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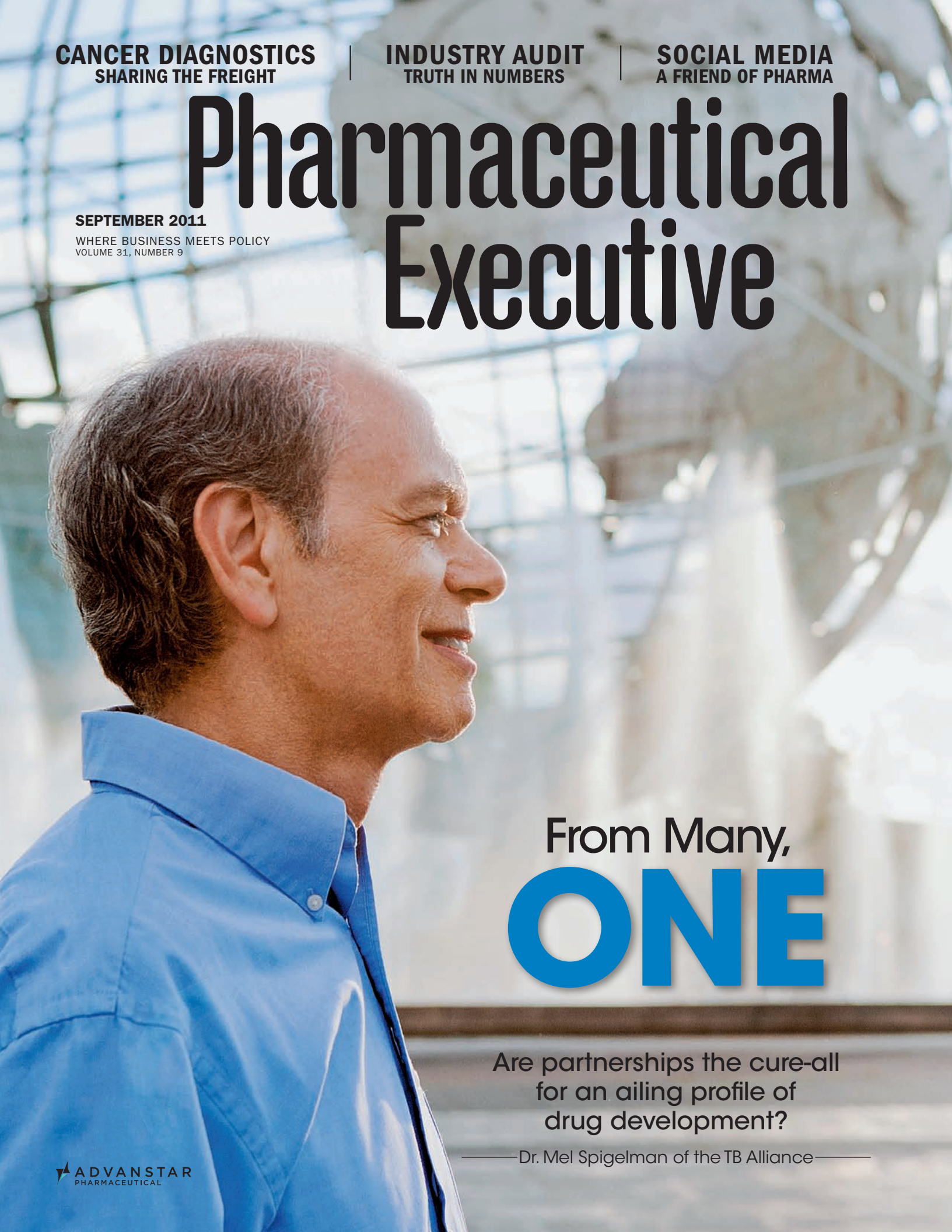
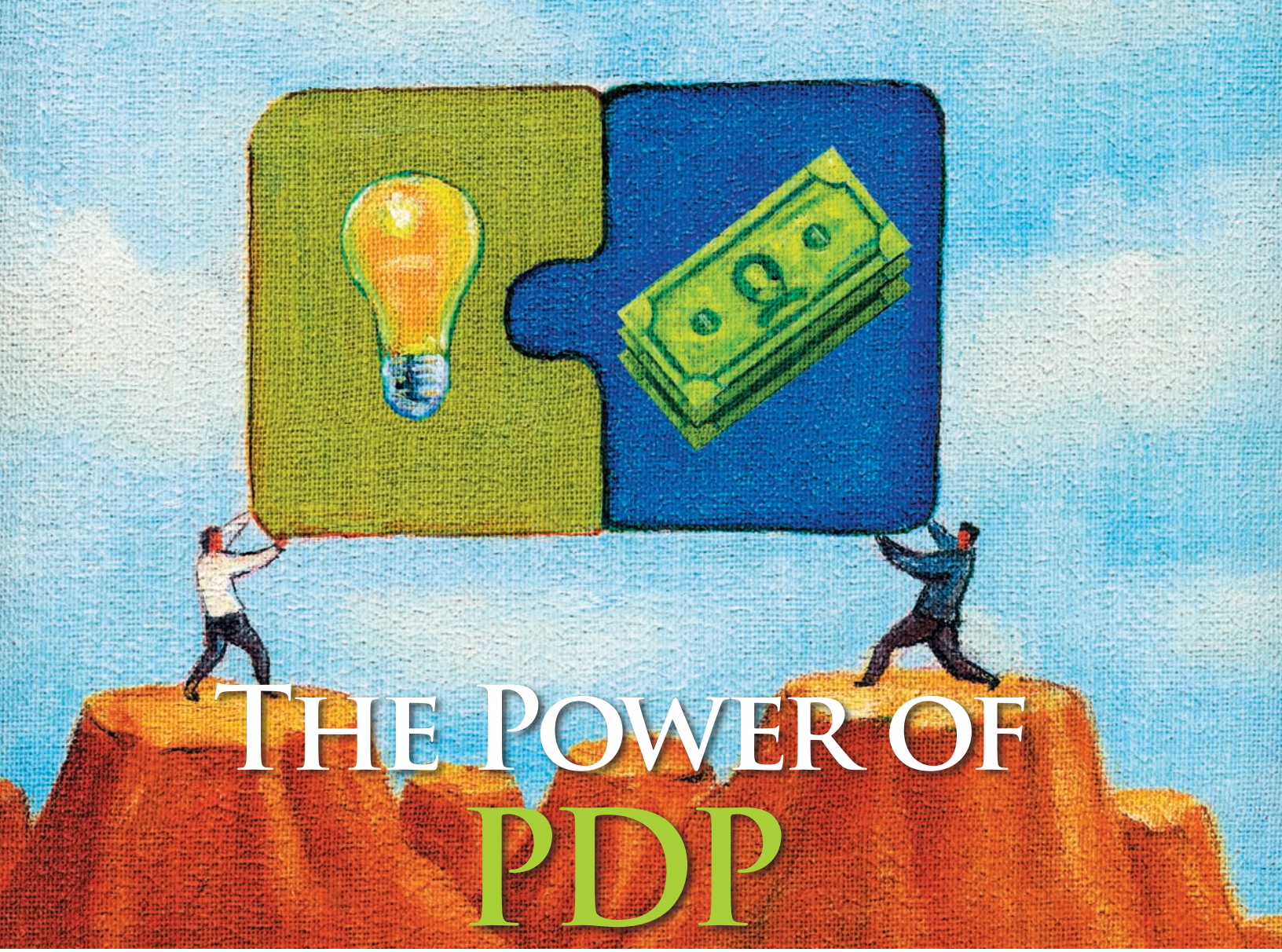


