1 October 2012 | 11 pages

Drugs (Citi)
Europe

White House Calls for FDA to take More Risk

R&D ROI will double; sector remains materially undervalued

■ Industry Overview

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- **PCAST initiatives indicate intent to materially increase FDA risk appetite.** We see the initiatives proposed in the just published PCAST (President's Council of Advisors on Science and Technology) report as having a very significant positive impact on industry R&D productivity. The significance of this PCAST report will likely only be fully appreciated in retrospect. The indicated PCAST initiatives will enhance the positive impact of self-help initiatives already underway in the industry, outlined in our report Shrink Smarten Spin. Three Killer Apps to Improve R&D Productivity. Companies with pipelines addressing serious or unmet medical needs will benefit the most from these proposals. Key European beneficiaries include Roche and Novartis. We continue to see considerable value in the sector – the current terminal growth rate of -3% fails to discount the impact of R&D initiatives coupled with fiscal stimuli such as patent boxes. BUY rated Bayer, GSK, Sanofi, Novo are key names

- **What's New?** In a landmark 75 page report published Friday evening the influential PCAST outlined a comprehensive series of practical initiatives over the next 1-5 years to be undertaken by the FDA and the industry with the stated goal designed to "double the output of innovative new drugs by the FDA". The report is a response to intensified political concern over industry's and VC's disinvestment in R&D.

- **Isn't this just pre-election rhetoric?** The industry disinvestment in research is a bipartisan concern. The report was co-authored with the input of the current FDA commissioner, independent academic and economic leaders and support of the industry. Key initiatives include guidance/ instructions to the FDA to significantly increase the use of accelerated approvals on surrogate endpoints, and critically to allow accelerated approvals on the back of so called "intermediate clinical endpoints" which related to how patients "feel and function". A supplementary clinical pathway is described "Special Medical Use". Details in report.

- **Can one report make a difference?** We strongly argue yes. The 2006 Institute of Medicine's 'The Future of Drug Safety - Promoting and Protecting the Health of the Public' report was a key factor in increasing the risk adverseness of the FDA and the subsequent decline in industry R&D returns. We see the PCAST report as the logical progression of a series of initiatives that Congress and the FDA have explored over the last 12-24 months outlined in our brief report. The removal of the Avastin breast indication, declining off-label drug use and the invalidation of the pre-emption product liability events were key enabling events for the PCAST initiatives.

- **What could derail these initiatives**? A Romney victory would likely result in a new FDA commissioner, but the worst case would likely only delay some of these initiatives. The emergence of a Vioxx like safety concern would likely derail these reforms, but the tightened pharmacovigilance makes this a low probability event.

FDA Risk Appetite Set to Increase

Political anxiety related to industry R&D disinvestment has reached record levels

Why now? The political and industry unrest over depressed R&D productivity and sustained low approval rates has intensified with industry's ongoing disinvestment in R&D and several critical areas of research (especially Alzheimer's and psychiatric illness). The PCAST guidance with implied buy in from the FDA Commissioner's Office (given they were contributors) is the accumulation of a series of enabling factors that have allowed the FDA to move from a position of risk adversity to one of calculated risk appetite. The PCAST report is available on request.

Enforcement Activity by the Department of Justice has effectively curtailed off label promotion

Enforcement Activity by the Department of Justice has effectively curtailed off label promotion. A lower assumed level of off label promotion allows the FDA to take more risk in their regulatory decision. The fines and settlements levied by the Department of Justice have increased from $500m in 2000 to $6bn in 1H 2012 alone (Figure 3, 4). The bulk of these fines related to the illegal promotion of drugs under the False Claims Act. As a consequence of this punitive activity, compliance in the industry has been materially strengthened with relatively low levels of off label promotion in the US, we believe. We anticipate that the reduction in off label promotion as a consequence of the heavy burden of enforcement is an important contributory factor in allowing the FDA to take greater regulatory risk in approving new drugs.

