans.

"Quite a lot has changed since the legislation was passed 25 years ago," says Timothy Coté, M.D., MPH, director of the FDA's Office of Orphan Products Development (OOPD). "There have been amendments to streamline the process but the original spirit has remained. There is a ramped-up process that clearly has been successful as demonstrated by the increase in ODA designations in the last three years."

The Market

BCC Research reports that total global market sales for orphan drugs were $58.7 billion in 2006 and are expected to reach $81.8 billion by 2011. Biologics dominate the orphan drug industry, accounting for more than 60% of the market according to a 2007 market analysis by BCC Research; 2006 sales of orphan biologics were $35.3 billion, an increase of $5.1 billion from 2005. The market for biologic orphan drugs is expected to increase to $53.4 billion by 2011.

Of the drugs approved, 32% are biologic drugs. Within nonbiologics, synthetic/semi-synthetic drugs accounted for 62% of total orphan drug approvals, and synthetic polypeptides and hormones together accounted for 6%. Among biologics, growth hormones and growth factors together have the largest number of approvals at 8% of the total. Market approvals received for plasma products

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▲ DR. MICHAEL BOSS
Xanthus Pharmaceuticals

THE ORPHAN DRUG ACT ALLOWS AN EXCLUSIVE MARKET PERIOD OF SEVEN YEARS FOLLOWING APPROVAL, WHICH IS A VERY IMPORTANT DRIVER FOR THE DEVELOPMENT OF THESE PRODUCTS.

ROB GLIK ▼
IMS Health

PAYERS EVENTUALLY WILL SHIFT THEIR COST BURDEN FOR ORPHAN DRUGS TO PATIENTS. PATIENT ASSISTANCE PROGRAMS WILL BECOME CRITICAL AS A WAY TO ATTRACT AND TARGET THE PATIENT.

account for 5%, whereas monoclonal antibodies and interleukins/interferons each account for 4% of total approvals.

According to a 2007 report from the Pharmaceutical Research and Manufacturers of America (PhRMA), biopharmaceutical research companies in the United States currently have 303 orphan medicines in human clinical trials or awaiting FDA approval. This compares with 189 medicines in development in 1992.

Advances in this drug class have occurred not only because of the ODA but also because of the increased understanding of molecular and genetic causes of disease and the development of new tools for research exploration.

"All of the signs point to traditional pharmaceutical blockbusters coming to an end, and personalized medicine coming more into vogue," says Michael Boss, Ph.D., chief business officer of Xanthus Pharmaceuticals. "This trend will be true for rare diseases as well. The incentives to produce orphan drugs are not meaningful for big pharmaceutical companies."

A major area of research in rare diseases is rare cancers, accounting for more than a one-third of research. Other important areas are neurological disorders, multiple sclerosis, muscular dystrophy, genetic disorders such as cystic fibrosis, and infectious diseases such as anthrax and West Nile virus.

Xanthus Pharmaceuticals has two products that have been granted orphan drug designation as rare cancer therapies; both products are awaiting FDA approval. The first is an oral fludarabine, an antimetabolite cytotoxic agent for treating chronic lymphocytic leukemia.

Xanthus licensed the exclusive rights to develop and commercialize oral fludarabine in the United States from Schering AG (now Bayer Schering Pharma AG) in October 2006.

Chronic lymphocytic leukemia (CLL) is a cancer of the white blood cells and bone marrow, which arises predominantly in older people. CLL is the most prevalent type of leukemia and, according to the American Cancer Society, about 15,300 new CLL cases were diagnosed in the United States in 2007. Oral fludarabine is currently marketed by Bayer Schering Pharma AG in the European Union and Canada for the treatment of relapsed B-cell chronic lymphocytic leukemia (CLL).

"The intravenous formulation has been approved since 1991, but the oral formulation should eliminate the hassle of daily infusions in the physician's office and the cost associated with this type of treatment," Dr. Boss says.

