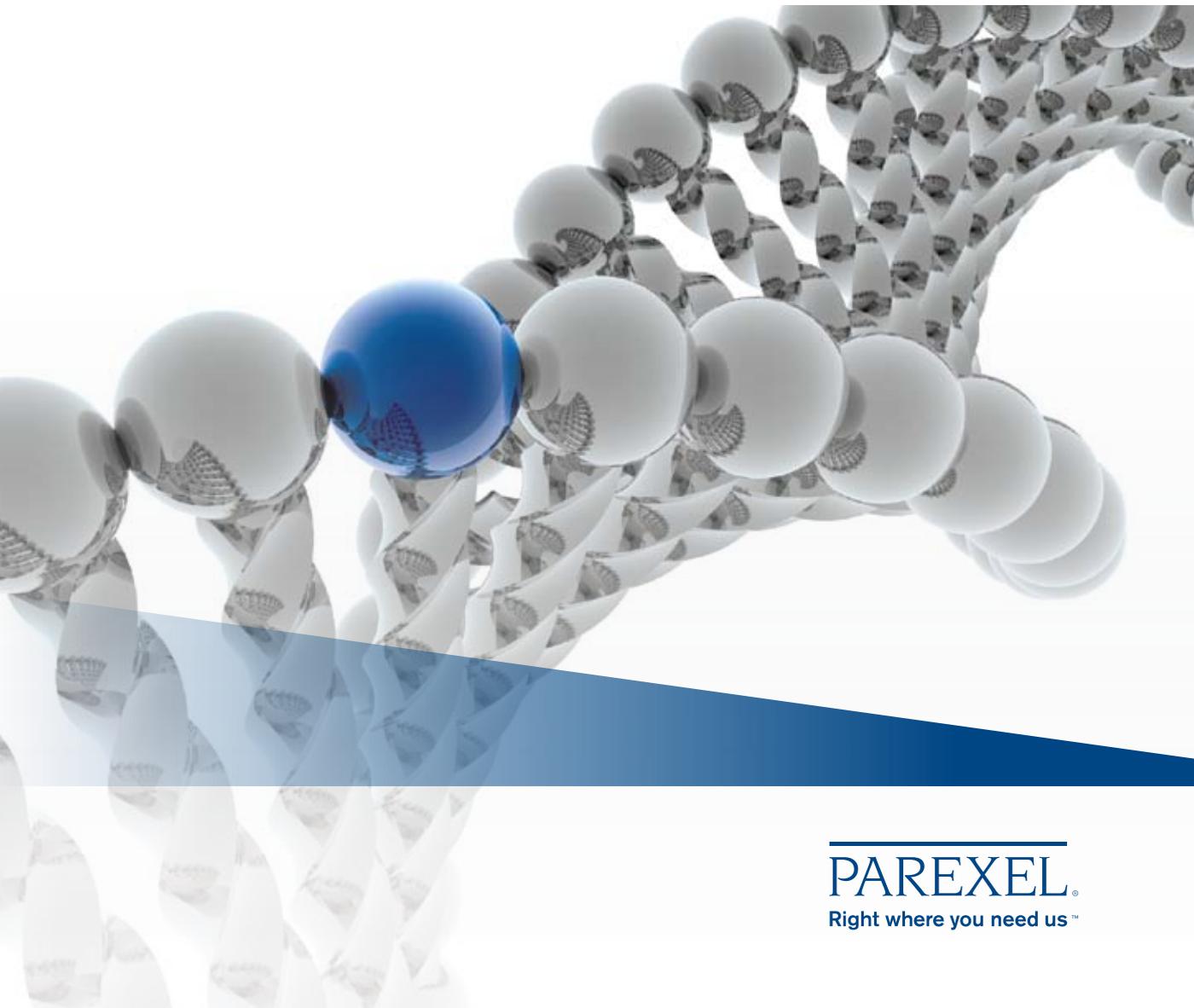


Drug innovation, approval, market access, and the “new normal”