Demise of the Pre-emption defense

Demise of the Pre-emption defense. During the period 2008-early 2010, risk appetite at the FDA reached an all time high, we believe. Post Vioxx withdrawal, the FDA was under intense political and medical scrutiny as the plaintiff lawyer lobby sought to undermine the FDA as a means to the preventing the Supreme Court from upholding the Pre-emption defense as a valid product liability defense. Following the negative ruling for Wyeth's in the Supreme Court ruling on pre-emption in Wyeth vs. Levene in 2010, there was a notable diminution in the negative political and media focus on the FDA. Consequently, the risk appetite at the agency appeared to improve to notable effect. Most recently, we note the approval of two novel drugs for obesity, an area with significant historic safety risk (Fen/ Fen, Meridia, Acomplia etc).

FDA believes its risk detection systems have improved

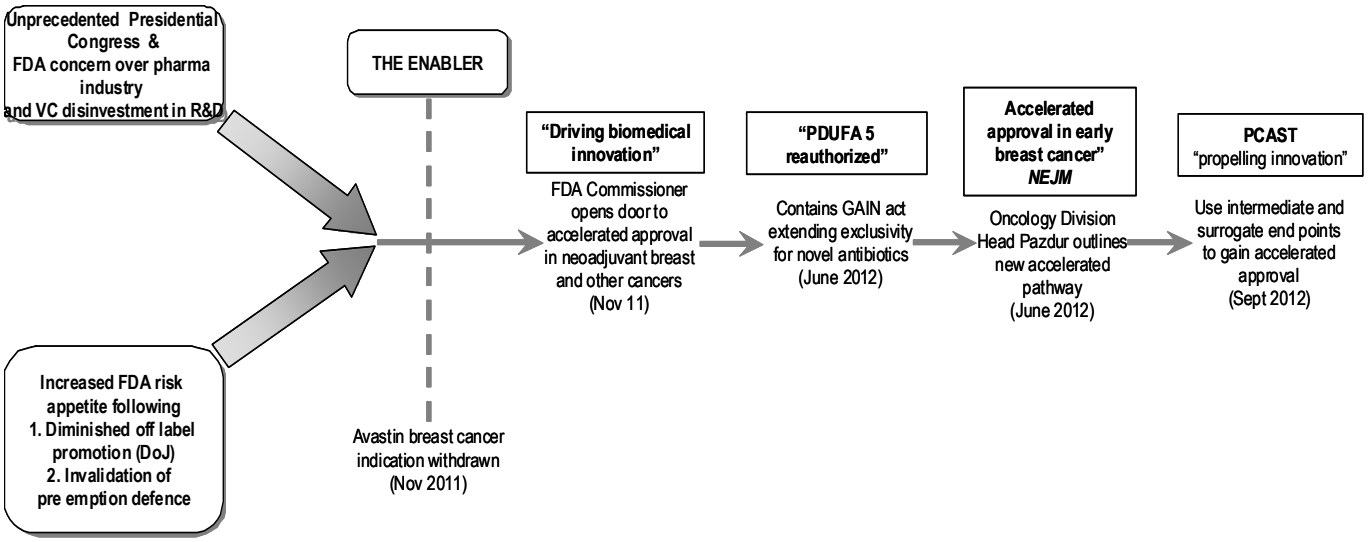
FDA believes its risk detection systems have improved. An additional factor aiding the agency's migration to a greater risk appetite is the build out of both REMS (risk monitoring programs) coupled with mini SENTINEL and SENTINEL safety initiatives.. All three systems are designed to leverage the increase availability and quality of real world data to detect latent safety signals at an early stage post approval.

