



November 2009 Monthly Newsletter

FEATURED ARTICLES

The Off-label Drug Use Conundrum

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FDA regulations for drug approval mandate that companies initially prove their drug is both safe and effective in the treatment of one indication (or main use). This is done to bring focus to an already rigorous approval process, and most companies conduct clinical trials on the indication with the best chance of receiving initial FDA approval.

Since many medications are potentially effective against multiple diseases, the drug manufacturer is free to submit approval for other indications after this initial approval as long those submissions are also supported by data from clinical trials. Manufacturers have a critical cost-benefit decision to make when it comes to FDA approval for additional indications. The benefit to additional approvals is the ability of the manufacturer to actively market a product for all approved indications. Additionally, an approval implies adequate scientific data exists testifying to the safety and efficacy of the drug in the treatment of specific diseases, improving the likelihood that medical professionals, health insurance providers and, ultimately, patients will accept the medication for its approved uses. This all sounds pretty straightforward – pass the rigorous approval process and promote the benefits of the product in the healthcare marketplace.

However, what are physicians to do when they have exhausted approved treatment options or have theorized that approved medications may be beneficial for non-approved uses? To address this situation, the FDA permits doctors to use their best judgement in prescribing approved medications for non-approved uses, also called “off-label” use. Off-label use has its benefits. Doctors and patients benefit from having additional treatment options appear more quickly in the marketplace, drug manufacturers benefit from additional sales of their products without incurring the cost of clinical trials, and the healthcare system may benefit from the prevention of illness in patients receiving off-label prescriptions. Some of the best examples of these scenarios involve beta-blockers (approved for high blood pressure; off-label for angina and heart attack prevention) and statins (approved to lower “bad” cholesterol; off-label to reduce heart attack and stroke).¹ Based on these benefits, it is estimated that about one of every five medications in the US are prescribed for “off-label” use.²

Multiple treatment options, happy patients, less burden on the healthcare system, increasing profits for drug manufacturers....but there is a catch. In fact there are several. The most costly of which involves the promotion of off-label uses. In fact, this is strictly prohibited by the FDA as companies cannot promote the use of a drug for indications not stated in the drug’s labelling.³ In recent years, manufacturers have been fined billions of dollars to settle criminal and civil charges related to off-label promotion of their products.⁴

So there is an obvious compliance risk associated with the solicited distribution of information regarding unapproved uses of prescription drugs. Other concerns abound; of the off-label prescriptions, approximately 73% were for a use that lacked any firm scientific evidence.² When the off-label treatment is merely ineffective, the cost is the wasting of precious healthcare dollars. In the worst case scenarios, off-label prescriptions may bring harm to patients. An example of this situation involves drugs to treat anemia in cancer patients undergoing chemotherapy. Physicians assumed these medications would be effective in treating anemia caused by the cancer itself only to find some studies that showed these drugs could make the cancer itself worse and/or lead to a higher death rate.¹

Given the upside potential of off-label prescription use, many medical and industry experts are calling for ways to better differentiate between “good” and “bad” off-label use. This will likely involve striking a balance between theorized and definitive scientific evidence regarding the safety and effectiveness of a medication prescribed for non-approved uses.

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⁴ Benesh, P. *Pharma Seeks Cure For Off-Label Woes*. Investor’s Business Daily, October 26, 2009.

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Pharmaceutical Market Future Outlook

By John Jordan, CIS Senior Compliance Associate

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What are researchers saying about the future of the Pharmaceutical Market? Is it suppose to show growth or contraction? IMS Health is a company that gives the pharmaceutical world a measurement of global market dynamics. Researchers gather information, to relay market intelligence to both the pharma and healthcare industries, which is used by many of the world's largest pharmaceutical and biotech companies.³ What are they predicting for the pharma world? IMS is stating that the market is going to grow 4 – 6% in 2010, with a 4 – 7% expansion through 2013.¹

With this growth of 4 -6%, the market should exceed \$825 billion in US currency. The global market is predicted to expand up to, and could even exceed, \$975 billion by the year 2013.¹ Murray Aitken, senior vice president of Healthcare Insight, IMS, which makes predictions after analyzing key market dynamics, states:

