

PHARMA'S INNOVATION BAR AND THE NEED FOR LESS IMPERSONAL MEDICINE

Today's evidence-based market demands a higher level of innovation and the willingness to target subsets of patients for whom a drug's value can be unequivocally proven.

BY EDWARD C. SALTZMAN

- Pharmaceutical companies are too dependent on product life-cycle management and incremental improvement for new drugs.
- While innovation has slackened within pharma, the innovation bar has risen among payers who increasingly wield more power.
- Less impersonal medicine will benefit patients and allow pharmaceutical companies to maintain or even grow their existing return on investment.

The pharmaceutical industry is entering a new era for which it is ill prepared. The problem is not just that companies have become too dependent on fast-follower drugs and new products that are, at best, modest improvements over their predecessors. At the same time, the innovation bar has risen as the generic standard of care in most large markets has improved and the percentage of prescriptions covered by increasingly concentrated third-party payers with more bargaining clout has gone up. The answer will lie not just in developing new products, but in new ways of thinking about who these products serve.

The big primary care drug classes—statins, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs) and angiotensin II receptor blockers

(ARBs)—that have driven pharma's profits over the last 20 years are peaking in sales and are at imminent risk of genericization. Cowen & Co. estimates that 25 to 30% of US pharmaceutical sales, comprising 67 major drugs with roughly \$62B in US sales, will lose patent or exclusivity protection through 2009.

Beginning nearly a year prior to the genericization of simvastatin (*Zocor*), payers began to encourage therapeutic substitution with that brand, at the expense of other branded statins with longer patent horizons, especially atorvastatin (*Lipitor*). **Pfizer Inc.**'s head-to-head study designed to prove that *Lipitor* is superior to *Zocor* for the majority of patients did not turn out as it had hoped, and the study offered ammunition to the payers in their push to switch patients to *Zocor*

in anticipation of that product's patent expiry earlier this year.

Although the industry has historically focused on incremental improvements—from ACE inhibitors to ARBs, from H2 antagonists to PPIs—the rules have changed. It's no longer a matter of hanging on until the next cycle. Indeed, payers and analysts are questioning the value of **Johnson & Johnson's** late-stage risperdone (*Risperdal*) replacement, paliperidone, which is the active metabolite in *Risperdal*, and for which J&J received an approvable letter in September of this year. Today's evidence-based market demands a higher level of innovation and the willingness to target subsets of patients for whom a drug's value can be unequivocally proven.

HIGHER INNOVATION HURDLES ...

Future pharmaceutical growth will be driven by uniquely advantageous drugs—products whose worth are beyond debate, whether they be launched for unmet needs in large primary care indications or for specialized patient populations where the need in the larger patient population is already met. The answer definitely won't lie with incrementally differentiated drugs—slight improvements whose therapeutic or

pharmacoeconomic benefit is arguable in whatever the target patient population. Nor will it lie for pharma with simply scouring biotechs for assets to purchase. Though biotech firms are broadly more innovative than pharma, less than one-third of drugs for which biotech received approval were classified by the FDA as priority NMEs, the best proxy for novel drugs that target significant unmet medical needs. (See *Exhibit 1*.)

Key to the industry's success will be the ability to identify sub-populations and develop drugs for them. This is not quite the one-drug-for-one-patient fantasy of "personalized medicine." As Hilary Harris, PhD, a member of the Royal Society's pharmacogenetics work group has opined, "Pharmacogenetic testing could herald an era of more efficacious, cost-effective prescribing, but it's a long way off."

That's true, but the industry is still moving, if not to personalized medicine, toward a "less impersonal" type of medicine—a significant departure from the one-size-fits-all therapy represented by blockbuster drugs like *Lipitor*. The change is driven by increasing costs of large studies, growing demand for more than drug-versus-placebo evidence when a new product wants to take on the standard of care, and more intense attention to safety.