Emerging FDA review outcome trends for new drugs



“ And so even in the United States, we can approve drugs and we’ll get them on the market, but for them to be successful, they are going to need to have demonstrated value... If you can show tremendous value for your drug, even in a small patient population, the payers are going to pay for it, because there’s a population out there that will truly benefit. And I believe that’s the future. ”

Janet Woodcock, M.D., director, FDA Center for Drug Evaluation and Research, DIA Annual Meeting, June 17, 2010



Even as many pharmaceutical companies move to diversify their businesses and expand their global footprints into emerging markets to help drive industry growth going forward, their ability to secure approvals for truly innovative and valuable therapies in major markets remains the single most critical factor that will determine their fates in the near and mid-term. As companies wait for their emerging business strategies to gain traction, their key challenge remains converting their R&D pipelines to approved products—more specifically, gaining product approvals in key markets, such as the United States and Europe.

In two earlier executive briefings from our Intelligent Development Series (*Getting to Approval*, September 2008, and *The Innovation Imperative in the Safety First Era*, September 2009), PAREXEL Consulting identified and discussed a series of key industry and FDA drug approval performance metrics. In this, our third and latest installment in the series, we explore several emerging trends that PAREXEL Consulting believes provide fresh and valuable insights regarding the pharmaceutical industry’s goals in achieving new drug approvals in the United States, which remains the world’s single most lucrative pharmaceutical market.

In terms of both industry activity and output as well as FDA drug review outcomes and tendencies, much can change in a year. And this past year has been no different. In the past year, we have seen the following:

- A sudden and encouraging bounce in industry new molecular entity (NME) submission activity, even during the throes of a global economic crisis. While still well off the levels seen in the mid- and late-1990s, NME submissions surged during 2009, creating some hope that true industry innovation may be rebounding to some degree.

- A softening in first-cycle approval rates for new drugs, particularly for priority-rated drugs. A critical measure of industry performance and FDA tendencies, first-cycle approval rates for new drugs continue to have significant implications for new drug sales, effective patent lives, and company profits, as our analysis below will illustrate.
- A significant and continuing decline in priority designation rates. Because priority designations have such important implications for overall new drug review cycles and approval times (see analyses below), and are seen by some as markers of true innovation, shifts in designation rates can be useful harbingers of upcoming drug review outcomes and trends.

Given that such trends appear to be developing—and in some respects even deepening—just as the FDA has settled into its FDA Amendments Act (FDAAA)-related responsibilities and the 21st Century Review Process, we cannot help but ask the question: Does what we are witnessing today represent the “new normal” in drug reviews?

The road to drug approval: The U.S. outlook

While emerging markets are becoming increasingly important elements of pharmaceutical industry growth strategies because of their double-digit growth trends, securing new drug approvals in the United States and other key markets will remain critical—North America still comprised 40% of the world pharmaceutical market in 2009, according to IMS Health. As such, there is a universal and deep need to gain fresh insights into the current environment at the FDA, an environment that could determine the near and medium-term performance trajectories of even the largest pharmaceutical companies.

In this executive briefing, PAREXEL Consulting updates its Intelligent Development series by identifying and discussing a series of industry and FDA performance metrics that may challenge some perceptions of the current approval process and further inform others. This briefing will shed light on the current state of the FDA's new drug approval process, and provide a peek inside that process to see how new drugs are reaching their ultimate review outcomes today. It also explores some of the key success factors that appear to lead to the outcome that companies most crave and need—an approval in the very first review cycle.

Is innovation re-filling the pipeline?