From Many, ONE

Are partnerships the cure-all for an ailing profile of drug development?

—Dr. Mel Spigelman of the TB Alliance

ADVANSTAR PHARMACEUTICAL



The Power of PDP

Can cooperative ties between Big Pharma, NGOs, government, and international organizations pay the freight in making the fight against neglected diseases a permanent fix in global health?

By William Looney, Editor-in-Chief

There used to be a perfect wave that Big Pharma could surf to a safe harbor of steady profits. It was the blockbuster drug, developed in shuttered, in-house labs using a rote process of mass chemical screening to treat chronic, clinically undifferentiated conditions requiring a lifetime commitment from patients.

No more. Today's safe harbor is just an accounting term, as companies scramble to create a new research model around something stronger than a conforming indication for the average patient. The irony is that a new precedent for success is today being forged around an old construct: the Product Development Partnership (PDP), where pharma pools its logistical and financial muscle with government, NGOs, and academia to commercialize treatments for the big diseases that still kill millions because traditional market incentives are skewed.

Interest in repurposing this model is growing precisely for the very reason it was created: to minimize market uncertainty in 'neglected' therapeutic areas that look unpromising from a standard ROI perspective. Says Jan Twombly, representing the the Association of Strategic Alliance Professionals (ASAP), "It's no stretch to say that market uncertainty is becoming a standard assumption in *all* areas of investigation. The future of the pharma business depends on showing a direct link between investment and outcomes, one where product development can progress because there is an unambiguous social return that resonates value." The point is that the PDP is not a one-off activity designed to fill a charitable or reputational gap, but instead a platform for addressing fundamental strategic changes in the way medicines are developed, priced, distributed, and promoted.

