BY DENISE MYSHKO

The GLOBAL Regulatory Environment

The concerns of regulators around the globe lean toward the safety and the cost-effectiveness of prescription drugs.

Cost-containment has and will continue to be the buzzword as governments around the world struggle with slowing economies and rising healthcare costs. In fact, some industry experts are predicting that the current economic downturn will prompt payers in major markets to intensify cost-containment measures targeted at the pharmaceutical industry.

Mandatory price cuts or freezes are the measures that have the most immediate effect, according to a recent report from Decision Resources. Governments that operate reference-pricing systems might expand the scope of these systems or reduce reference prices sharply. Longer term, governments will increasingly rely on health technology assessments and may restrict approvals and reimbursements for those products with little added therapeutic effect.

Pricing and reimbursement policies have become paramount to success, says Doug Jermasek, senior VP of global marketing and strategic development, cardiometabolic and renal diseases, at Genzyme.

"Reference pricing, parallel importation, Internet pharmacies, and counterfeiting are important concerns for any global pharma company," he says. "Tiered product pricing strategies are becoming unsustainable. In the not-too-distant future, biopharma companies will have to become comfortable with their lowest selling price in any single market on the assumption that all other countries will demand the lowest price. Difficult decisions will have to be made that may result in a company choosing not to launch in a country that demands a price that is too low when applied to the global average selling price."

EVIDENCE-BASED MEDICINE IS FAST BECOMING ONE OF THE KEY CONCEPTS IN CLINICAL AND REIMBURSEMENT PRACTICES IN THE DEVELOPED WORLD.

ARROWHEAD PUBLISHERS

Analysts from IHS Global Insight point out that in emerging markets, regulators will be more concerned with raising standards and harmonizing policies with international standards.

"We're moving more and more toward a parallel environment around the world," says Brad Thompson, Ph.D., chairman, president, and CEO of Oncolytics Biotech. "The regional differences are beginning to disappear. Some of this is planned and some of it is just happening. This will make it a lot easier for pharmaceutical companies."

PRICING AND REIMBURSEMENT

Governments, especially those in Western Europe, have increased their cost-containment of drugs through incentivizing the prescribing of generics, says Raymond Panas, Ph.D., director of international clinical development at Sucampo Pharmaceuticals.

"Additionally, some countries are seeking a cost-benefit analysis and direct product comparison with available products before approving new drugs," he says. "While this is true in many countries, the United Kingdom, France, and Spain seem the most focused on cost-containment."

According to Arrowhead Publishers, evidence-based medicine (EBM) is fast becoming one of the key concepts in clinical and reimbursement practices in the developed world. In Europe, and in particular within the European Union, EBM has evolved much further beyond the formation of clinical guidelines.

The UK is regarded by many as a pioneer in the use of EBM in pharmaceutical reimbursement, through the creation of its National Institute of Clinical Excellence (NICE). While its guidelines are not legally binding, the recommendations on pharmaceutical and medical treatment made by this independent department are generally followed for the purposes of reimbursement within the UK's National Healthcare Service (NHS).

"The pricing and reimbursement procedures within the EU/EEA have presented the most complex forum in which the pharmaceutical industry has to operate," says Patricia Lovell Hoare, executive VP of regulatory affairs at Chiltern. "European law dictates that from a commercial perspective the free passage of goods is one of the foundation cornerstones, yet regulatory procedures on licensed products have to go through the specific provisions designated for each national territory. Unlike other industries, the healthcare sector has a number of third parties whose intervention from a regulatory perspective — governments, insurance statutory, and private wholesalers and distributors — will impact the final price."

Under the UK's revised Pharmaceutical Price Regulation Scheme (PPRS), which went into effect in January 2009, branded drug prices will be cut. A 3.9% price cut for drugs sold to the NHS has been instituted as of February 2009, with a further 1.9% reduction scheduled for January 2010. The Department of Health also plans to introduce generic substitution beginning in January 2010.

PROF. GEORG-B. KRESSE ● *Roche*

A regulatory framework for biosimilars should require the demonstration of the similar nature of the new product and a chosen reference product in terms of quality, safety, and efficacy to ensure a consistent and high level of patient safety.

DR. MERVYN TURNER ● *Merck & Co.*

Despite the increasing demand for biosimilars among patients, physicians, payers, and legislators, a clear global regulatory path for their approval has not yet been established.

But, Dr. Panas says, as cost-containment is already affecting Europe and healthcare costs are becoming a concern in the United States, the United States may be the country to watch.