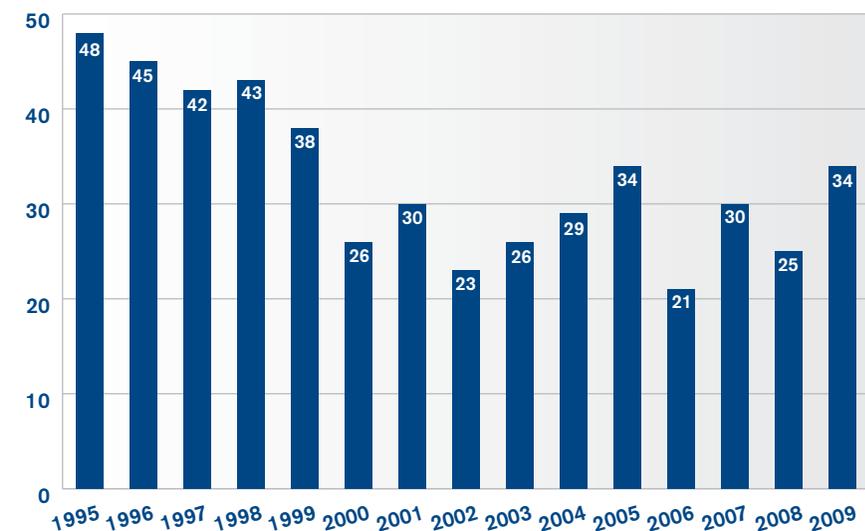
Although the number of NMEs approved by the FDA each year clearly is the purest measure of industry's innovative output and to some extent FDA's review productivity, there are other, further upstream measures that can offer additional insights into the pharmaceutical industry's level of innovation as well as the FDA's review pipeline for this closely watched category of products. And whatever else one has believed about the state of the FDA's new drug approval process in recent years, it is undeniable that there have been fewer drugs being evaluated under that process.

While the 34 NME filings in 2009 represent an encouraging sign, the NME submission level is still well off those seen in the 1990s, when industry submitted an average of 43 NMEs for FDA review annually. It is also important to keep in mind that FDA data suggest that increasing percentages of NMEs submitted for FDA review are never approved at any point after an initial submission (particularly standard-rated products).

Clearly, however, industry's output of NMEs reaching the submission stage has rebounded from the difficult 2000-2004 stretch.

For the second time in three years, however, we saw a sudden resurgence in NME submissions during 2009. Industry's NME submissions spiked 36% in 2009 to reach 34, matching 2005, their highest level since 1999 (see exhibit below).

Annual Number of Marketing Applications for New Molecular Entities Filed with the FDA, 1995-2009





First-cycle approvals: The true value in getting it right the first time

Regardless of the number of new drugs surviving the rigors of the clinical testing process to justify an NDA filing today, it is imperative that those that do survive gain approval quickly.

The shortest distance between an NDA submission and product launch is a first-cycle approval from the FDA—that is, an approval without the need for additional clinical or other testing/analysis, a sponsor resubmission and a second (or third) formal FDA review cycle to evaluate the resubmission.

For any drug company, to which time is such a critical commodity, the implications of a first-cycle review are enormous—for revenue flows, preserving effective drug patent lives, and market share. And for those NMEs approved in 2008 and 2009, the total approval times of those cleared in a single review cycle were, on average, almost two years shorter than those that were not (see exhibit below). Keep in mind that this gap applies to drugs that, in the end, proved to be sufficiently safe and effective to obtain FDA approval.

Unfortunately today, at least several factors make the prospects for first-cycle new drug approvals seem as uncertain and as challenging as ever before, including:

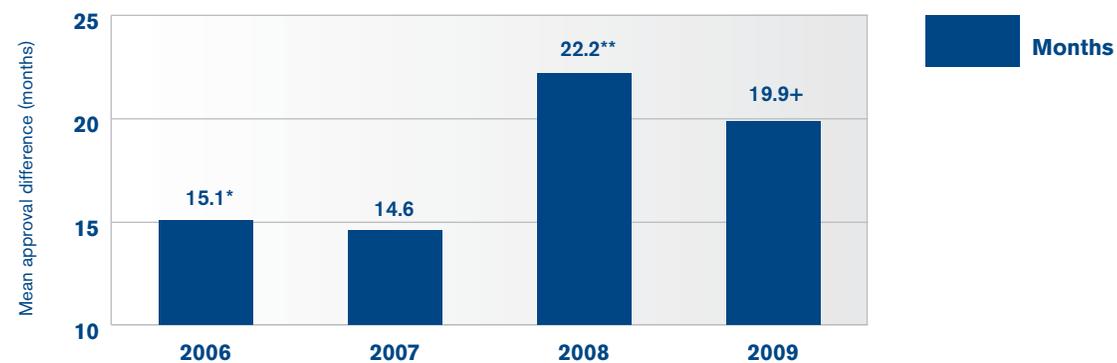
- The FDA's continuing implementation of the Safety First Initiative, under which CDER has declared that "drug safety is our first priority." Many outside the agency fear that the initiative will lead to more first-cycle review failures as FDA reviewers interrogate possible safety issues even more carefully than in the past, and as drug applicants may be asked to provide more pre-approval evidence of safety.
- CDER's increasing use of its powers under the FDA Amendments Act of 2007 (FDAAA), in particular the authority to require companies to implement risk evaluation and mitigation strategies (REMS) in better controlling drug use and monitoring post-approval effects, and the degree to which this is creating new demands late in the NDA review process.