Industry certainly has a range of precedents to choose from. ASAP has more than 2,000 company members drawn from an array of industries, with life sciences constituting the

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biggest share. In pharma, 12 PDPs are now functioning in 17 therapeutic areas in 36 countries and involving the participation of more than 150,000 experts and patients through the conduct of clinical trials and other investigatory platforms. There were no PDPs in place a decade ago. The timeline means that a few of these early partnerships are beginning to bear fruit in the form of approval-ready products.

Catalyst for Change

There are other benefits that derive from the special organizational characteristics of a PDP. Due to the multiple parties involved, a PDP facilitates capacity building, especially across geographies and demographics. Specifically, it encourages the Big Pharma partner to consider a wider range of options in distributing medicines in unfamiliar but high-opportunity emerging markets. This leads to a better understanding of the consumer; for an industry that lags in even defining where its customer base begins and ends, such basic awareness can increase levels of access and adherence to drug therapy. Likewise, many Big Pharma companies—ranging from GlaxoSmithKline and Lilly to Japan's Otsuka—believe that investment in a PDP creates synergies with other, more profitable business segments through the technology transfers that seed the growth of a permanent local science and manufacturing infrastructure in markets where they want to expand their footprint. Many PDPs now have direct experience in emerging and developing countries, helping Big Pharma avoid the pitfalls of operating in these unfamiliar markets.

The scalable, focused approach of a PDP can also have a powerful, positive impact on employee motivation, since the ground rules for engagement around an unmet medical need are fairly clear. Finally, as noted in a Feb. 16 commentary by FDA officials in *The New England Journal of Medicine,* PDPs are able to facilitate codevelopment around novel combination drugs—an under-represented intervention that is critical to building efficacy in treatments for complex big diseases such as TB and malaria. PDPs are particularly helpful in bringing private companies together so that their best compound assets can be tested, regardless of sponsor.

Adding Public Power to Private Enterprise

Perhaps for this reason, the PDP is being embraced by governments in emerging countries as a preferred platform to advance national industrial policies around the life sciences. Brazil's state- financed Oswaldo Cruz Foundation (Fiocruz) is an example of the trend, with dozens of partnerships inside and outside the country that focus on compound licensing; direct acquisitions; technology transfer in manufacturing; basic and applied research collaboration; and education and training.

Founded in 1900, Fiocruz is today the largest biomedical research institute in Latin America, with a reputation as a skilled negotiator in leveraging the power of partnership to become the dominant player in generics and vaccines geared to low-income patients. Its market clout is such that it has local manufacturing rights to eight of the 16 drugs commonly used in "cocktail" combinations by HIV patients. "The lower prices obtained through this route from the foreign drug makers allow us to subsidize access to these life-extending medicines to the entire HIV+ population in Brazil, securing a key public health policy objective," Fiocruz representative Carlos Morel tells *Pharm Exec.*

More important, Fiocruz has a set of partnerships with Big Pharma linked to the transfer of technologies to develop new medicines for commercial sale, both inside Brazil and globally. "Fiocruz has as its key objective the capacity to patent, develop, license, manufacture, or sell new medicines to treat priority diseases worldwide," Morel says. "In that sense, we are decidedly not a philanthropic enterprise."

One example is the PDP that Fiocruz has inked with GSK for the production and development of vaccines. Here, the UK drug maker is distributing pneumococcal vaccine to an estimated 3 million to 5 million Brazilian children a year, while Fiocruz concentrates on improving and then sharing the science around infectious diseases. "One goal of the partnership is to develop and commercialize a global vaccine for dengue fever, which is a huge public health problem in Brazil," says Morel. "We are creating the science and GSK is contributing its production know-how." Such synergies have allowed the PDP to fill some resource gaps, with Fiocruz recently purchasing from GSK a local manufacturing plant that now makes some 70 essential medicines—ranging from anti-hypertensives to patented ARVs for AIDS—supplied by the Brazilian Ministry of Health for low-income patients.

Bigger Health Impact?