The movement is also fueled by opportunism and an effort to salvage something from trials with disappointing results. When **NitroMed Inc.**'s congestive heart failure (CHF) drug isosorbide (*BiDil*) failed an initial late-stage study, the company, noting that African-Americans seemed to have responded well, directed further research to a subgroup of CHF patients that were African-American. *BiDil* became the first drug ever approved for a single racial group. Unfortunately, the product, a combination of the generic drugs isosorbide dinitrate and hydralazine hydrochloride, was priced at up to almost \$11 a day as compared with pennies for a daily course of its two generic components, and it has done poorly. (See "*NitroMed's Bidil Pricing: A Test for a Whole Class of New Companies*," IN VIVO, October 2005.)

Trying to prove that fast-follower products and minor upgrades are worth their price will carry huge costs and high risk.

Today's new drugs face a higher bar to acceptance by payers than yesterday's big sellers like lovastatin (*Mevacor*) and *Lipitor*. The general consensus has been that *Exubera*, Pfizer's inhaled-insulin product, is a likely blockbuster. But Michael J. Russo and David Balekdjian, writing in *Business Week* online, said it's "more likely to become a disappointment for Pfizer." Their rationale? Managed-care payers have adopted an outcomes-based approach to drug coverage and Pfizer has shown no

evidence that switching patients to *Exubera*, which will be priced well above injected insulin—the current standard of care—will lead to better compliance or a decrease in expensive diabetic complications. Indeed, in the UK, the National Institute for Health and Clinical Excellence (NICE) has recom-

mended against *Exubera's* use in type 1 or type 2 diabetes except in selected patients. NICE said the product does not offer sufficient benefits over injected insulin to be cost effective.

... AND REVISITING RISK

In addition to demands for more data on efficacy, we have entered an era with a heightened awareness of risk. FDA's Endocrinologic and Metabolic Drugs Advisory Committee recently recommended **Merck & Co. Inc.** and **Bristol-Myers Squibb Co.**'s diabetes drug muraglitazar (*Pargluva*) for approval, but the drug was ultimately issued an approvable letter and then scrapped after independent researchers looked at the company's data. They concluded in a study published online by *The Journal of the American Medical Association* that the drug more than doubled the risk for heart attack and stroke. (See "*Shadow FDA? Researchers Are Taking Approval Matters into Their Own Hands*," IN VIVO, November 2005.)

Then there's **Sanofi-Aventis'** rimonabant (*Acomplia*). The FDA rejected *Acomplia* as a smoking-cessation treatment and gave conditional approval for the drug as a weight-loss medication. The agency wants more clinical testing for the latter indication. The delay could last several years, creating substantial uncertainty over what has been con-

sidered the company's most important late-stage pipeline asset. In June of this year, *Acomplia* was approved for marketing for certain obese and overweight patients in the EU. (See "*Positioning Acomplia: Has the Drug Arrived Before the Disease?*" IN VIVO, November 2005.)

And modafinil (*Sparlon*), **Cephalon Inc.**'s promising new formulation of modafinil for ADHD, was intended to be promoted as an agent with an improved safety profile. The drug, an older version of which has been on the market for years to treat narcolepsy and related disorders, has been discontinued after having been relegated to approvable status over a report of a single case of skin rash.

These episodes—and others—suggest that an era of evidence-based medicine will reward only exponentially innovative drugs whose value is beyond debate, or incrementally innovative drugs capable of winning the debate with solid efficacy and safety research findings. Trying to prove that fast-follower products and minor upgrades are worth their price will carry huge costs and high risk. This includes combinations of marketed compounds, like *BiDil*. Pfizer's torcetrapib/atorvastatin study is the largest clinical program in the company's history. It includes 25,000 patients and will cost \$800 million. For reference, that's approximately equivalent to Pfizer's entire R&D budget in 1991 and 1992.