Withdrawal of Roche's Avastin breast cancer indication was a critical "enabler" for proposed PCAST initiatives

"The Enabler". Even with the aforementioned contributory factors, the PCAST proposals would be unthinkable in the absence of the 2011 removal of the breast cancer indication for Roche's Avastin in the US. Roche's Avastin was given approval under the Accelerated Approval pathway in 2008. However, the requested confirmatory trials failed to meet the FDA's hurdles and to much surprise, the agency revoked the conditional approval and removed the breast cancer indication. While this was clearly a profound negative event for Roche, we see the removal of the breast cancer indication as an important positive event for the industry. The ability of the agency to remove an indication from an established commercially significant agent, effectively gave the FDA the remit to broaden the accelerated approval (conditional approval) pathway to many more agents.

Since the Avastin withdrawal, we have been able to detect a number of regulatory proposals by the FDA as well as legislative action which lay the path for many of the initiatives outlined in the PCAST document. These are summarized and listed in Figure 1.

Figure 1. PCAST Recommendations Will Help to Transform Industry R&D Productivity

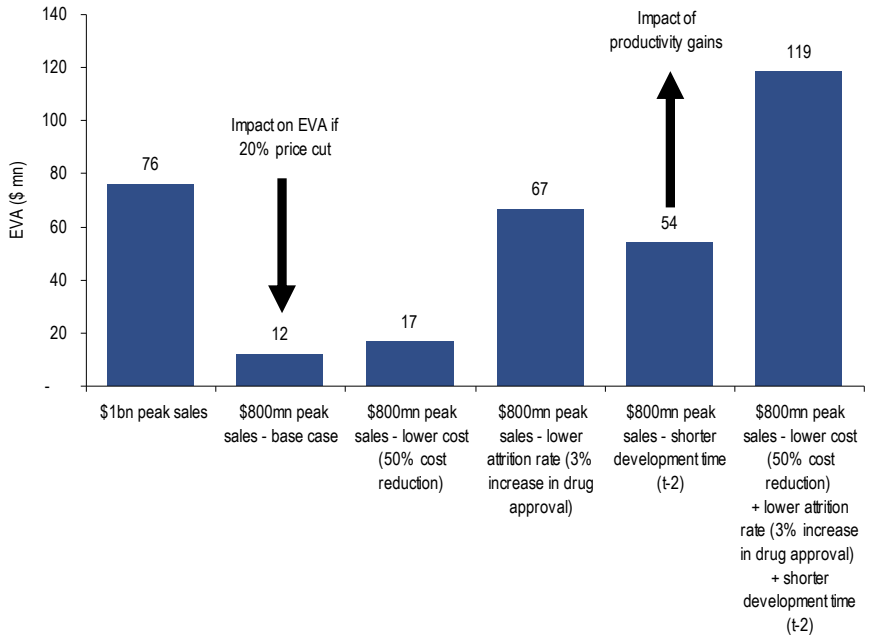


Source: Citi Research

Approval Times for Early Stage Breast Cancer could be accelerated by 4 years

Approval Times for Early Stage Breast Cancer could be accelerated by four years. One notable recent example is the pathway for approval of novel agents for adjuvant (early stage) breast cancer. We understand that the FDA is considering allowing accelerate approval for high risk adjuvant breast cancer patients, on the back of trials showing novel agents significantly increase pCR (partial complete response rates) in neo adjuvant patients. If such a pathway is validated, it could potentially accelerate approval for the important adjuvant (early stage) population by up to 4 years. Multiple novel agents including PI3 kinases, anti-Her2 therapies and others could stand to benefit. Within cardiovascular medicine, we may have to reconsider our cautious stance on Novartis's Relaxin .when we assess their phase III data at AHA. While the major potential beneficiaries of these changes is potentially the patient, a 4 year reduction in time to market has a dramatic impact on EVA as demonstrated in the exhibit below.