Meeting rising public expectations of the R&D-based industry is vital to preserving that basic "license to operate," the absence of which could break the entire cycle of medicines innovation. This suggests in turn that one of the unheralded merits of the PDP model is its potential to address the very biggest challenges in health, strengthening the industry's association with innovations that require no metrics—because they save lives. "The reputational impact when pharma engages in

this space far outweighs any costs," says former Merck CEO P. Roy Vagelos, who pioneered the basic concept of the disease-based partnership back in the 1980s, with Merck's Mectizan program to eliminate the parasite that causes the debilitating condition known as river blindness. "It's become an open-door asset for doing business globally. It is surprising that it has taken the industry as long as it has to recognize that."

MANY PDPS NOW HAVE DIRECT EXPERIENCE IN EMERGING AND DEVELOPING COUNTRIES, HELPING BIG PHARMA AVOID THE PITFALLS OF OPERATING IN THESE UNFAMILIAR MARKETS.

TB: If You Can Make it Here

A strong example—rich with promising precedents—is evident in the work of the PDPs now under way to address the lag in new pharmaceutical and vaccine interventions to combat tuberculosis (TB). The script is very simple: the cupboard of new therapies is bare despite a rising incidence of infection and resistance to the existing arsenal of multidrug therapies, which risks leaving the public defenseless against a killer that can easily be transmitted through casual contacts.

In fact, when you examine the profile of TB, all the elements of a "grand challenge" for the innovative drug industry are there:

Unmet medical need. TB is deadly and highly contagious, responsible for nearly 2 million deaths a year, second only to HIV, to which it also contributes as a key factor in mortality. About one-third of all HIV+ patients also have TB. There are few boundaries against infection and the incidence of TB is rising, with an estimated 9.4 million new cases reported in 2009. There is no doubt that TB is a formidable threat to public health, due to its unique link to other chronic infectious diseases and its role in suppressing the immune system. Even with the science and technological breakthroughs since the gene code was broken a decade ago, it is astounding that today there are more active cases of TB than at any time in history.

Significant indirect economic costs. TB scores among the highest in the global burden of disease, with an estimated cost of $12 billion annually, distributed among all countries—rich and poor. Every year a TB victim goes undiagnosed, he or she will infect another 12 people. In the US, hospitalization charges for a patient with multidrug resistant (MDR) TB can average around $600,000; in developing countries, the cost to administer the standard DOTS drug package is often higher than the annual income of the recipient patient. Failure to treat also carries a spinoff effect by accentuating the adverse public health impact from other communicable diseases that are easier for TB patients to contract. This means there are also fewer resources to address the increasing toll from non-communicable ailments.

Medicines are the vital defense against TB. While preventive public health measures, infrastructure improvements, and overall economic development are critical to eliminating TB, planning for that is complex and long-term. Drugs provide the stopgap solution in regulating the disease and slowing the pace of new infections, yet basic individual therapy guidelines—requiring four or more drugs administered rigorously to ensure patient compliance over six to 30 months—have not changed. The last new drug for TB was introduced over 40 years ago. Yet the sanitariums that once confined TB victims in a cocoon of protection—to benefit the healthy—have been closed. Can a larger pandemic just be waiting to happen?

TB is a test case for new medical innovation. A key barrier to controlling TB is simplifying the treatment regimen, by reducing the number of drugs taken through high-value combination therapies; shortening the length of treatment; and better targeting of the bacillus to control resistance or latent infection. In the latter case, there is an urgent need for drugs to fight MDR TB, which accounts for nearly 5 percent of new cases and is now found in every region, including the US and Europe. At present, however, given the length of treatment, required use of injectables for the first six months, and the cost and complexity of administration and monitoring, global scale-up of MDR treatment is—from a practical point of view—not an option. Drugs that can be designed to combat co-infection with HIV are needed. A new TB vaccine should also be part of the mix.

Market Disconnects

Despite these big drivers of demand, there is a significant missing link: the incentive to devote scarce resources to these new medicines is not measurable, largely because normal market signals are either non-transparent or don't exist. The current market for TB drugs is characterized by rampant commoditization and a skewed, unpredictable supply chain. Demand tends to fluctuate because purchasing is increasingly dependent on budget cycles in government and donor agencies as well as consumer out-of-pocket spending. What private-sector development there is tends to focus on finding that magic bullet against MDR strains of TB. This has the consequence of crowding out earlier drugs that form the basis for second-line treatments, a segment controlled by only a few suppliers who operate on the basis of very tight margins. Completing the cycle, it discourages real competition.

Another factor behind the low take-up of TB drug research is the challenge of mounting clinical trials around a highly diverse cohort of patients, with multiple symptoms and damaged immune responses that are hard to render

statistically. There is a significant capacity constraint in finding the right test population and establishing an acceptable trial infrastructure in impoverished areas. On top of that, there are ethical issues that must be addressed simultaneously.