The biggest problem with these expensive, high-profile studies is that you don't always win. In the FIELD study of **Solvay Pharma SA's** (see Fournier's) fenofibrate (*TriCor*), the drug failed to reach its primary end point of a reduction in coronary heart disease events. With 10,000 patients and a cost of more than \$100 million over seven years, the results didn't achieve statistical significance.

The PROVE-IT study, a head-to-head comparison of Bristol-Myers Squibb's pravastatin (*Pravachol*) and Pfizer's *Lipitor*, sponsored by BMS, found that 80 mg *Lipitor* was more effective than 40 mg *Pravachol*. Two years, 4,000 patients, and quite a bit of cash later, Bristol-Myers lost.

BECOMING LESS IMPERSONAL

So other than buying biotech companies, counting on mass-market blockbusters, and taking a flyer on risky head-to-head studies of similar drugs, what is the answer for the pharma industry?

That brings us back to the industry's early moves toward personalized medicine. Not

everyone agrees with the report from Britain's Royal Society that posits that it's all in the future. Geoffrey S. Ginsburg, MD, PhD, and Misha Angrist, PhD, writing for the Personalized Medicine Coalition, a Washington, DC, nonprofit, point out that the daily use of the Framingham Risk Score by doctors treating patients for hypertension represents an evolving paradigm of "risk stratification based substantially on genotype, albeit indirect measures of genotype." They say, "The 'new' personalized medicine, exemplified by *direct* correlation of genotype with drug response, dosage, disease state and/or prognosis, is merely a step further along a continuum of care that is already well established."

Pharma is a long way from the latter point, but the first steps have been taken, and they are promising—NitroMed's missteps in commercializing *BiDiI* notwithstanding. As noted above, *BiDiI* was resurrected from the ashes of a failed study of the broader population and has succeeded in demonstrating safety and efficacy in a subpopulation of African-Americans. This suggests that a trial-and-error process is leading to—if not *personalized* medicine—at least a *less impersonal* brand of medicine.

In another example, late last year **Cell Therapeutics Inc.** initiated a women-only trial in lung cancer with its modified paclitaxel

drug *Xyotax*. This decision was based on analysis of data from its STELLAR 3 and 4 trials, which failed to demonstrate superiority of *Xyotax* to paclitaxel in first-line therapy across all patients taken together, but which did show prolonged survival in women with performance status 2 disease. Most cancer drugs are given to specific subpopulations based on empirical experience; there exists one definitive example, trastuzumab (*Herceptin*) in breast cancer, of usage based on genetics of the tumor. The development of *Xyotax* represents a novel example of prospective, gender-based targeting. Further preclinical and clinical data do suggest that *Xyotax's* metabolism by lung cancer cells may be influenced by estrogen, and akin to measuring estrogen receptor positivity in breast cancer, estrogen levels in NSCLC could be used as predictors of response to the drug. In the subsequent PGT202 trial, women with lung cancer treated with *Xyotax* who had normal estrogen levels had significantly better median survival than those with low levels. Cell Therapeutics was rewarded for its tenacity—in September 2006, the biotech licensed worldwide rights to *Xyotax* to **Novartis AG** for a handsome fee: a \$15 million equity investment and up to \$270 million in regulatory and sales milestone payments, in addition to an undisclosed net royalty on sales.

Avant Immunotherapeutics Inc. took a slightly different approach. The company recently announced a failure that analysts considered a success; it even drove up the firm's stock price. Avant's TP10 complement inhibitor did not meet its end point of reducing the incidence of death and heart attack in females occurring after cardiac surgery with cardiopulmonary bypass. The good news? In a previous trial, although the drug had failed for women, it showed a statistically significant effect in males. So Avant went back and retested in women to establish the negative hypothesis. This sets the stage for Avant to go for a males-only indication, where the company would have a product for a well-defined subpopulation.