"Overall, market growth is expected to remain at historically low levels, but stronger-than-expected demand in the U.S. is lifting both our short- and longer-term forecasts. The economic climate will continue to be a dampening influence in most mature markets, particularly in those countries with rising budget deficits and publicly funded healthcare systems. In the U.S., pricing flexibility and inventory management actions are contributing to much higher growth than anticipated earlier this year, and are the main reasons for the upward adjustment to our five-year forecast."¹

One of these dynamics is the improvement of the US market that was driven by stronger near-term growth, and the showing of both changing inventory stock patterns, as well as price increases. With the economic troubles many companies have seen, inventory levels are being monitored much more closely and, in doing so, are leading to greater purchasing volatility than was seen in earlier years. According to IMS, the US is to show a growth of 4.5 – 5.5% growth in 2009, and 3 – 5% growth in 2010.¹ Another country's market that will add to this global growth is China. China's market is predicted to expand 20% or more annually through the year 2013.¹

However, there are some key negative dynamics that are preventing the global expansion from becoming even greater. Growth has slowed in countries such as Russia, Turkey, South Korea, and Mexico, where there is high out-of-pocket spending on pharmaceuticals. Also, the impact of patent loss imbalance is predicting to limit growth. A "patent cliff," which shows an imbalance of new product introduction and patent losses, will contract the market from reaching double digit expansion.⁴ One example, in regards to the patent cliff, is provided by Business Monitor International, which states that the US will show a -0.35% contraction towards their growth over this time period.² Within the next couple of years, products that currently generate \$137 billion in sales are suppose to lose their patents and face generics; Lipitor®, Plavix®, and Seretide® are some examples.

Other dynamics that were assessed include healthcare access and funding under intensifying pressures due to "economic climate that heightened concerns" by the public. This creates awareness for the public to dive into finding research over price cuts, reimbursement of innovative therapies, and economic incentives for prescribers and pharmacists to shift to generic alternatives.¹ Manufacturers are setting up or sponsoring websites and other various outlets to promote patient assistance programs, which can help lessen the financial burden on eligible patients.

As Aitken quotes, "While our outlook for the global market is more positive than earlier in the year, the fundamental dynamics of the innovation cycle, funding pressures, and the broader macroeconomic environment will result in mid-single-digit growth over the next five years. Notwithstanding the improved prospects in the U.S. market, the drive by pharmaceutical manufacturers to adapt to the longer-term marketplace trends and evolving patient needs will continue undiminished."¹

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FDA's Slow Approval Times for Cancer Drugs and New Drugs

By Venessa Piper-Givler, CIS Compliance Manager

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It takes years of development and testing to move a new drug from the laboratory to the patient. In 2000 the average approval time for new drugs with new molecular entities (NME) never before seen on the market was 15.6 months, with an average NME approval time of only 11.6 months in 1999. It is now believed that the 15.6 months for approval is no longer accurate, and the new drugs on fast track approval that were averaging six months are now averaging nine months.¹ For many patients, this timing is critical, especially for those with cancer.

On average, new cancer drugs take about seven years to reach approval whether they were a part of the accelerated process or not. According to a study by the National Cancer Institute, 19 new cancer drugs have received accelerated approval by the FDA since 1995, but 32 others were granted regular (not accelerated) approval.² "This is a disappointment," says Charles Bennett, a professor at Chicago's Northwestern University Feinberg School of Medicine. "The accelerated approval program is supposed to allow promising drugs to go to market early, in order to save the lives of people with a short time to live."² Most cancer patients are willing to accept a higher level of risk if they have no other hope for extending their lives.

Bennett goes on to explain that "none of the cancer drugs given accelerated approval were recalled for safety. Although the program began well, its progress has stalled in recent years."² When it is decided by the FDA that a drug's benefits outweigh its risks, the drug is approved for market. "When the program began, the FDA approved many drugs based on smaller studies without comparison groups. Today, the agency prefers that companies perform larger studies with comparison groups, although it may accept interim results, says Richard Pazdur of the FDA.² With clinical trials requiring so many more patients, these large-scale studies cost more than \$600 million and can take an additional five years. Many smaller companies do not have the budget to spend on these types of large-scale studies, while many cancer patients cannot afford to wait this long for a study to be completed and a drug to be approved.²