Big Pharma's Product Play

Nevertheless, the potential to score something big means that Big Pharma has been willing to keep some irons in the fire on TB. "The PDP platform has been the lure that attracted private-sector interest in making a contribution to TB drug development," observes Joanna Breitstein, communications director for the TB Alliance, the chief PDP sponsor of TB drug research (see page 40). "Before the launch of the Alliance in 2000, there were no drugs in clinical development for TB," she continues. Today, it is very different—among Big Pharma, Eli Lilly, Johnson&Johnson, Novartis, GSK, AstraZeneca, Bayer, Sanofi-Aventis, and Pfizer have made varying levels of commitment to the disease.

Outside of drug development, Lilly is perhaps most visible due to its emphasis on the transfer of technology rights to build local capacity to manufacture TB drugs. The focus is on finding new compounds to tackle MDR, in addition to the overall fight against drug resistance. In the latter case, there is the potential for a very large market—including the higher-priced regions of Europe and the US—*if* the therapy represents a breakthrough. The specific motivation around MDR is that the development pathway for these compounds is quicker due to the targeted level of need and the interest of governments and payers in expediting access against the soaring cost of acute care treatment.

Promising Partner Leads

An emerging player on the industry side is Otsuka Pharmaceuticals, which is the largest single funder of clinical development work on medicines to treat MDR TB. It ranks third—after the Gates Foundation and the US National Institutes of Health—in spending against TB overall. "Otsuka is unique in several ways: we are ahead in advanced testing of promising compounds to attack MDR, our commercial commitment to TB is the focus of a special business unit, and we pay all the costs associated with clinical trials ourselves," Patrizia Carlevaro, a Lilly veteran who now heads, among other activities, Otsuka's global TB health awareness programs, tells *Pharm Exec*.

Most important, Otsuka, along with J&J's Tibotec division, is top of the list on prospects for approval of the first new treatment for TB in more than 40 years. Delamanid, a highly potent compound in the nitroimidazole class, began clinical trials in 2004 and recently has shown encouraging results in countering MDR in a large-scale Phase II (b) trial. Otsuka intends to carry these results forward to Phase III and possible approval by licensing authorities in the near future. The Tibotec entry, TMC-207, is also showing gains against MDR in a trial that Tibotec is leading.

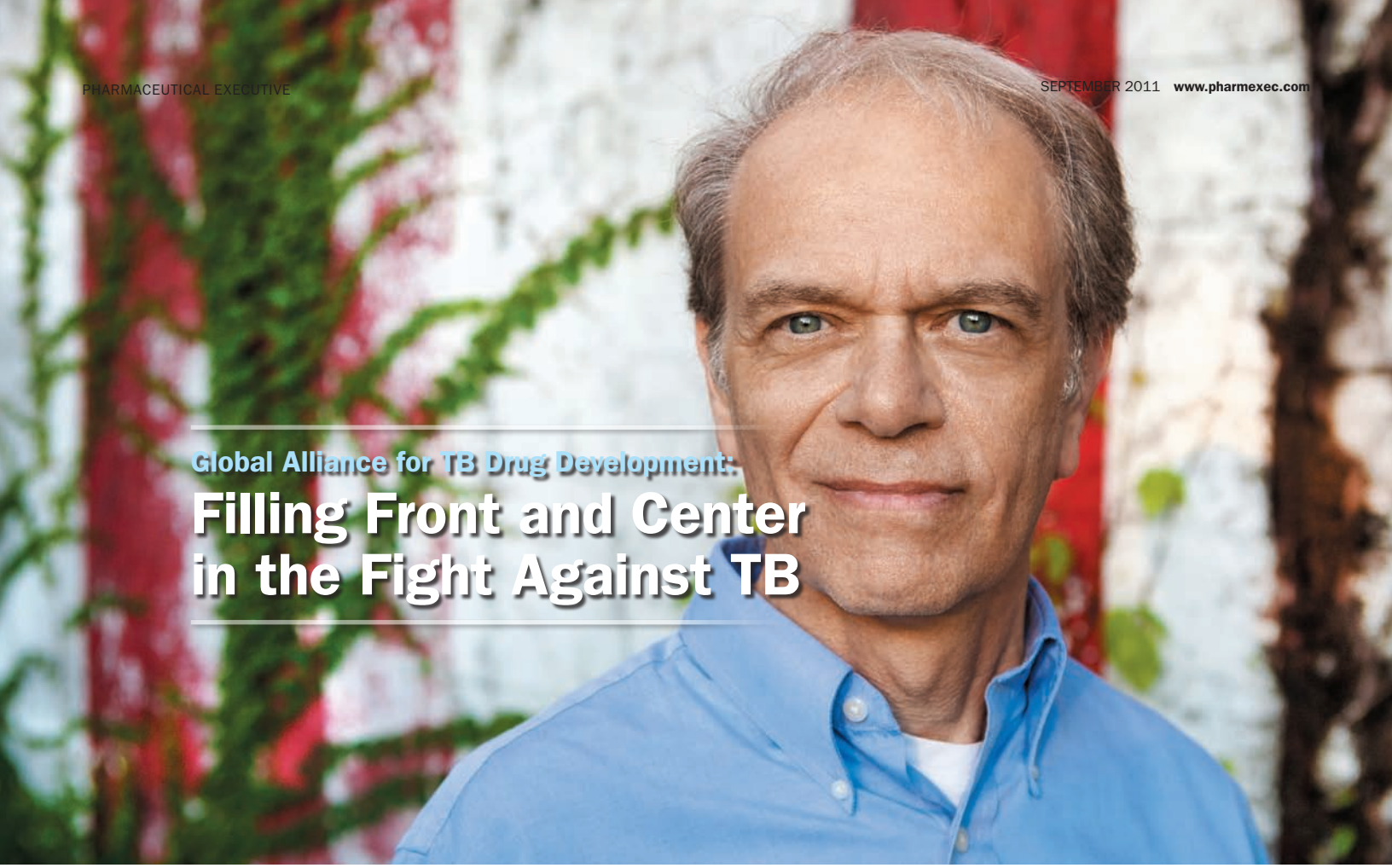
Says Carlevaro, "The premise behind a strong PDP is that each party performs to its strengths. Industry must focus on science and clinical development, while ensuring synergies with NGOs, governments, and international organizations in developing programs linked to access and care." She adds that the goal of a PDP is analogous to a disease management scheme. "What remains to be done is the cost-efficient execution of a package of customized services that take the patient from diagnosis, to treatment, to cure."