"Until now, the United States has had free pricing of prescription medicines, and companies have been able to increase prices over time," he says. "HMOs and other healthcare plans have already started some cost-containment efforts through the promotion of generic prescribing and entering into risk-sharing agreements with pharmaceutical companies for high-priced drug products."

Dr. Panas says while quality of life is seldom a rationale for drug approval, this measure can help demonstrate the superiority of a product and potential cost-benefit ratio in comparison to standard-care products.

"While efficacy and safety endpoints are still key, an analysis of a new drug candidate's ability to deliver a greater health benefit needs to be integral to new drug development strategies," he says. "Additionally, as regulatory agencies consider pharmacoeconomic measures, quality of life can further help play into that analysis. The selection of an appropriate quality-of-life measurement should be carefully considered during the drug-development process, as not all measures are equal or appropriate for various medical conditions."

Mr. Jermasek says his hope is that the global reimbursement authorities will understand that innovation comes at a price.

"It takes a lot of time and a lot of money for pharmaceutical companies to develop innovative products, and if the companies don't have the opportunity through reasonable pricing, premiums, or otherwise, then fewer R&D activities will happen and less innovation will occur," he says. "It's in the general good of society globally to reward innovative products with appropriate prices for those products. I think the trade-off is that in order to purchase these innovative and more expensive products, the pressure on less-innovative products will become ever greater."

A recent study by the Rand Corporation looked at the impact of regulation on pharmaceutical revenue in the 19 nations that are members of the Organisation for Economic Co-operation and Development. They found that imposing price controls would offer a modest benefit to the current generation but pose substantial risks and potentially high costs for later ones. By contrast, financing consumer price reductions without affecting manufacturer revenue appears beneficial for both current and future generations.

Rand used the Global Pharmaceutical Policy Model, a demographic and economic tool for estimating the effect of baseline health, health behavior, and rates of innovation on population health and mortality several decades into the future. The model incorporates the effect of pharmaceutical breakthroughs. In general, price controls reduced life expectancy over time.

BIOSIMILAR TRENDS

Analysts from IHS Global Insight say an increasingly cost-conscious environment will speed up the development of legislation on biosimilar treatments, allowing more such medicines to be approved in the EU, Japan, and Switzerland over the next 12 months.

As an increasing number of biologic products approach the end of their patent life, there has been a growing interest in developing biosimilars, says Mervyn Turner, Ph.D., chief strategy officer for Merck & Co., and senior VP, worldwide licensing and external research, for Merck Research Laboratories.

"Despite the increasing demand for such products among patients, physicians, payers, and legislators, a clear global regulatory path for the approval of biosimilars has not yet been established," he says.

The European Union was the first region globally to introduce, in 2005, a particular regulatory framework for biosimilars. Several other countries — Australia, Switzerland, Turkey, Malaysia — have adopted or are considering — Canada and Japan — regulatory pathways that follow the same principles.

In November 2008, the EMEA also recommended the approval of two additional biosimilar versions of filgrastim: Zarzio by Sandoz (Switzerland) and Filgrastim Hexal by Hexal (Germany).

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Neupogen is the Amgen trademark for Filgrastim, which is recombinant methionyl human granulocyte colony-stimulating factor.

Outside Europe, Canada and Japan are two highly regulated markets that are most advanced in terms of passing a biosimilars approval pathway. Both of these countries are expected to have a biosimilars approval pathway in place in 2009.

"A number of biosimilar products have been licensed in the EU, whereas other applications were rejected or withdrawn, demonstrating that this pathway is viable and appropriate to allow," says Prof. Georg-B. Kresse, VP, biologicals research strategy and communication, Roche. "Biosimilar products are not identical, but are at best similar to their reference products. Therefore, it is mandatory that the regulatory framework requires the demonstration of the similar nature of the new product and a chosen reference product in terms of quality, safety, and efficacy to ensure a consistent and high level of patient safety."

Prof. Kresse notes that the FDA has clearly stated that biosimilar proteins should meet the same high standards for approval as reference biological products.

"Although the regulatory pathway in the United States may be different from the EU regulation because of legal requirements, it is expected that the same scientific principles will apply," he says.

Scott Treiber, senior VP of clinical operations for inVentiv Clinical, says with regard to the kind of data required to file a biosimilar application, the EU legislation is based on the principle that a one-size-fits-all approach is unworkable in this area.