In fact, Office of New Drugs Director John Jenkins, M.D., noted in late 2009 that "incorporating development and approval of a complex REMS during the first review cycle is almost impossible." As Jenkins has also noted, REMS are far more likely to be relevant to priority-rated drugs, which ironically have been the very products most likely to obtain first-cycle approvals in the past.

- The outcome of the controversial mid-2010 assessment of Avandia's safety will have, at a minimum, ripple effects for the FDA's entire drug review process and, some analysts maintain, could lead to fundamental shifts in how the agency considers drug risks and benefits. In particular, the outcome of the Avandia case could re-mobilize agency critics who maintain that the agency should have separate drug centers for approving new drugs and monitoring postmarketing drug safety. Other issues, including emerging questions about the value of Avastin for advanced breast cancer (for which it received accelerated approval), could have equally significant implications.

The First-Cycle Review Imperative, 2006-2009

Approval time difference between NMEs receiving 1st cycle approvals and those requiring multiple cycles (two or more)



*Excluding one extreme outlier, 6-year review of Pylera

**Excluding multi-cycle 60.3-month review of Vasovist

+Does not include Sabril

First-cycle approval rates soften: Is REMS driving the “new normal”?

Perhaps confirming the concerns of some about the repercussions of the Safety-First Initiative and more conservative FDA decision making in new drug reviews, there is emerging evidence of a softening in first-cycle approval rates for certain classes of new drugs. After setting a user-fee era record by granting first-cycle approvals to 51% of the original NDAs submitted in the FY2006 cohort, CDER has approved modestly lower percentages in the subsequent years. With about 70% of the FY2009 NDAs having received first actions (as of March 31, 2010), CDER had approved only 42% of the applications. If this rate holds, it would represent the lowest rate since the FY2003 cohort.

Interestingly, what appears to be driving the overall NDA rate lower is a somewhat more dramatic downturn in first-cycle approval rates for priority-rated NDAs. Following an impressive several-year run up to what is likely a record 70% rate for the FY2007 priority NDAs, first-cycle approval rates for priority NDAs have declined for the two more recent cohorts. After declining to a 63% rate for the FY2008 priority NDA cohort, the first-cycle approval rate for the FY2009 priority NDAs slumped to 53% (with one pending priority NDA as of March 31, 2010), which would be the lowest rate since the FY2003 cohort.

Originally, there was some thought that the first-cycle approval rate for the FY2008 NDAs might have represented a temporary dip caused by CDER’s staffing/workload challenges and the early implementation of the FDAAA requirements, in particular the REMS requirements, which were most relevant for priority-rated drugs and were particularly difficult to address in the context of a six-month priority review.