Evidence that this approach is already working is the recent rollout of a new, simplified diagnostic for TB, GeneXpert, that permits a clinician to identify positives for TB in as little as two hours, compared to the prevailing standard of as long as two months. Besides the technological breakthrough, it marks a significant improvement in the struggle to secure patient compliance. If a physician can obtain a diagnosis without the patient having to make a return visit, prospects for tracking and monitoring that patient's treatment will soar. Again, the PDP approach paid dividends. While a private company did much of the heavy lifting in creating the product, it was Gates Foundation money that provided the incentive.

Window on the Future

Looking forward, expansion of the PDP approach will depend heavily on a record of results in the form of new products developed, approved, and circulating in the market. Thus, convener groups like the TB Alliance are the crucible for success. Observers also note that through the partnering that represents the essence of the PDP model, overall development costs for new drugs will be lower, which will attract additional entrants to the field.

What is likely is a broadening of the PDP concept as society's definition of a "neglected disease" expands beyond infectious conditions of the very poor to chronic ills of the more affluent, such as diabetes and heart disease, where it is not only the efficacy of the drug that matters, but how it is delivered, and to whom. PDP lessons learned here are every bit as applicable to the rich, mature markets as they are to the developing and emerging countries. And universality bespeaks legitimacy. PE



Global Alliance for TB Drug Development:

Filling Front and Center in the Fight Against TB

Pharm Exec Editor-in-Chief William Looney recently sat down with TB Alliance president and CEO Mel Spigelman, MD, to review his organization's priorities in discovering, developing, and making available faster and more affordable drug regimens to cure TB

William Looney: *A signpost of progress against disease is the capacity of institutions to innovate—to stay one step ahead of the contagion. How do you read the current climate for innovation, and is the pace sufficient to register gains against TB?*

Mel Spigelman: Innovation is the key driver for progress. Many people associate innovation with research in the classical sense of the word, but innovation is not the exclusive province of the scientist; in global health, innovation is also a social imperative and a responsibility to be borne by everyone in the field. The good news is that, after decades of nearly no innovation, the past five years have seen major strides in exploring innovative approaches to discovering, developing, and now delivering tools to combat TB.

