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The Big Reset

By Walter Armstrong

As the curtain drops on the first decade of the 21st century, the media has rushed to try to catch history in a jar. Were the "naughty aughties" (Russell Gold in The Wall Street Journal) the "decade from hell" (Time), the "flimflam decade," or the "Big Zero" (The New York Times' Frank Rich and Paul Krugman, respectively)?

Shifting the focus specifically to pharma, we might wonder if it was both the best of times and the worst of times. The industry began the decade with revenue growth close to 10 percent, and ends it with a growth rate of barely 1 percent, according to IMS Health. On the other side of the ledger, pharma's much-maligned R&D machine produced major medical breakthroughs, including the triple-drug cocktail for the global HIV epidemic and the first vaccine for cancer.

Looking ahead, the new year promises no respite from the radical disruptions pharma faces, according to the experts we spoke with. If there's one common theme, it's that market forces are mostly out of pharma's control, so the best M.O. is to go with the flow—or risk not going at all. "Globalization, healthcare reform, enabling technology, rising consumerism, and the focus on health outcomes rather than products are changing the incentives in the healthcare ecosystem," says Ernst & Young's Global Pharma Head, Carolyn Buck Luce. "And when you change the incentives, you change the system. Old players leave, new ones come in."

With the uncertainty of healthcare reform receding and the economy no longer in free fall, "2010 has a more positive outlook than a year ago," says Murray Aitken, senior vice president of IMS Health. "Above all, there is a more realistic commitment among pharma leaders to ensure that their businesses are sustainable beyond the patent cliff. We are emerging from a period of denial, when hope was the only strategy."

—Carolyn Buck Luce, Ernst & Young

But not everyone is on board with this new realism. "Turning to emerging markets and buying very expensive biotech revenue streams are not strategies for long term success," says Michael Russo, partner at the Bruckner Group. "There needs to be a fundamental reset of the industry."

Over the past decade, pharma has been colonized by venture capitalists who invested in "revolutionary technology," along with advertising agencies that preached consumerism and selling Nexium Part 5, according to Russo. "The future has arrived, but the revolution has not," he notes. "We need to wrestle the industry back to making science central."

Is it possible to go back to your roots and look to the future at the same time? That and more will be required of pharma CEOs in the next decade.

Business Models and Biotech Deals

If 2009 was all about megamergers and healthcare reform, 2010 will at least offer a change of subject. Few headline-grabbing mergers are predicted for the new year; top pharmas are content with smaller, strategic plays. But most analysts agree that this fragmented industry will gradually bend to the law of consolidation. "The growth aspirations of the industry don't match the capacity of the markets to develop it," says Peter Tollman, Boston Consulting Group's global pharma leader. "Consolidation is one way of getting rid of the excess." Meanwhile, the market share of the top players remains in the single digits, although Pfizer could break 10 percent this year as it digests Wyeth.

Pharma's relentless pursuit of organic growth by tapping emerging markets and specialized drugs is the leading indicator for expansion. At the same time, most major drugmakers will continue to deconstruct the monolithic, primary care business model (with its dramatic spikes and drops in profits) in favor of fast-acting, flexible, independent units. The industry's new, youngish leaders are attempting nothing less than turning drug behemoths into global healthcare networks that girdle the world with as wide a range of products and margins as possible.

The difference is more than a name change, says Ernst & Young's Buck Luce. "Pharma is moving from selling pills to selling outcomes, from being a low-volume, high-priced, developed-world business to being a high-volume, low-priced global one."

Internal restructuring—"right-sizing"—will result in more layoffs and other cost cutting. And in R&D, CEOs seem to be daring one another to drive the knife deeper. Sanofi-Aventis CEO Chris Viehbacher currently holds the record, having matter-of-factly told analysts that he will cut R&D by 20 percent, to $5 billion, by 2011. Of the top pharmas, only Merck, Bristol-Myers Squibb, and Lilly plan to increase their 2010 R&D budgets. BMS and Lilly are also the two biggest pharmas to buck the diversification trend by hewing to a strictly pure-play course.

The road to becoming an industrial healthcare company is paved with many acquisitions, and 2010 will see its share of bolt-on deals. "With over $100 billion in cash on their collective balance sheets, pharma will continue to identify M&A as the only way to ensure growth," says John Campbell, CEO of Campbell Alliance.

Although biotech has averted an industry-wide implosion (so far), many early stage shops went belly-up in 2009. That trend may slow, but not stop, in 2010. "Over the next year, there will be even fewer VC players," says Sherrill Neff, founding partner of Quaker BioVentures. "That means you can get some extraordinary opportunities, though it takes some looking."