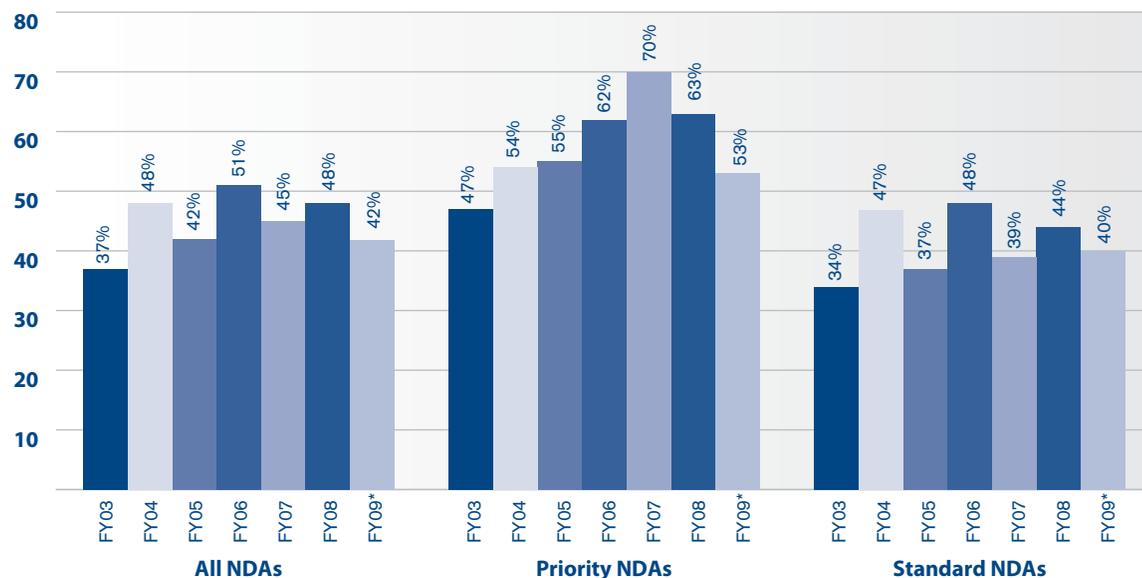
But the further decline in first-cycle approvals for the FY2009 cohort might suggest that CDER continues to have difficulty in reviewing and approving certain REMS programs within the priority-review setting.

Given that CDER review divisions no longer had the option of missing PDUFA review goals for the FY2009 priority NDAs (to the same extent as they did for the FY2008 cohort), it could be that the divisions needed the multiple review cycles to address REMS and other postmarketing issues. If so, could this be the “new normal” for priority drug reviews?

Perhaps lending further credence to this theory is the fact that first-cycle approval rates for standard-rated NDAs have remained virtually unchanged for the last three NDA cohorts, with no signs of a softening. With about 70% of the standard FY2009 NDAs receiving first actions as of March 2010, 40% had been approved in the first review cycle, compared to 44% in FY2008 and 39% in FY2007.

FDA officials have pointed out that REMS requirements and their time-related demands are not as relevant to standard-rated NDAs as they are to priority-rated NDAs—that is, because the types of safety issues that would call for a REMS would likely preclude the approval of a standard-rated therapy.

First-Cycle Approval Rates for Original NDAs, FY2003-FY2009



* through March 31, 2010

How much is a first-cycle approval worth?: An EvaluatePharma®/PAREXEL Consulting analysis

A first-cycle approval is worth almost \$400 million in U.S. sales on average for the NMEs and new biologics approved in 2009, according to a July 2010 analysis by EvaluatePharma® and PAREXEL Consulting. The figure is based on the 19.9-month mean approval time difference between those NMEs cleared in the first review cycle in 2009 and those that took multiple review cycles (two or more) to secure FDA approval.

To monetize this considerable review time gap, PAREXEL Consulting and EvaluatePharma® calculated the lost revenue based on May 2010 EvaluatePharma® projections for the fifth-year postlaunch sales of the NMEs/new biologics approved in the United States during 2009. Specifically, EvaluatePharma® projected that, in 2014, the 32 NMEs/new biologics approved in 2009 would create \$7.44B (\$233M per drug) in U.S. revenue. Applying the \$233M per-drug figure to the 19.9-month review-time gap (1.66 years) results in \$386.4M as the average value of a first-cycle approval in 2009 (i.e., the average incremental sales that a 2009-approved drug stood to gain through a first-cycle approval).

The \$386M figure is misleading in at least one respect, however: As in past years, this analysis is driven largely by the top-tier drugs/biologics—the top five-selling drugs/biologics accounted for 54% of all fifth-year post-launch sales for the 32 products approved in 2009. For one of these top five-selling products, the value of a first-cycle approval rises considerably—to a stunning \$1.32B.