Another way to improve safety and efficacy odds is to identify a marker that can be measured in a regular medical practice and used to segment the population. **Titan Pharmaceuticals Inc.** is testing an orally active analog of thyroid hormone, DITPA, as a treatment for congestive heart failure in patients with low serum T3, one such marker. Studies have shown that this subgroup has significantly higher mortality rates than those with normal T3. Titan is not studying everyone with CHF, it is betting that DITPA can be uniquely advantageous and beyond debate in a well-defined subpopulation.

It's not a tidal wave, but with several other examples out there, it is apparent that a shift toward less impersonal medicine is on the horizon. Either way, it's an important beginning that provides a more practical and immediate impact. Gradually subdividing the patient population isn't necessarily new, and unlike genotype-based medicine, it's actually happening all the time. Treatment of hypertension is already somewhat "less impersonal"; doctors use what is practically a "cook-book recipe" to segment patients when following guidelines laid down by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Although there may or may not be a genetic basis behind the recommendations, the breakdown of patients into subtypes based on co-morbidities is extremely well-established by dozens of major clinical trials.

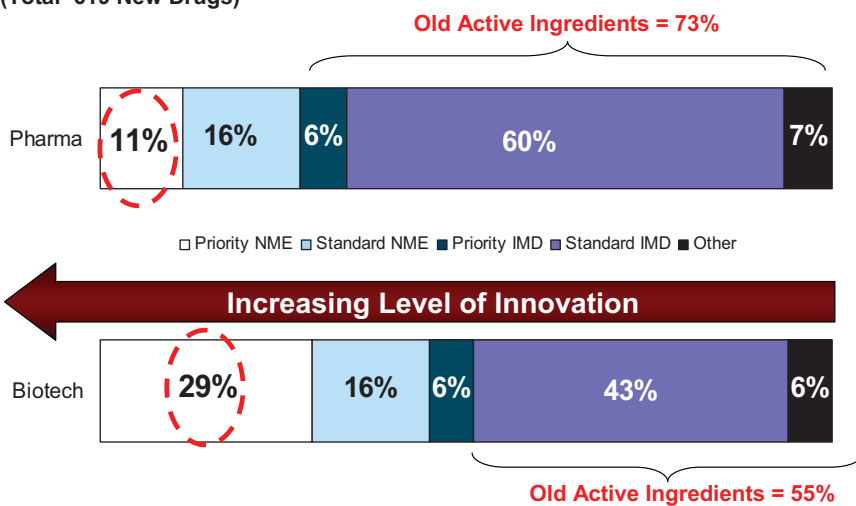
BLOCKBUSTER OPPORTUNITIES REMAIN

These are the trial-and-error early steps toward a new approach to marketing pharmaceuticals. It is likely that drug companies will keep taking the data from their

Exhibit 1

Though Better Than Pharma, Biotech Has Its Own Innovation Gap

Distribution of NDAs, Pharma vs. Biotech (Total=619 New Drugs)



*NDA sponsors were designated either Biotech or Pharma; includes BLAs USFDA; DH analysis

SOURCE: Defined Health

trials—whether successful or not—and use it to search out subpopulations. This avoids some of the significant risks and costs inherent in trying to prove the superiority of poorly differentiated products over today's excellent generic standard of care in certain disease areas. To add to the mix, large pools of data exist at CMS and private-payer companies that can be mined to gain a retrospective understanding of which patient subsets do best or fare worse on which drugs and drug combinations, and this information can be used to prospectively design trials for selected patient subsets.