(Hot tip: In 2010, smart shoppers will check out parallel fields like diagnostics, devices, and healthcare services.)

Biotechs with "revolutionary technology" or just a good-old Phase III products will still fetch high prices because demand far outstrips supply. Says Peter Young, president and CEO of Young & Partners: "Pharma is in the driver's seat, but with fewer very attractive targets, the competition for an acquisition can drive up the price."

With M&A being the new R&D, options-based, pay-for-performance biotech agreements will proliferate as Big Pharma hones dealmaking into a science. Yet the jump in the number of givebacks in 2009 may signal a resurgence in acquisitions in 2010, says Jan Heybroek, president of The Arcas Group. "You have to very actively manage licensing relationships, and there's plenty of evidence that the divorce rate is as high as it is for people."

Cliffs, Launches, and China

—Murray Aitken, IMS Health

CEOs may be looking past patent cliffs, but Wall Street is still fixed on quarterly results. Close to $16 billion in brand-name drugs will be exposed in 2010 as blockbusters including Pfizer's Aricept, Sanofi-Aventis' Taxotere, Merck's Cozaar, and AstraZeneca's Arimidex go generic. While every top pharma has its own cliff to leap—with a 40 percent drop in prescription drug sales not uncommon—AstraZeneca, Lilly, and Bristol-Myers are facing even steeper falls, according to Bernstein analyst Tim Anderson.

For Lilly, in particular, 2010 could be a make-or-break year. With patents on Zyprexa and Cymbalta expiring by 2014, and the firm's future riding almost entirely on its mid-stage pipeline, analysts will be eyeballing its recently launched antiplatelet drug, Effient, as it hastens to grab market share. But Effient's window of opportunity may close in 2011, when knockoffs from Plavix flood the market.

With FDA under new management, drugmakers can expect to see faster, more decisive action on the drug-review front. "The new leadership is positive for the industry," says Don Hannaford, senior vice president of Levick Strategic Communications. "[FDA Commissioner Margaret] Hamburg has taken on a broader mandate around a holistic view of health. FDA scientists should feel they're not going to get in trouble for making decisions."

But energy may not translate into approvals, as safety remains the priority issue and the new REMS framework is pressed into service. IMS Health projects 25 to 30 new launches in 2010, which is in line with recent years.

Here are a few of the new drugs to watch for:

In CNS: Novartis' first-in-class melatonin receptor agonist, agomelatine (for depression), as well as two next-generation atypical antipsychotics, Lundbeck's sertindole and Schering-Plough's asenapine, all look promising. Novartis also boasts the new front-runner in the race for the first oral Multiple Sclerosis drug, following the "refuse to file" setback at FDA for Merck KGga's candidate. In Alzheimer's, Phase III data will be released for what could be two huge entries: Medivation/Pfizer's Dimebon and Elan/Pfizer/J&J's bapineuzumab. The pileup of codevelopment deals shows how cozy companies have grown.

In diabetes: Two first-in-class drugs—Merck's DPP-IV inhibitor, Januvia, and Lilly/Amylin's GLP analog, Byetta—may finally face some competition, as FDA rules on BMS/AstraZeneca's Onglyza and Novo Nordisk's liraglutide.

In cardiovascular: The market will likely embrace its first new oral anticoagulant in 40 years if FDA gives a thumbs-up to factor Xa inhibitors Bayer/J&J's Xarelto, Pfizer/BMS's apixaban, and Daiichi Sankyo's edoxaban. Other blood thinner news: AstraZeneca's just-approved Brilinta proved superior to Plavix and Effient, while Boehringer Ingelheim's Pradaxa for atrial fibrillation bested veteran work horse warfarin. Taken together, these medical advances indicate that the blockbuster model is not entirely dead.

Meanwhile, 2010 could be decisive for Amgen as it desperately seeks approval for denosumab, a novel monoclonal antibody for osteoporosis and bone cancer, which is the biotech stalwart's sole hope for much-needed sales.

Cancer will remain the hottest therapeutic category, claiming fully half of the industry's pipeline. Likely stars of 2010 include Cougar/J&J's albiraterone, for prostate cancer; Medarex/BMS's ipilimumab, for malignant melanoma; and two non-Hodgkin's lymphoma treatments—Lilly's Enzastaurin, a first-in-class inhibitor of the wildly popular PI3K pathway; and Cell Therapeutics' Pixantrone, a novel major groove binder.