The Value of a First-Cycle Approval for an NME/New Biologic Approved in 2009

(based on EvaluatePharma® fifth-year post-launch sales projections for 2009-approved NMEs and biologics)



There is also the initial hint of a related phenomenon within certain high-profile CDER drug review divisions, even those that have had the most predictable review outcome patterns in the past. The Division of Antiviral Drug Products, for instance, has seen the percentage of NDAs gaining priority designations plummet from 96% in FY2006/FY2007 to 8% in FY2009. Interestingly, however, the division has seen the first-cycle approval rate for the standard-rated NDAs soar to 80% (from 60%-70% previously), higher than even its first-cycle approval rate has been for priority-rated drugs (or overall) in any of the last several years. Is this a sign that it is just easier, in many cases, for divisions to address the emerging FDAAA- and Safety First-related demands in the context of a ten-month review than a six-month priority review? Is this another sign of the “new normal”?

It is worth pointing out that, over the years, differential and counter-intuitive first-cycle NDA review outcomes for several divisions appear to suggest that the units have struggled with six-month reviews. In certain divisions, such as the Division of Neurology Products and the Division of Metabolism and Endocrine Products, priority NDAs have struggled far more (e.g., in terms of first-cycle approvals, filing assessments) than their standard-rated counterparts, in sharp contrast to center-wide trends.

The “Innovation Imperative”: Advantages persist for priority drugs

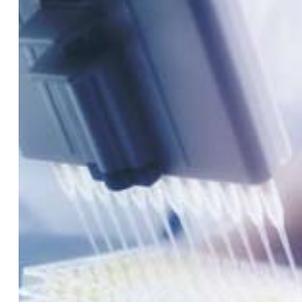
Despite the recent downturn in first-cycle approval rates for priority-rated medicines, we believe that there remains strong and convincing evidence supporting what we have termed “the innovation imperative”—the concept that the most innovative new drugs will enjoy clear advantages in critical regulatory and coverage/reimbursement reviews. This evidence includes the following:

- A significant mean approval time gap favoring NMEs with priority ratings. Among the new drugs approved in 2009, priority NMEs were cleared 8.2-months faster than standard-rated NMEs. Although down from previous years (the gap had averaged 12.8 months from 2005-2008), the 8.2-month gap remains substantial. Put another way, the priority rating will be worth \$159M in terms of incremental sales to the NMEs cleared in 2009, applying the EvaluatePharma®/PAREXEL Consulting estimates above to this review-time gap.

- A significant post-submission survival advantage for priority-rated NMEs. According to emerging data released by the FDA in late 2009, almost 80% of all priority NMEs submitted for FDA review during PDUFA III had obtained agency approval (the agency also projected that the ultimate approval figure would flatline at this rate). In the same analysis, the FDA projected that only ~57% of the standard-rated NMEs submitted in the PDUFA III cohort would ultimately gain approval (based on the 50% that had obtained approval by the 30-month mark post NDA submission). While both priority- and standard-rated NMEs have seen their submission-to-approval survival rates decline since the beginning of the user-fee era (1993), the decline has been much more severe for the standard NMEs.
- A far more predictable approval path for priority new drugs. Of the six priority NMEs cleared in 2009, for example, all but one obtained approval in the first FDA review cycle. In contrast, only half of the standard-rated NMEs cleared in 2009 earned their approvals in the initial review cycle.



Obtaining priority designations: Is the window of opportunity closing?



As priority designations continue to offer the advantages cited above, new data obtained by PAREXEL Consulting suggest that obtaining such designations has become more challenging just recently. After granting priority status to a many-year high of 30% of original NDAs submitted in FY2005, CDER provided the coveted rating to less than half that percentage of FY2009 NDAs.

In fact, the 13% designation rate for the 2009 NDAs is the lowest rate since FY2002, which was a difficult period for the new drug review process following the withdrawal of several drugs, including a few high-profile medicines.

The priority designation rate decline has been most stunning in the antiviral and oncology categories, the two therapeutic areas that have driven CDER's overall priority designation rate in previous years. Designation rates for cancer-related NDAs have been in a straight-line decline for several years, from 65% of the NDAs in the FY2003-FY2005 cohorts to just 18% of the FY2009 NDAs. The decline in AIDS and other antiviral therapies has been even more precipitous—antiviral NDAs have seen their priority designation rates fall from 95% for the FY2006/FY2007 NDA cohorts to just 8% for the FY2009 NDAs.