Innovation is a hallmark of the TB Alliance. Our very organizational platform is in many ways an innovation. We were the first TB drug-based organization to be structured as a Product Development Partnership (PDP). Our sole purpose is to produce an innovative set of therapies that significantly advance the standard of care for treating TB and bring those innovations to where they are most needed. The establishment of the Alliance back in February 2000 occurred when there was not a single new drug in development to treat TB—the last real breakthroughs, the first combination therapies, date back to the 1950s and 1960s. We've worked to lower the barriers to TB drug development so that industry partners are more willing to participate. Today, we have more than 20 new drug projects in various stages of development; three are in advanced Phase II or III trials. There are 10 drugs in total in the global pipeline.

More important, we recently completed the first clinical trial that validates a new drug development paradigm that could decrease the time it takes to develop novel TB treatments by about 75 percent—from decades to years. The trial, called NC001 or New Combination 1, tests multiple novel drugs together early in the development cycle, with the goal of advancing the best combination of drugs—the way TB treatment is given. This is an approach that could be used in other diseases areas for which combination treatment is also a necessity, like malaria, cancer, and hepatitis. For TB, this is a major innovation because a novel regimen could be used for treating both drug-sensitive and drug-resistant TB in a single, shorter, safer, and improved cycle of therapy—an advance that has the potential to be truly transformative.

WL: *What you are saying is that innovation is as much about broad process improvements—of which the Alliance's NC001 trial is an example—as it is about individual product advances?*

MS: Exactly. As a PDP, the science behind a new product is important, but if you do not

innovate right through the entire value chain, all that is innovative about the science could come to naught. In addition to classical scientific innovation, the TB Alliance has a three-step test in evaluating the potential impact of our work: Will the therapy be affordable? Will it be made available? Will it be adopted? The premise is that we might have the most innovative single drug, but if it is not combined in the best regimen and we cannot get those drugs into the places where they will have a significant clinical impact, and the right patients cannot afford or do not have access to them, we will have failed. This is why one of our priorities is seeding our PDP delivery platform at the country level, such as the memorandum of understanding (MOU) we signed in March with the International Scientific Exchange Foundation of China (ISEFC). The agreement will pave the way for the formation of the first Chinese PDP dedicated to global health called the Global Health Research and Development Center of China, or GHRC, facilitating the transfer of technologies and skills between TB Alliance and GHRC to help develop new global health tools and contain the spread of TB both in and outside of China. We are also pursuing a similar arrangement with a government agency in India to engage that country in the global development of new drugs and regimens for TB.

WL: *Do you believe the PDP structure is still relevant now that the TB Alliance is entering its second decade?*
MS: Yes—more than ever, given the growing need to leverage multiple public and private sources of funding and partnership. What we need is not just the discovery of individual new drugs, but the coordinated efforts of all drug sponsors and relevant institutions to make the process of new therapy development and introduction faster, cheaper, and better. We will never defeat TB unless we make that happen. Today, we have multiple companies who are willing to work and even test their drugs together, and coordinated efforts in multiple spheres on the parts of government institutions, academic centers of excellence, and even civil society. The strategy is embedded in the Critical Path to TB Drug Regimens (CPTR) initiative, where we work with major drug companies, regulators, multilateral institutions like the World Health Organization (WHO), and a variety of other partners to streamline competencies around developing and making available shorter, more effective multidrug therapies. In another partnership, the TB Alliance is working with the CDC and the NIAID with funding from the FDA and the Bill and Melinda Gates Foundation to set up a mechanism through which biomarkers for TB could be quickly identified and validated. Effective new biomarkers for TB treatment effects could revolutionize the process of TB drug R&D.

The good news is that, after decades of nearly no innovation, the past five years have seen major strides in exploring innovative approaches to discovering, developing, and now delivering the tools to combat TB.

WL: *These examples provide some metrics to demonstrate to Big Pharma that working with you is not an exercise in irrelevance.*
MS: We should rename the PDP concept and call it instead the PIP: the Product *Impact* Partnership. Our true goal is not development of products, but [maximization of] the impact of the products we develop. Impact is also critical in today's challenging economic climate, when it is more important than ever to demonstrate a significant return on investment, whether one uses public or private resources.

Perhaps the greatest challenge we face today is that of tremendously constrained resources. Given the scope of the challenge, TB drug R&D is still woefully underfunded. The Gates Foundation has been essential to the financing effort, as the Alliance would likely not exist without Gates Foundation support. However, when you compare even the total Gates Foundation support of all PDPs to what Big Pharma spends every year just on R&D, it becomes obvious that multiple other mechanisms of support are necessary. And we also should not forget the leveraging capacity of organizations like the TB Alliance; through a variety of mechanisms, the total cost or value of TB Alliance programs is more than twice our investment—meaning every dollar given to the TB Alliance produces roughly $2 in impact.