Sales of monoclonal antibodies are set to hit $20 billion in 2010, according to Thomson Reuters analyst Alexandra Kibble. Yet the growth rate of the oncology market has already started to fall, from 15 percent in 2008 to 10 percent in 2009. And with a 12-week course of treatment averaging about $20,000 —and survival benefits often measured in mere months—Big Pharma's rush to cancer may turn into a rush off a cliff as payers begin to push back. "Given the level of R&D investments in oncology and the assumptions on which they are founded, one wonders if oncology is a bubble waiting to burst," says BCG's Peter Tollman.

—Billy Tauzin, PhRMA

According to IMS, the total value of the global pharmaceutical market will grow 4 to 6 percent, to more than $825 billion, in 2010. China, at 21 percent, again tops the list of fastest growing markets. By contrast, the US market will expand only 3 to 5 percent. The usual suspects in the emerging world, such as India and Brazil, clock in at 12 to 14 percent. But the economic recession will continue to erode share in markets such as Russia, Mexico, and South Korea, where out-of-pocket spending is high. "China is increasingly in a class of its own," says IMS's Aitken. But China's new policy of favoring domestic innovators over foreign companies for government contracts is already raising protests among US firms.

The European pharmas will maintain their lead in 2010 in the race for world domination. Says Aitken: "They are broadening their portfolios to meet the specific needs of each market, not only through the acquisition of products but also by developing drugs to treat prevalent diseases." This R&D increasingly takes place in situ; Sanofi and Pfizer launched major labs in China last year, while Novartis will be breaking ground in 2010 for what it bills as China's biggest pharma research plant (which is also CEO Daniel Vasella's $1 billion snub of India for rejecting the Glivec patent).

Branded generics will continue to gobble up market share, especially in generics-packed markets where consumers hunt for quality. In 2010, Takeda and other Japanese pharmas look poised to make a big push into India's generics industry, following the Daiichi Sankyo/Ranbaxy deal.

Yet as its commitment to emerging markets deepens, pharma is already dealing with partners' control issues. In Turkey, for example, a budgetary shortfall led the government to reset the benchmark for all brand-name drugs at the lowest price in Europe, cutting private-payer costs by a third. If this trend goes global—what's to stop it?—emerging markets could fast morph into mature ones.

The Healthcare Reform Epidemic

—Michael Russo, Bruckner Group

When the dust settles on the sound and fury of healthcare reform, the actual legislation should remain pretty painless for pharma—at least for a few years. At press time, PhRMA president and CEO Billy Tauzin, who negotiated the trade group's controversial $80 billion, 10-year "back-room deal," predicted that Congress would pass a bill in time for the president's State of the Union address in late January. "But first, the Democrats will do a lot more work in terms of closing the hole in the [Medicare] doughnut," he says. In order to prevent further compromises, the industry is reportedly willing to add $25 billion more in discounted drugs to close the hole.

Even so, the industry's decision to play ball has resulted in a winning record. The legislation preserves the status quo—flexible drug pricing—blocking consumers from importing drugs from Canada and the federal government from negotiating Medicare Part D prices. In the provision mandating FDA to establish a regulatory pathway for biosimilars, pharma scored 12 years of market exclusivity for innovator products.

Yet the bill's long term effects are likely to be transformative. By expanding and improving private insurance, the healthcare overhaul is likely to jack up drug sales. Some 31 million more Americans will have access, lifetime caps on insurance will be removed, copays may be more predictable, and coverage for vaccines and other products will be increased. According to some estimates, it will only take four new monthly prescriptions per year per newly insured life to cover the cost of the $80 billion deal.

But not all the math goes in pharma's favor. To pay for the $871 billion overhaul, the bill mandates a total of $480 billion cuts over a decade in Medicare payments to providers. Big Pharma price gouging, critics say, will be the likely first target, if only because reducing waste and inefficiency caused by hospitals, physicians, and consumers has so far proven politically unpopular. "I look at pharma's 80-plus percent margins and know that there is not another industry alive that depends so heavily on government purchasing," says Sherrill Neff. "That margin level is simply unsustainable."

In addition, PhRMA's deal with elected officials appears to have secured the industry a victory against price controls and other key issues without making its "protect innovation" case relevant to the public. Future concessions, if not reversals, seem certain. "By not promoting discussion of the central issues of healthcare reform, pharma missed the opportunity to show how drugs are cost-effective," says Aitken.

The healthcare reform bug is proving contagious in the EU, too, as budget deficits cause governments to "bend the curve" in spiraling spending, says Fabio Pammolli, professor of economics at the University of Florence, and a advisor to the WHO on pharma regulation. "Reforms will shift more of the cost burden from government to the private sector—employers and consumers," Pammolli says. As a two-tiered healthcare system emerges, degrading the time-honored social ethic of equal access for all, the public outcry will force governments to narrow the gap—and the easiest target to hit for more savings will be drug prices.