Unarguably, there is the need to determine how to assimilate less impersonal medicine into future pharma, biotech, and specialty pharma business models. As a beginning, Big Pharma needs to rethink its rote desire to seek the broadest possible label for its drugs, understanding that attempting this in markets with well-established standards of care has become unacceptably risky. Importantly, a strategy to develop less impersonal medicines does *not* mean abandonment of the mass-market blockbuster. Clearly in areas with an ineffective or even toxic standard of care for the majority of patients, huge opportunities remain. Despite conventional wisdom not all of these opportunities are in cancer. For example, for all practical purposes, there exists no good drug therapy for peripheral vascular disease, a condition that afflicts eight million people in the US. Any reasonable improvement over the current standard of care would likely receive wide and enthusiastic reception from all stakeholders. There are numerous other diseases for which the outcome for the majority of patients is poor and/or for which drugs are either toxic or ineffective. All of these contexts will continue to offer broad-label blockbuster opportunities. However, the continued push for new drugs to replace those that are broadly effective is likely to produce only increased failure.

Companies will need to deepen their understanding of each disease opportunity and its attendant patient base—from physiological pathways to the effect of multitudes of key patient attributes such as age, sex, and race, to concomitant conditions and medicines. Each can help determine the efficacy and safety of a novel drug candidate. From this enhanced understanding will come a clearer view of patient subpopulations that fare poorly in otherwise well-served categories.


Concerns that developing drugs for more

targeted and less satisfied patient populations will produce smaller revenue products than traditional mass-market blockbusters are justified. However, pharmaceutical companies should more properly reflect on more than the top-line sales number. The opportunity to reduce development costs and increase success rates—therefore improving the overall return on R&D investment—is just as important. Drugs that have demonstrated significantly superior efficacy in under-served populations should face more realistic safety hurdles to approval, and adverse events and safety issues should be considered in the proper context of each medical need, reducing the need for product withdrawals.

The industry's inevitable transition to a strategy to develop less impersonal drugs will force structural and organizational changes in Big Pharma, many of which may be painful. For starters, late-stage projects aimed at securing broad labels for new drugs where the widespread unmet need is dubious will need to be re-examined and, most likely, terminated. Few if any companies can afford to take the risky bet Pfizer is placing with its \$800 million clinical development gamble on torcetrapib. However, the benefits of a strategic shift to emphasize less impersonal therapeutics may outweigh the pain. With smaller trials and lower development and promotional costs, less impersonal drugs will enjoy greater pricing, and hence margin flexibility, than comparable broad-label programs with their far greater development expenditures. Of course, depending on the extent of the unmet need in the poorly served patient population, pricing premiums may be well-justified. Although there has been much discussion of the commercial failure of NitroMed's *BiDil* for CHF in African-Americans, the problem arose from the fact that the drug combination utilized in the product is composed of old off-patent agents and the price charged was a multiple of several hundred times the component cost. An NCE program with the same outcome would have commanded at least the price premium NitroMed was demanding for *BiDil* and maybe significantly more.

Finally, promotional strategies and spending will need to

be re-thought and most likely reduced, with potentially significant savings. Alongside the broad-label strategy comes the promotional costs necessary to make as much or more noise as the next undifferentiated competitor. Promotional efforts for less impersonal drugs will likely be both less expensive and more nuanced. Sales forces may need to be pruned. Sales reps may need to focus on educating physicians as to how to best identify poor responders to mass-market drugs either by patient interviews or by clinical test results. Importantly, the knowledge and tools to identify suboptimal responders in many cases exists today and does not depend on the availability of pharmacogenomic profiling. The return of pharmaceutical *selling* to actual *detailing* may be a welcome change that could bring much-needed public image relief to an industry otherwise beleaguered by its poor reputation.

Many pharma companies have already begun to question the wisdom of pushing forth with a primary care focus, believing that a specialty care strategy is less risky and costly. However, a shift to considering less impersonal medicines supersedes the primary care versus specialty debate. Nor is less impersonal medicine only about showing efficacy in "treatment failures," as these are complicated by issues such as progressive disease and drug resistance. Less impersonal products can be and should be developed as first-line choices for patients who for whatever reason do not or should not be expected to respond to the available standard of care. As companies increase their intellectual capital in this field, they will naturally come to view *less impersonal* medicine as a first option rather than a "second-line" consolation prize after the failure of a broad-label program. 

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