While some might attribute the sudden and steep decline in priority designations to emerging demands in the latter stages of the NDA review process (e.g., REMS-related demands), and specifically to review divisions' recognition that they cannot meet these demands in the context of six-month priority reviews, FDA officials disagree. Rather, they see the higher hurdles for priority designation as a function of the natural progression of treatment standards as new drugs over time are expected to clear a progressively higher "bar of innovation" and actually deliver a more significant benefit than previously approved drugs in the same therapeutic class (see quote box below). In other words, true innovation is part of a "new normal."

"The FDA's 13% priority designation rate for FY2009 NDAs mirrors the low rate at which some health care plans and other payers are finding value in newly approved drugs. In a study released in late 2009, The Regence Group found that, over the previous year, it accepted less than 15% of all newly approved drugs onto its formularies.¹ In assessing the value of drugs approved between July 2005 and June 2009, Regence found that 56% failed to exhibit value beyond existing therapies, while only 15% exhibited improved efficacy and 1% showed improved efficacy. This illustrates the need for companies to take into account market-based clinical concerns in the product development process."

Charles A. Stevens, Vice President and General Manager, Reimbursement and Market Access, PAREXEL Consulting

Percent of All Submitted Original NDAs Obtaining Priority Review Status, FY1997-FY2009

	% of Submitted NDAs Granted Priority Status
FY 1997	22%
FY 1998	26%
FY 1999	25%
FY 2000	24%
FY 2001	10%
FY 2002	13%
FY 2003	19%
FY 2004	22%
FY 2005	30%
FY 2006	23%
FY 2007	20%
FY 2008	23%
FY 2009	13%

"We have not changed the definition or application of our priority review policy. We have seen fluctuations in the percentage of applications that are granted priority status over the years and this is likely a reflection of variations in the application cohorts and not a shift in FDA policy. One issue that may come into play in areas like oncology and antivirals is that as new treatments are approved that meet previously unmet medical needs, subsequent drugs that may have been granted a priority designation for the same indication in the past may no longer warrant that status if they do not appear to offer any advantage over available therapy, which would now include the FDA-approved product. So, successful development of new drugs for a particular indication may reduce future priority designation for drugs for the same indication unless the new drugs show an advantage over the previously approved drugs."

FDA Office of New Drugs Director John Jenkins, M.D.

¹ Diller, "What Payers Want: Reliable Data," The Pink Sheet (Elsevier Business Intelligence), November 30, 2009, pp. 28-30.



Conclusion

Our analysis supports the conclusion that the delivery of innovation and success in the initial NDA review cycle remain critical for a new drug's prospects—and for the preservation of its effective patent life. With the FDA's rising expectations for original NDA submissions in the context of the 21st Century Review Process and the new FDAAA-related demands on both the FDA and sponsors (e.g., REMS, safety), sponsor focus on innovation in the pre-submission period clearly has become a factor even more critical to success in the new drug review process.

Whether the above-cited trends represent temporary developments in response to the demands/realities of the Safety First Initiative, FDAAA, or the 21st Century Review Process, or whether they are instead part of a “new normal,” they have important implications for the FDA's drug review process.

And despite such trends, there remains strong and convincing evidence supporting what we call “the innovation imperative” — the concept that the most therapeutically valuable drugs continue to gain preferential treatment in terms of the regulatory (e.g., priority designation, first-cycle approvals) and coverage/reimbursement reviews that are so critical to their ultimate success.

Detailed Findings in this White Paper

To obtain the more detailed findings of PAREXEL Consulting's recent study, on which this white paper is based, please contact Mark Mathieu, Director of Strategic Research, PAREXEL Consulting, mark.mathieu@parexel.com. The detailed findings, which are provided on a complimentary basis, include new drug outcome trends and findings within specific CDER review divisions, among many other areas.

Your feedback, comments or ideas for future topics are also welcome. For your convenience, this white paper is available on the web at www.parexel.com/our-thinking.

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