Xanthus' second product is Xanafide (amonafide), which just started Phase III trials and is under a special protocol agreement (SPA) with the FDA. It is a unique topo-2 inhibitor for the treatment of secondary acute myeloid leukemia.

Another company that is developing several treatments for rare diseases is Ovation Pharmaceuticals. In fact, Ovation markets the first drug approved through the ODA.

"Panhematin is still being used after 25 years for treating acute intermittent porphyria, and we have been growing volume at 20% CAGR over the last four years," says Michael

The NIH estimates that there are 6,000 rare diseases affecting 25 million Americans.

Burke, chief commercial officer of Ovation Pharmaceuticals.

Porphyria is a rare disorder that, if left untreated, may lead to long-term or permanent paralysis, coma, or even death.

Within Ovation's portfolio of drugs that concentrate on areas of unmet need is NeoProfen (ibuprofen lysine), which is used to treat patent ductus arteriosus (PDA). It was approved and launched by Ovation in 2006. PDA is a potentially life-threatening congenital heart defect in premature infants, in which the blood vessel in the heart fails to close after birth. In 2003, according to the March of Dimes, 2% of all live births with fewer than 32 weeks of gestation were at risk of PDA-related problems. About 30,000 infants are treated pharmacologically each year for PDA.

Two Ovation drugs in development with orphan drug designations are Sabril for infantile spasms and clobazam for Lennox-Gastaut Syndrome.

Sabril (vigabatrin) is being reviewed by the FDA as a monotherapy for patients with infantile spasms, which has an orphan indication, and as an adjunctive treatment for adults with refractory complex partial seizures. The company is anticipating approval for these indications later in the year.

To date, there are no medications approved by the FDA for the treatment of infantile spasms, a devastating form of epilepsy that usually strikes infants between 3 months and 6 months old. In the United States, infantile spasms constitute about 2% of childhood epilepsy and 25% of epilepsy with onset in the first year of life. Clobazam is in Phase III trials as an adjunctive treatment for LGS, which is a catastrophic form of childhood epilepsy that frequently persists into adulthood. It is responsible for about 3% to 10% of all childhood epilepsy.

Since 1983, more than 1,800 treatments have been designated with orphan drug status, and 319 products have been approved by the FDA.

Meeting the Challenges

Despite the incentives provided by the OOPD there remain challenges, experts say.

"Obviously, when companies are developing drugs to treat rare diseases there is less of a population to draw from for clinical trials,"

GLOBAL REIMBURSEMENT ISSUES

Although a fully functioning system for orphan drugs has been initiated in the EU via the Committee on Orphan Medicinal Products of the EMEA, each country makes its own decisions on the pricing and reimbursement of orphan drugs. If payers think the budget impact will be too high, they may restrict the reimbursement of new orphan drugs to subpopulations of patients or, more frequently, force patients to go to specialist centers.

FRANCE: Patients diagnosed with rare diseases must attend a "Centre of Reference." Specialists at these centers confirm diagnosis before the patient can receive a high-priced orphan drug.

ITALY: "Rare Disease centers" are the only official centers allowed to prescribe orphan drugs. These centers collect efficacy and safety data relating to products used; they also enable the tracking of any indication restrictions placed on these products.

UNITED KINGDOM: Access is often controlled by centers designated by the National Specialist Commissioning Advisory Group. Control is usually designated only for ultra-orphan drugs (less than 10,000 patients), such as those used to treat lysosomal storage disorders (e.g. Gaucher's disease, Fabry's disease, and mucopolysaccharidosis). Only the six nationally designated centers are funded to prescribe these treatments.

Although the cost of orphan drugs is not a major concern today (they make up 1% or less of most nations' pharmaceutical budgets), the number and cost of such products is increasing. Of 62 drug approval applications submitted to the EMEA last year, 13 were for orphan drugs. In the United States, 61 products received orphan designation in the past 12 months, including 11 new marketing approvals. In addition, six orphan drugs launched in the past 24 months cost more than $100,000 annually.

