



ri monitor

ri reimbursement intelligence
Investment Strategies for Biocapital

Issue 1

Insights for BioCapital Investors

From the Editor's Desk

Dear Colleague,

Welcome to the first issue of RI Monitor. The goal of this publication is to provide you with an informed source for reimbursement trends, news, and strategies that will help you negotiate your way through the multifaceted process of developing, investing in, and successfully marketing medical innovations.

Now is the time to recognize how private and CMS payers will impact the success of products now in development — products such as specialty and biologic therapies and advanced device technologies that can carry significant price tags.

Higher drug pricing and implementation of the Medicare drug benefit will require new approaches to controlling costs. Whether you're an investor or an innovator, you will likely face reimbursement obstacles. Therefore, it is vital to obtain answers about how to proactively prepare for and address reimbursement challenges that may influence the success of your product in managed markets.

I hope these articles provide you with the critical information about the formulary process, due diligence, and specialty pharmacy trends needed to support your business planning and revenue forecasting efforts.

We would appreciate your feedback on our new publication, and welcome your suggestions on topics you would like to see covered in future issues.

Here's to your success,

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Medicare Part D: A Key Consideration for Biologics

Since its implementation in January 2006, Medicare Part D drug benefit has had a dramatic effect on the use and cost of prescription drugs in the United States. According to the U.S. Department of Health and Human Services, just 3% of prescription drugs were prescribed through Medicare in 2004. In 2006, this figure jumped to 28%.

This continuing trend is a significant consideration for manufacturers of so-called non-preferred and 'fourth tier' drugs, many of which are biologics.

As much as 35% of the target audience for rheumatoid arthritis, diabetes, and oncology drugs could be among the pool of Medicare beneficiaries. Since Medicare Part D patients make up such a large percentage of the target audience for biotech products, it's crucial that manufacturers give serious due diligence consideration to a product's prospects under Medicare Part D.

Higher costs for patients

With higher patient deductibles, initial coverage limits, and out-of-pocket thresholds, the total out-of-pocket cost for drugs prescribed under Medicare continues to rise.

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FDA Proposal on Off-Label Journal Articles: Opportunity or Pitfall?

Recently, the FDA issued a draft document on "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices — Draft Guidance." That's a mouthful... but what does it mean for drug makers, medical device manufacturers, and biotech companies, who now have an opportunity to present off-label uses like never before?

While the draft guidance theoretically eases restrictions on the use of article reprints distributed to doctors —

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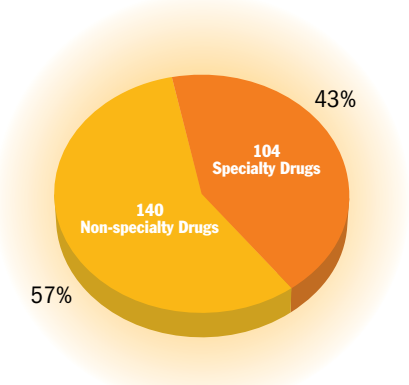
Reimbursement: Closing the Due Diligence Circuit

Reimbursement due diligence must move beyond a broad overview of the marketplace, analysis of competitors, start-up costs and potential patient populations. It must focus on all of the marketplace forces that have reimbursement implications and can affect sales projections, revenue growth, and profit margins.

“Experts estimate that 4% of Americans will be using specialty drugs by 2010, accounting for 60% of drug spending.”

Great new medical innovations don't always result in blockbuster products. Without an effective strategy for access and reimbursement, even the best science can fail in the marketplace. Business forecasting should be based on real-world analyses that offer a more detailed, more reliable look at future conditions and trends.

The Pharmaceutical Pipeline in 2006: Potential New Pharmaceuticals in Late-Phase Development



Reimbursement due diligence should be integrated into the overall business planning process. There are three key steps in business forecasting that relate to reimbursement:

- I. Assess the managed care marketplace
- II. Examine current treatment options and characterize unmet medical needs
- III. Provide payers with a product profile and clinical trial protocol for evaluation

Below is a snapshot of how these three steps lead to an effective due diligence strategy:

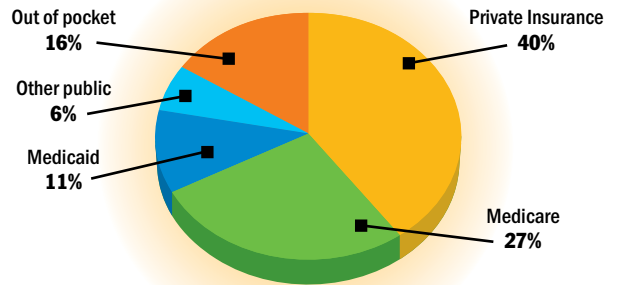
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Step I: Assessing the managed care marketplace

The Managed Care landscape encompasses all customer segments that influence your product. In the chart below, you can see how drug spending is divided between commercial and government payers.