WL: *Can you identify the Alliance's most promising compounds in development?*
MS: NC001 is the first Phase II, proof-of-concept study of a novel regimen that combines two new or unapproved TB compounds, PA-824 and moxifloxacin, with one current TB drug, pyrazinamide. The results of our recently completed study of this regimen are very exciting, as this regimen does not include the established older drugs, isoniazid or rifampicin, resistance to which defines multidrug resistant TB (MDR TB). As predicted in the preclinical models, this regimen appears to perform at least as well as our best standard therapy for drug-sensitive TB. This would be particularly important for MDR TB, where the current therapy now takes more than two years to treat and is so complex and expensive that less than 10 percent of patients with MDR TB are presently even treated. The new combination would cost a fraction of what health systems pay now. Similarly, the data emerging from NC001 are equally encouraging on the results of a combination of a novel drug discovered by Johnson&Johnson's Tibotec subsidiary, called TMC207, when that drug is combined with pyrazinamide.

WL: *What about vaccines?*
MS: The one TB vaccine in use, BCG, is extremely old, and confers minimal protection or benefit. Thus, the need for highly effective TB vaccines is also great. Improved immunogenicity and protection are needed, with the ultimate objective of preventing TB either entirely or at varying stages of infection. PDPs have also played tremendous roles in the area of TB vaccines. For example, Aeras, a PDP

focusing on TB vaccines, has multiple vaccine candidates in its pipeline with two vaccine candidates currently being tested in three Phase II (b) clinical trials.

WL: *Administering a "global alliance" must come with its share of challenges. What hurdles have you had to surmount in leading the organization?*

MS: The greatest challenge I find today is mobilizing the resources that will allow us to proceed quickly to deliver on our mission. TB is a disease of the poor and neglected. Therefore, there are precious few with any significant clout willing to advocate for funding the innovative work that needs to be done to make TB a disease of the past. In addition, bringing together the many disparate partners necessary for success always carries with it some unique challenges. There are always potential tensions in any set of relationships as broad as the ones we have. Managing those tensions requires from me two things: to set a goal for the organization that is very specific, with parameters that are non-negotiable; and the ability to understand what drives each of our 120 partnering stakeholders, so that we can anticipate problems before they occur. This latter capability is very important for any organization to build and maintain the trust of its partners. We may not always agree, but we have to be open, honest, and truly understand the constraints within which our partners work. It is crucial for everyone at the Alliance to realize that all successful partnerships work when all parties feel successful and derive benefit from the partnership—a 'win-win' proposition. Working with Big Pharma can also present challenges related to the size of the organizations and the fact that there are not infrequently competing interests within such large organizations. Ensuring alignment with especially large partners can be difficult, whether they are in the private or public sectors.

WL: *Is the fact that the Alliance has yet to bring any of its compounds to full registration approval a drain on morale?*

MS: We have had sufficient successes that morale has not been an issue. While it would be great to have a product registered, we are proud of what we have accomplished in a brief period of time. The size and diversity of the pipeline, the number of drugs in clinical development, the scope and depth of our partnerships, the innovative initiatives ranging from discovery research through our market access work—all these and other accomplishments have maintained morale. Interestingly, a common theme we hear from so many of our partners is that the morale within their organizations is always extremely high among those individuals who work on neglected diseases.

What we need is not just the discovery of individual new drugs, but the coordinated efforts of all drug sponsors and institutions to make the process of new therapy development faster, cheaper, and better.

WL: *Based on your practical exposure to the PDP field, what are the key elements of a good partnership?*

MS: Clarity, consensus, and consistency about the rationale of the partnership—and why you are in it—is paramount. We must be aware of a potential partner's real needs and whether these needs complement our own. It's all about relationship alignments, of a joined-up purpose and shared motivation. These attributes cannot be covered adequately in a contract; the relationship has to be grounded in the human interest because no legal document can possibly cover all that might go wrong. So if you don't have that primal feeling of trust going in, stay away. The other factor I would cite is that every one of our partners is unique. You can't work to address their needs in a cookie cutter fashion—for example, some of our industry partners want to be involved in all aspects of the value chain, from discovery research through marketing, while others want to focus on one specific aspect and hand the baton off to us.

WL: *What's next up for the Alliance?*

MS: Product registration, introduction of new regimens, and impact on the global TB epidemic. We now know it can be done and we can be successful. How quickly we can accomplish these goals will be very dependent on our ability to generate increasing funding and resources. Innovative funding models like advanced market commitments, unique partnerships with selected governments, greater involvement of the private sector—all these elements will be important in defining our impact. PE