Given the increasing scrutiny of market access for orphan drugs, improved clinical data will be more critical moving forward. In the EU, payers are already more critical of clinical data for orphan drugs, so the quality of the data will become even more important. For example, payers will want to see real endpoints rather than surrogate endpoints.

The use of health economics data in the EU will also become more critical in the future. More EU payers will scrutinize budget impact, comparing the economic benefits of a new orphan drug with alternative therapies or with the disease burden, potentially creating a less favorable market access environment for future orphan launches.

The labeled indication is critical to access. In the United States, most payers will not cover off-label use, but do not restrict the labeled indication either. Ensuring that the indication is broad enough to maximize the patient population while also restricting usage to severe patients to justify price, will become increasingly important.

Given the growing importance of proving the value of orphan drugs, it will be critical for companies to consider various factors in launching orphan drugs, including:

- Cost of alternative therapies
- Gain in life expectancy/survival data
- Patient yearly out-of-pocket costs
- Budget impact and potential payer behavior
- Patient life-time maximum coverage in the United States

Corporate and personal responsibility for patient access also needs to be considered, such as having a comprehensive patient assistance program and working with patient assistance groups to ensure access for those with limited financial means.

Source: IMS Pricing & Market Access Review 2006, authored by Rob Glik and published by IMS Consulting, Pricing & Reimbursement Practice, IMS Health, Norwalk, Conn.
For more information, visit imshealth.com.

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Dr. Boss says. "Companies also have to be cognizant of the cost of development, which is not necessarily linked to market opportunity."

Mr. Burke agrees that the smaller clinical populations are a challenge and one that can add to the time to complete a clinical study.

"When dealing with a rare disease and a smaller population, the clinical program timeline must take condition incidence and prevalence into consideration," he says. "Fortunately, the FDA understands this and, where appropriate, allows some flexibility."

Mr. Burke says in addition to clinical obstacles there are marketing challenges that need to be overcome as well.

"In some cases, new orphan products will be the first therapy offered for a specific disease," Mr. Burke says. "Marketers may need to start from scratch, defining market segments and targets. Therefore, the challenge is to find both the patients affected by the condition and the physicians who would treat those patients without existing data. Creativity is key in these cases."

To overcome some of the obstacles, he suggests working closely with advocacy and professional groups, targeting centers designated for the specific condition, and reaching out to thought leader networks around the world.

"Launching an orphan drug has its challenges, but patient demand is not one of them because of significant unmet needs in orphan markets," Mr. Burke says. "The opportunities lie in education; we have the opportunity to provide valuable education about the disease and treatment and to bring needed pharmaceutical therapies to those with few, if any, treatment options."

In addition to fewer patients for clinical studies and limited data for promotional purposes, companies that focus on orphan drugs are facing increased scrutiny by payers in terms of reimbursement.

Today, orphan drugs enjoy very good market access in the United States and European Union. But Rob Glik, senior principal of pricing and reimbursement at IMS Health, warns that given the large number of recently launched and pipeline orphan drugs, access may start to become more difficult, especially in the European Union.

"Today in the United States, payers do not have a separate reimbursement process for orphan drugs but often solicit input from key opinion leaders before determining appropriate prior authorizations," he says. "KOLs are usually favorable toward any new orphan therapy since it enables them to treat previously untreatable patients, and payers traditionally put no major restrictions on these drugs. For example, MCOs and PBMs typically do not limit patient population reimbursement, other than by enforcing reimbursement for the labeled indication. For products on the medical side, MCOs have historically covered all infused orphan therapies — even the most expensive ones.

▲ **MIKE BURKE**
Ovation Pharmaceuticals

LAUNCHING AN ORPHAN DRUG HAS ITS CHALLENGES, BUT PATIENT DEMAND IS NOT ONE OF THEM BECAUSE OF SIGNIFICANT UNMET NEEDS IN ORPHAN MARKETS.