Pammolli also expects 2010 to feature a jump in pharma/payer pay-for-performance agreements, such as Celgene's recent offer to pay Britain's National Health Service (NHS) for its $6,000-a-month multiple myeloma drug, Revlimid, for patients who stay on it longer than two years.

Here Comes Cost Effectiveness

In coming years, the industry will confront escalating pricing pressure on many fronts. Private insurers will pass the costs of increased regulation on to pharma by squeezing prices and reimbursements. One predictable response? Hike prices!

In 2010, expect to see drugmakers attempt to maximize profits before reform kicks in by raising the wholesale price of their brand-name prescription drugs. How high? The 2009 increase was about 9 percent, the highest annual rate of inflation for drug prices since 1992. Although the media noted that pharma was erasing the first year of savings it had promised in its Senate finance agreement, the bad press got lost in the general din.

—Peter Tollman, BCG

More importantly, the reform bill's mandate for comparative-effectiveness research (CER) will add momentum to the drive toward EU-style health technology assessments—a pharma bugaboo due to its potentially withering effect on market flexibility and diversity. Yet many analysts argue that bill or no bill, some form of CER is unavoidable. With the first Baby Boomers signing up for Medicare in 2011—and expecting access to two more decades of medical advances at any price—healthcare costs are on course to absorb about 40 percent of GDP by 2040. "You just have to look at NICE in the UK, which the US consults with, to see where all this is heading," says BCG's Tollman.

Whether CER will gain traction next year remains to be seen, however. "There may not be the political will to push for it," says Aitken, noting that CER was also a feature of 2006's Medicare Modernization act, to little effect.

While CER boasts bipartisan congressional support, healthcare reform revealed, if nothing else, that no policy is above partisan politics. Government involvement in comparative cost-effectiveness analysis is clearly a frightening, if only dimly understood, prospect for many Americans, and the rhetoric of "death panels" shuts down serious discussion of how much patient choice the system can or should tolerate. The fact that such analysis is increasingly practiced not only by public healthcare systems in other industrialized nations but by private insurers in the US has gone largely unexplored by the media.

"There is going to be tremendous dissent in the marketplace," says Cyndy Nayer, who heads the Center for Health Value Innovation. "Comparative effectiveness is a population health measure, and consumer advocates will say, 'That's not what matters to me." Manufacturers of drugs and medical devices will say, 'Our product can't be measured head-on with that product.' And employers doing plan designs will say, 'You know what? I don't have that kind of expertise.'"

In fact, the Senate healthcare reform bill authorizes the government only to fund CER while blocking it from using the results to inform its healthcare coverage decisions. The Patient-Centered Outcomes Research Institute will be governed by a board including the directors of AHRQ and NIH, three consumer reps, five physician and hospital reps, three private-payer reps, and three pharma reps. Critics say this setup protects the interests of the healthcare industry from cost controls. In the November issue of *The New England Journal of Medicine*, Harry Selker and Alastair Wood argue that the inclusion of industry could undermine the entire enterprise. "If healthcare reform legislation does not promote CER that is free of the potential taint of commercial and political meddling, the public will have little confidence in the results of such research."

The industry will have to decide how to address public skepticism about its credibility, particularly around its own comparative trials and data. "Does every drugmaker pour its money into one general pharma pot, and nobody knows which company [is paying what], and it may hurt you and help me or vice versa?" asks Charlotte Sibley, senior vice president of business management at Shire. "These questions need to be asked."

In the end, politics may trump the trend toward evidence-based healthcare pricing in 2010. Congressional Republicans are already talking about campaigning to repeal healthcare reform in the midterm elections. Across the pond, the big news may not be entirely different: Germany's Institute for Quality and Efficiency in Healthcare (IQWiG) has been charged by a 2007 healthcare reform law to make cost-effectiveness recommendations based on a new methodology. IQWiG has rejected NICE's controversial cost-benefit unit, the QALY (quality adjusted life year), in favor of a vague "efficiency frontier" concept that has drugmakers

scratching their heads. Rumor has it, however, that the new center-right government may scuttle these plans and sack the IQWiG's leader because he is an outspoken critic of Big Pharma.