"The type and amount of preclinical and clinical data are not predefined in legislation, but are determined on a case-by-case basis, on the basis of the relevant scientific guidelines," he says. "This approach reflects the wide spectrum of molecular complexity among the various products concerned, ranging from relatively simple molecules such as insulin to far more complex ones. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class-specific."

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SCOTT TREIBER ●
inVentiv Clinical

Efforts for price control by national authorities will increase on a global basis, and hence it will be very important for companies to have a combined clear, well-defined, drug development and marketing strategy.

The first EMEA guideline on biosimilars was released for consultation in November 2004. This was a general guideline designed to introduce the concept of biosimilarity in scientific terms. Since then, a number of guidelines have been issued, most notably on general quality aspects; general preclinical and clinical aspects; product-class-specific preclinical and clinical aspects on insulins, growth hormones, erythropoietins, and granulocyte-colony stimulating factors; and immunogenicity of biotechnology-derived therapeutic proteins.

"All of these guidelines relate to molecules that can be thoroughly characterized with state-of-the-art analytical methods and for which extensive regulatory experience is available," Mr. Treiber continues. "From a legal perspective, it is not necessary that the EMEA issues guidance in one area to enable manufacturers to submit applications. Besides, EMEA guidelines are usually not legally binding alternative approaches that depart from available guidelines, if properly justified by the pharmaceutical manufacturer, may also be accepted. In the case of biosimilars, however, the legislation makes explicit reference to compliance with the detailed guidelines to be issued by the EMEA."

One company working aggressively to develop biosimilar products in the United States is Merck. In December 2008, Merck BioVentures was launched. This new division of Merck was created to build on the company's acquisition of GlycoFi, a New Hampshire-based biotech company that brought proprietary yeast-based glycoengineering technology to Merck and to capitalize on the market potential for follow-on biologics.

Additionally, in February 2009, Merck announced that it would acquire Insmed's portfolio of follow-on biologic therapeutic candidates and its commercial manufacturing facilities located in Boulder, Colo. ✦

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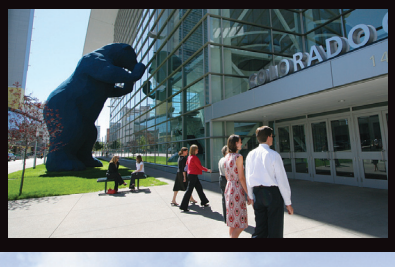

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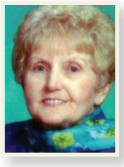

Eva Mozes-Kor

Ethics in Medicine and Research: Lessons from Dr. Mengele

Eva Mozes and her family were deported to Auschwitz Concentration Camp in 1944. On the selection platform at Auschwitz, Eva and her sister Miriam were identified as twins and taken to join other twins who were to become part of Dr. Josef Mengele's medical experiments. As twins, they were seen as nature's natural guinea pigs. One child was used as a control and the other had experiments conducted on her/him. If a twin died, the other twin was killed by an injection into the heart and comparative autopsies were done on the two.

Today Eva devotes much of her time to speaking about what happened to her and to serving the C.A.N.D.L.E.S. Holocaust Museum and Education center which she founded.

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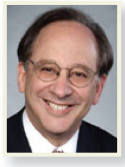

Bert A. Spilker, PhD, MD, FCP, FFPM

Dr. Spilker, is an independent consultant who was most recently the Senior Vice President of Scientific and Regulatory Affairs for PhRMA (Pharmaceutical Research and Manufacturers of America) based in Washington, D.C.

He was President and cofounder (in 1993) of Orphan Medical, Inc., a public pharmaceutical company that develops and markets important medical products for patients with uncommon diseases. He is well known as the author of 15 books on clinical trial methods and the processes of drug discovery and development. These books are considered by many as the standard references on clinical trials and drug development.

He has worked at four major pharmaceutical companies for over 20 years (Pfizer, Philips-Duphar, Sterling-Winthrop, and Burroughs Wellcome) in medicine discovery, development, and management.

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- **S032:** Civil and Criminal Liability from Clinical Trials: What are the Legal Risks?
- **S005:** First in Human Trials—Warning—Be Careful at Your Site
- **S049:** Liposomes as Nanocarriers in Biomedical Research and Medicine
- **S058:** Global Trial Planning—Determining the Optimum Mix of Countries and Sites
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- **S090:** Clinical Leadership: Exploring New Strategies for Service and Professionalization
- **S086:** The Genetic Information Non-Discrimination Act (GINA)
- **SP094:** Monitoring for Quality: Risk-Based Clinical Monitoring
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