FDA AND THE ORPHAN DRUG ACT

The law behind the Orphan Drug Act offers a drug developer certain financial benefits and incentives from the government in exchange for researching, developing, and receiving approval for a drug intended to treat a rare disease or condition:

- Tax credits for the costs of clinical research
- Annual grant funding to defray the costs of qualified clinical testing expenses ($14 million total for 2008)
- Assistance in clinical research study designs
- Seven-year period of exclusive marketing after an orphan drug is approved
- Waiver of Prescription Drug User Fee Act (PDUFA) filing fees (about $1,000,000 per application for FY 2008)

These benefits will help manufacturers recover the costs of developing a drug for small patient populations.

Since being enacted in 1983, the ODA has been amended by Congress several times — 1984, 1985, 1988, 2007 — to provide further incentives for treatment development. In addition, in 1982 the FDA established the Office of Orphan Products Development (OOPD) to identify orphan products and to promote the development of those products that demonstrate promise for diagnosing or treating rare diseases.

Source: Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

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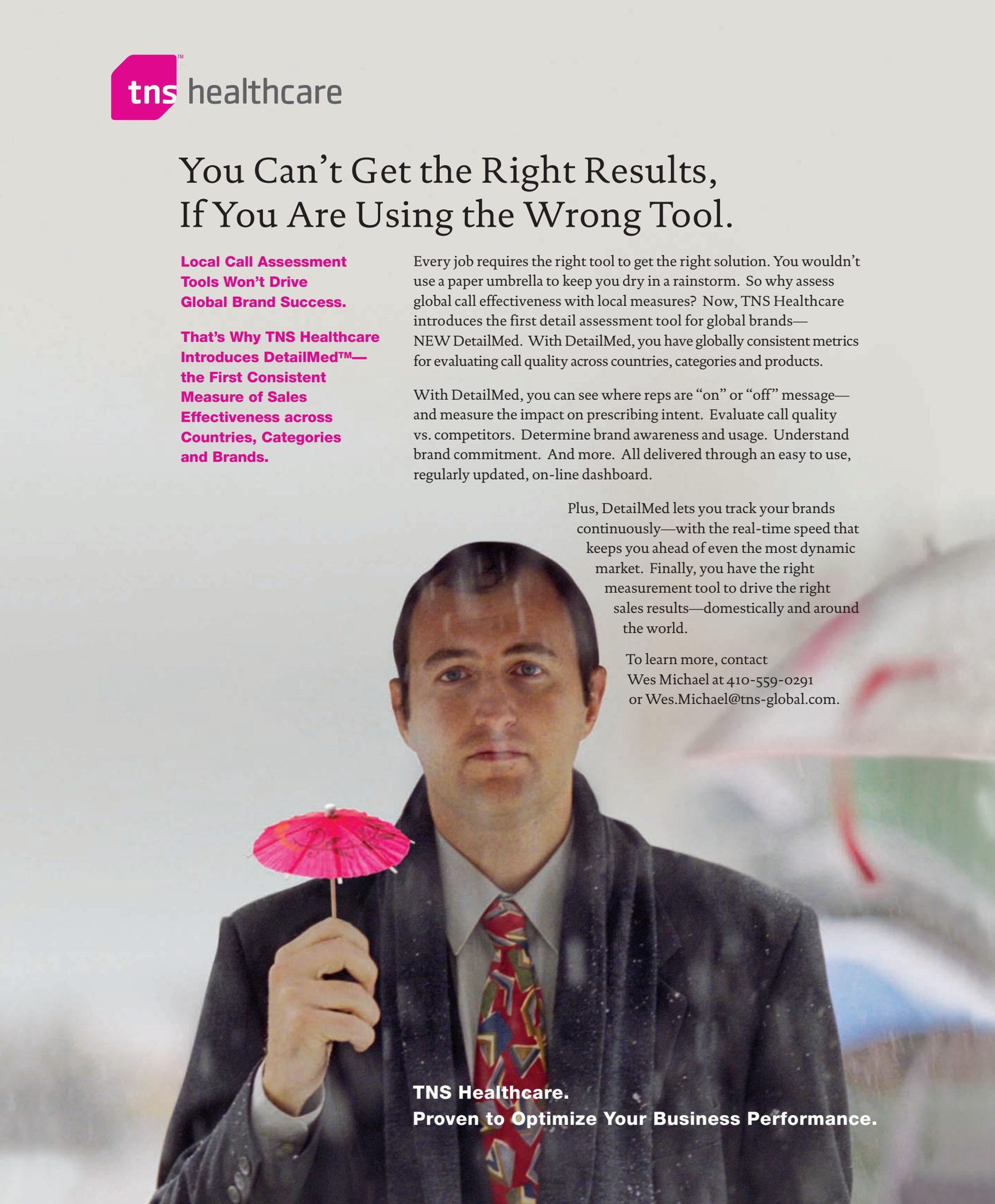