There seems to be a greater concern that there is more caution coming from the FDA's cancer division, the Oncology Drug Advisory Committee (ODAC), and that delays in approving new drugs may have a dramatic impact on the lives of cancer patients.³ There are private organizations that seem to be pushing the FDA to allow seriously ill patients with no other options access to promising drugs still in the approval pipeline. Says Steven Walker of the Abigail Alliance, organizations like his are fighting for patients "because most terminal patients are too busy battling their diseases to fight the FDA."⁵

However, the FDA regulators state that overall the FDA approved more new drugs in 2008 than the prior three years. The FDA approved 24 new or first-of-a-kind drugs in 2008, more than the 18 approved in 2007, the 22 approved in 2006 and the 20 approved in 2005.⁶ The agency also approved dozens of other new drug applications for new formulations or new uses of existing drugs. "The FDA doesn't try to have any certain number of new drug approvals each calendar year," states FDA spokesperson Sandy Walsh. She states that "it's hard to compare one year's figures with a previous year because drug applications come in on a rolling basis."⁶

The industry's analysts explain that the new drug approvals are welcomed, but are frustrated by the delays in the approval process and many missed deadlines.⁶ According to PharmaManufacturing.com, "John Jenkins, the director of the FDA's office of new drugs, told an industry conference this month that the agency has 'been struggling to meet [drug approval] goals for the past several years' and earlier this year made a "management decision" that it simply couldn't meet all of its deadlines in 2008 given the workload and a staff shortage."⁶

The FDA explained that it missed its action deadlines on 32 out of 159 new drug applications through October 31, 2008 which amounts to 20% of the time. It was explained that the agency had hired 800 employees, but that training those employees takes time. Per Jenkins, "the agency hopes to be closer to the goal of reviewing 90% of drug applications on time next year."⁶

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REMS Helps Patients Decide—Does the Benefit Outweigh the Risk?

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If the FDA approves a drug for market, then it must be safe, right? This has been the general public's perception, but has it been accurate? As we have seen in the recent past with the removal from market of popular drugs like Vioxx, Meridia and Baycol, *safe* does not necessarily mean harmless (even though any thesaurus would indicate otherwise).

So, how can the public be reassured that drugs approved by the FDA are not going to cause more health problems than they remedy? This is the question that appears to be upmost in the FDA Chief's mind. Dr. Margaret Hamburg told the Cleveland Clinical Medical Innovation Summit in early October that "her top priority is restoring public trust in the agency."¹

What the public may not consider is that when it comes to any drug, "*safe* means that the benefits of the drug outweigh the risks for the population the drug is intended to treat and for its intended use."² When it is decided by the FDA that a drug's benefits outweigh its risks, the drug is approved for market. Post-marketing surveillance is used to identify safety issues with a new medicine that were not observed prior to approval. This may be due to the much larger size of the potential public consumption of a marketed drug compared to the number of people who participated in the clinical trials – the more people that take it, the more likely there will be additional safety issues; safety issues also may be due to people not taking the drug as anticipated or recommended.²

Risk can never be completely eliminated, so it must be mitigated. For the majority of approved products, labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits. However, the Food and Drug Administration Amendments Act of 2007 (FDAAA) granted the FDA the authority to require the submission and implementation of a Risk Evaluation and Mitigation Strategy (REMS), if deemed necessary, to ensure that a drug's benefits outweigh its risks.³

A REMS is a plan to manage a known or potential serious risk associated with a drug. A REMS can include a Medication Guide (21 CFR Part 208), Patient Package Insert, a communication plan with healthcare providers about risks of the drug, elements to assure safe use (i.e. periodic monitoring or tests), and it must include a timetable for assessment of the REMS. The FDA is increasingly looking for companies to commit to using multiple and alternative vehicles to get safety information out to consumers, including methods that can be tracked or audited. REMS must include assessments at 18 months, 3 years and 7 years after the plan is approved.³

The main question for a company to ask when considering if a REMS is required for a drug is whether or not the FDA will consider labeling alone to be sufficient to ensure that benefits outweigh risk. The FDA is still refining its process for developing and approving REMS, but this is certainly one step taken that may help lead to improved public confidence in the FDA.

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