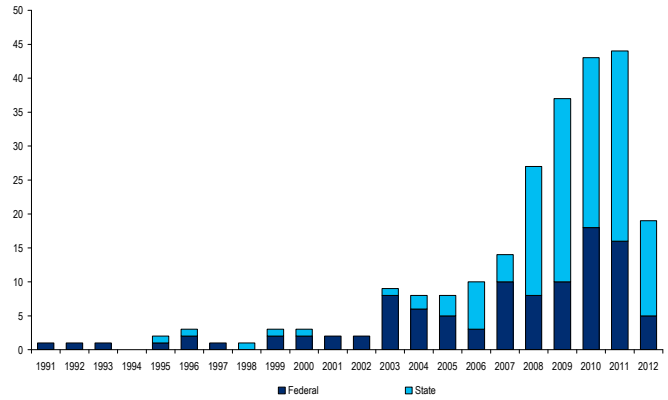
Figure 2. Shorter development time has a dramatic positive development on EVA (Citi Risk adjusted EVA R&D model)



Source: Citi Research estimates

What about Europe? In recent years, the EMA has been notably less risk adverse than the FDA for the aforementioned factors. However, we believe the situation is set to reverse with the FDA likely being a driver for greater risk appetite at the EMA going forward.

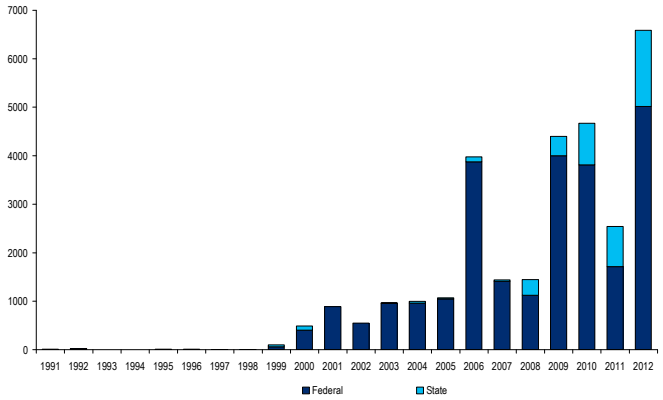
Figure 3. Number of Pharmaceutical Industry Settlements, 1991 – July 18, 2012*: State vs. Federal



*Totals for years 1992, 2000, 2003, 2004, 2005, 2007, 2008, and 2009, are slightly discrepant from the 2010 report. Since that report, one additional state case in CA in 2000 has been found and added and another state case in WV in 2009 has since been successfully appealed by the company and removed from the database. Ten cases (one in 1992, two in 2000, two in 2003, one in 2004, one in 2005, one in 2007, one in 2008, and one in 2009) that were classified as state settlements in the 2010 report were reclassified upon further review as federal settlements

Source: Source: Public Citizen: Pharmaceutical Industry Criminal and Civil Penalties: An Update, September 2012, Citi Research

Figure 4. Pharmaceutical Industry Financial Penalties have increased from $500m in 201 to almost $7bn in 1H 2012



*Totals for years 1992, 2000, 2003, 2004, 2005, 2007, 2008, and 2009, are slightly discrepant from the 2010 report. Since that report, one additional state case in CA in 2000 (for $85 million) has been found and added and another state case in WV in 2009 ($4.5 million) has since been successfully appealed by the company and removed from the database. Ten cases (one in 1992 [$22 million], two in 2000 [$149 and $255 million], two in 2003 [$62 and $80 million], one in 2004 [$1.5 million], one in 2005 [$30.7 million], one in 2007 [$5.5 million], one in 2008 [$1.1 million], and one in 2009 [$20 million]) that were classified as state settlements in the 2010 report were reclassified upon further review as federal settlements

Source: Source: Public Citizen: Pharmaceutical Industry Criminal and Civil Penalties: An Update, September 2012, Citi Research