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"As with other non-orphan drugs, however, many payers are now passing more of the cost burden to patients by increasing the co-insurance or by moving products to the pharmacy side where the patient shares more of the cost burden," Mr. Glik continues. "Payers also are starting to manage expensive orphan drugs in the pharmacy channel, such as by placing them on fourth tiers with high co-insurance, thereby limiting access."

Given the current favorable access environment for orphan drugs, and the large number of new, expensive orphan drugs recently launched (at least 15 new orphan drugs have been launched in the past 24 months, including six priced at more than $100,000 per year), according to Mr. Glik, U.S. payers will inevitably consider becoming more restrictive. The current payer system, however, is limiting payers' ability to contain costs. Additionally, limited options for orphan diseases, as well as political sensitivity in this area, further reduce payers' abilities to be more restrictive with orphan drugs. (See box on page 68 for more information related to reimbursement issues.)

The Future of Orphan Drugs

While a great deal of progress has been made to address the needs of patients who suffer from rare diseases, FDA officials are working to further improve the process for the approval of orphan drugs.

"The new drug application is simple, but we want to make it simpler," Dr. Coté says. "We want to make it easier for companies, and we want to do additional outreach. The goal is to have a seamless process. Currently we ask for two requirements for orphan designation, a medical rationale that a company believes will be effective, and the statutory prevalence that less than 200,000 people are affected. This is purposely liberal in an effort to incubate ideas."

In fact, the U.S. and European drug regulatory agencies have adopted a single application form that may be submitted to both agencies when companies are seeking orphan drug designation. This is yet another step toward simplifying and speeding up the process by increasing efficiency and decreasing costs. Previously, companies had to apply to both the FDA and the European Committee of Orphan Medical Products, a part of the European Medicines Agency (EMEA).

ORPHAN DRUGS IN DEVELOPMENT

Autoimmune Disorders	16
Blood Disorders	3
Cancer	81
Cancer, Blood	42
Cancer, Skin	19
Cancer-related Conditions	9
Cardiovascular Diseases	7
Genetic Disorders	26
Infectious Diseases	28
Neurological Disorders	35
Respiratory Disorders	13
Transplantation	7
Other	37
TOTAL	**323**

Source: Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.
For more information, visit phrma.org.

The common application form contains a section for common information required by both the EMEA and the FDA. It also has sections for requirements unique to each agency. A sponsor that wants to submit an orphan designation application to the EMEA alone may also use this form. The EMEA and the FDA will still conduct independent reviews of such submissions to assure the data submitted meet the legal and scientific requirements of their respective jurisdictions.

"We hope to continue to broaden the scope of this office," says Dr. Coté. "Additionally, we hope to increase the grants program, which reached $14 million in 2007. Overall the infrastructure is in place. We are poised and ready to move forward." ✦

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

Experts on this topic

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