Data States and Innovation Gaps

That industry trade groups endorse comparative effectiveness ("in theory") indicates that Big Pharma recognizes at some level that a new era of evidence-based medicine is in the offing. For one thing, the writing is on the wall at FDA, where follow-on drugs that fail to prove superiority are increasingly getting shot down, marking the emergence of "stealth comparative effectiveness," according to former deputy FDA commissioner Mary Pendergast. The agency is also attempting to neutralize the volatile issue of drug safety by demanding that drugmakers do large-scale, long term postmarketing studies as a condition of drug approval.

FDA may not officially acknowledge that superiority has replaced non-inferiority as the new standard. What matters more is what payers want, says Phil Katz, codirector of Hogan & Hartson's pharma practice. "If insurers and the government are not going to pay for a new drug unless it's proved to be superior, then FDA approval is, to some degree, beside the point. Drugmakers will push the new standard down into pre-approval clinical trials on their own."

In the outcomes business, pharma will have to prove the value of its products with more compelling data than FDA requires, says Buck Luce. "Brands will no longer be built around promising potential efficacy, but around optimizing the patient experience," she says. This redefinition of commercial goals will require, in turn, a reorientation toward data. "Drugmakers need to be asking themselves, 'How do I unbundle my value?'—in terms of all the knowledge they have about a drug. And then 'How do I make money off of that?'" Buck Luce says.

The transparency of data disclosure has ceased being merely an ethical imperative and taken on economic significance. "The concept of full transparency, and that 'customers are beginning to know more about our drugs than we do' is still new to the industry," says Tollman. New "sunshine" requirements in the reform bill address publicizing both positive and negative results from all clinical trials; these may get drugmakers up to speed with transparency in 2010.

As CER gathers steam, FDA's Sentinel Initiative will also get up and running. By reviewing electronic claims and medical-records data from public and private payers, the agency will attempt to detect safety signals in real time rather than waiting years for voluntary reports to accumulate. The new system will deliver, for the first time, a vast trove of new information about the real-world effects of drugs into a public forum. Between CER and Sentinel, pharma will be forced to reckon with potential blowback from big retrospective studies that are out of its control. "Retrospective analysis is useful, but it has to be used with caution. I foresee a lot of work that generates findings that are non-significant," says Aitken. "That could be a big problem for pharma companies."

As the knowledge about a drug becomes more open-access, drugmakers are likely to find themselves competing with other industries for its commercial application. "When all of that knowledge can be owned by someone else, who's going to monetize it? Companies may discover that the value of a drug is different once the knowledge of what's efficacious has shifted," says Buck Luce.

As if this prospect was not disorienting enough, drugmakers also face a regulatory thicket blocking their access to consumers, who play an increasingly complex role in this real-time, knowledge-generating feedback loop. "Pharma is at a disadvantage in the social-media competition because of FDA regulations. That leaves room for other players to get in between the drugmaker and the consumer," Buck Luce says. In 2010, the agency has promised to produce long-awaited recommendations, if not firm regulations, about the use of social media by pharma.

In 2010, expect PhRMA to take on the issue of the US's innovation gap. "We're asking the White House for a deep dive by a blue ribbon panel that takes a serious look at whether the environment for innovation in this country is degrading or not," says Tauzin.

By framing its lobbying efforts around innovation, PhRMA aims to get policymakers to consider, from pharma's point of view, a host of issues ranging from education in the sciences to tax-and-trade laws to the

FDA approval process. And by arguing that anything that threatens pharma innovation also threatens the nation's health and economy, PhRMA angles to catch public appreciation for the unique value created by the medicine-making business.

This is certainly one approach to resetting pharma's public image. Whether it will have any effect on the drug-pricing squeeze, not to mention the many other upheavals rocking the industry, is an open question. Some analysts believe that cost effectiveness and other healthcare transformations are not only inevitable but beneficial—though not necessarily to pharma's short-term bottom line. They hope that the industry will lead the way, and help shape change, but they fear it will resist instead.

Pharma CEOs can be forgiven for their resistance. The enterprise of discovering treatments and cures for diseases is hard enough without a other pressures. Yet cutting R&D budgets may not be the best way to reboot the innovation system. Wall Street is always lurking in the background, with its bottomless hunger for strong quarterly results, even though the biggest bets demand a lengthening development horizon overshadowed by growing risk.

As industry leaders wait for this experiment's results, they have a new entire decade to practice their new realism. Megablockbusters are a thing of the past. Hundreds of thousands of people have been laid off. The value of the industry is down by a trillion dollars.

"The revenues of the industry haven't declined yet, but projections say they will," notes Tollman. "Growth rates have gone down significantly, so it's certainly not a growth industry anymore. That's a very long journey."

—Carolyn Buck Luce, Ernst & Young
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