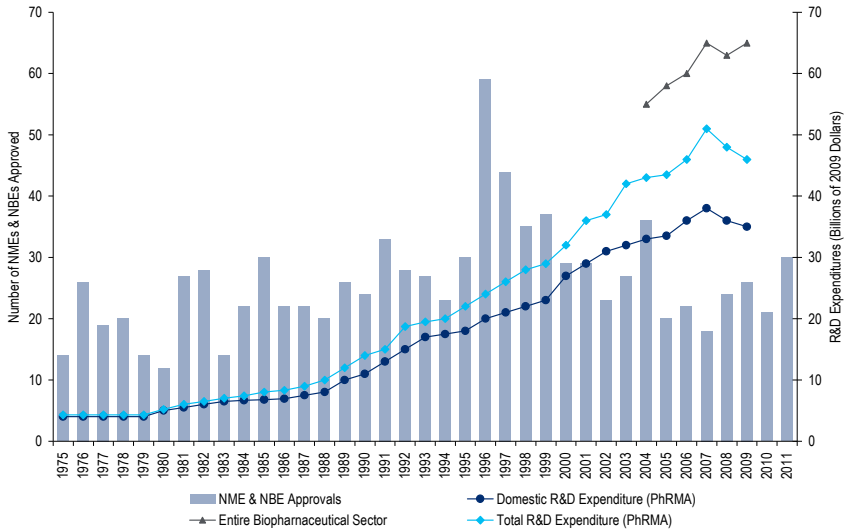
The "anti" IoM Report. In 2006, we failed to pay enough attention to a report from the influential Institute of Medicine that was highly critical of the FDA ability to measure safety. The IoM report coupled with the withdrawals/ near withdrawals of Merck's Vioxx and GSK's Avandia were critical factors that resulted in heightened regulatory hurdles over the following period. Since 1980 the capitalized cost of drug development has increased from $100m to an estimated $2bn in 2011 (Tufts).

Just as the IoM report was a catalyst for the FDA to significantly diminish its risk appetite, we believe the PCAST report represents the converse. The delivery of these recommendations is not unexpected. We highlighted in our 2011 report Shrink, Smarten, Spin that the regulators and governments are keen to aid the industry in improving R&D productivity. The closure of significant industry research efforts and withdrawal from anti-biotic and psychiatric drug development across the industry has critical societal and economic implications.

The PCAST proposals address the broad sweep of research through development and approval. In research, the initiatives relate to greater partnering and transparency between stakeholders to eliminate redundancy and speed time to development. However, we see the main impact of the report being in drug development times and approval rates. In short the proposals effectively calls on the FDA to lower their hurdle in areas of high risk unmet medical need by the adoption of novel endpoints with a lower burden of proof. The existing accelerated approval pathway which allows for conditional approval is already in place but remains infrequently used. The report calls on the FDA to dramatically increase usage in higher risk patient subgroups. In addition, the report calls on the FDA to allow the use of very rarely accepted clinical intermediate endpoints to allow conditional approval in areas of serious unmet medical need. Examples cited in the report include the 6 minute walk test for cardiovascular disease, cognitive function in mild Alzheimer patients, muscle strength in dystrophy, bacterial clearance endpoints for antibiotics and Fixed Vital Capacity Measurements for Spinal muscular atrophy or Motor Neurone Disease.

In addition, PCAST report recommends a novel pathway to approval, the "Special Medical Use". This development pathway would identify a specific subpopulation at high risk from a disease and show the risk benefit in that subpopulation. The SMU label would be intended to send a strong signal to potential physicians and payors and therefore limit off label use and reimbursement. Given a likely lower risk of off label use, the implication is that the risk adverseness of any FDA review would likely be less conservative than it may otherwise have been.

Figure 5. Annual New Molecular Entity and New Biologic Entity Approval vs. R&D Expenditure in 2009 US$



Source: Executive Office of the President's Council of Advisors on Science and Technology, September 2012 & Citi Research

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Novartis AG (NOVN.VX; SFr57.55; 2)
Novo Nordisk A/S (NOVOb.CO; Dkr916.50; 1)
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Appendix A-1

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