Overall Drug Spending By Payer Type

Projected 2006 Prescription Drug Spending by Payer Type (\$210.28)



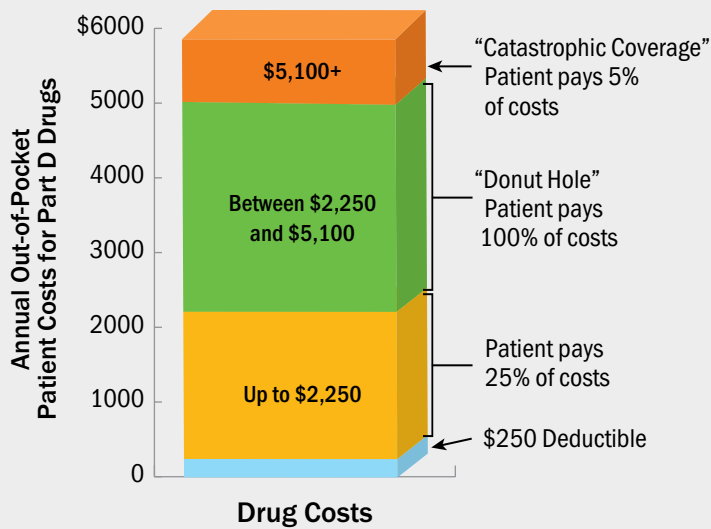
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Medicare Part D from page 1

Under Medicare Part D, patients pay a significantly higher co-pay for brand name and generic drugs compared to commercial plans. For example, the average co-pay in 2007 for non-preferred brands under commercial or employer plans was \$43. However, under Medicare, it was \$71.

This disparity is by design. Plans recognize that a certain percentage of patients may switch to preferred or generic drugs instead of non-preferred medications. This obviously has greater impact on high-cost drugs, including biologics, which fall under the Medicare Part D specialty drug category.

According to *The New York Times*, the so-called “doughnut hole” coverage gap – the cutoff in Medicare drug coverage that occurs when a participant’s total drug costs reach \$2,250 – drives the use of generics in two ways. When an estimated 4.2 million Americans reached the gap in 2007, many switched away from name-brand drugs to control out-of-pocket costs. Others started using generics to avoid falling into the coverage gap completely.



The prohibitive cost of fourth tier coinsurance can impact patient outcomes because patients may become less compliant or settle for less effective but more affordable alternatives. The result? Increased illness and healthcare costs all around.

Forced to pay the large out-of-pocket costs, patients will start prioritizing and omitting medications to save money. Lower compliance can impact health plans because it may increase costs through utilization of other medical services or unnecessary care.

With an aging population, a growing number of people will become eligible for Medicare — and of increasing importance to biotech developers, who should develop strategies to address this significant market shift.

One approach might be use clinical data to leverage your position, by including patients 65 and older in phase two and subsequent clinical trials.

Reimbursement Intelligence Case Study: *One of our clients had a product that competed with a market leader. The market leader had over 85% of the market, but because our client was able to show clinical data on efficacy, safety, and tolerability in patients over 65 — and the market leader could not — the client was able to achieve a preferred position on the Medicare formulary. Does your product have data that show a distinct benefit over other products in a specific patient population?*

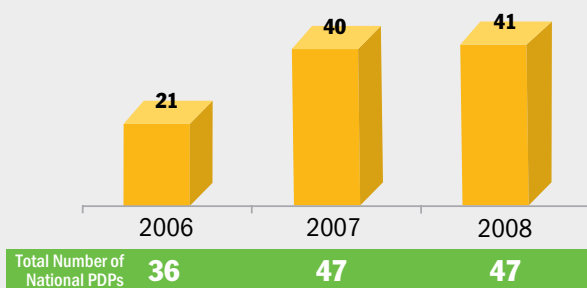
Medicare Part D has a tremendous effect on the revenue and profitability of new products coming to market. Clearly, it is crucial to start working on reimbursement and business planning strategies before they become necessities. ■

The “Fourth Tier”

Typically, prescription drug plans consist of three tiers: generic, preferred brand, and non-preferred brand. Now, many plans — including Medicare — are assigning drugs that cost more than \$600 per month to a specialty or “fourth-tier” category. About 12% of all prescription drugs fall into this new category, including the vast majority of biologics.

A patient taking a fourth-tier drug may pay 25-30% co-insurance for the prescription. In the case of drugs costing \$1,200 per month, that’s approximately \$300 — a considerable sum for a patient on a fixed income.

Number of Medicare Prescription Drug Plans Using Specialty Tiers, 2006-2008



Source: Headley et al. Analysis of data from the CMS Medicare Prescription Drug Plan Finder on Medicare.gov, 2006-2008, for the Kaiser Family Foundation.

Reimbursement from page 2

- The private insurance segment represents premiums paid to BlueCross/BlueShield, commercial insurance, HMOs, self-insured plans, and property/casualty insurance coverage for health care.
- The change in private insurance from 48% in 2004 to 40% (projected) in 2006 can be largely attributed to the implementation of the Part D senior benefit.
 - Specifically, many seniors' prescription drug coverage that was formerly covered under their employer (as retirees) is now covered by a Part D sponsor.

Companies need to continually monitor and research how the payer environment, which includes how payers are managing diseases, is changing. Without internal resources, an investor or emerging biotech company needs to consult a reimbursement expert. Important questions to ask include:

- What trends over the next two years can impact this product's access and reimbursement?
- What is the financial significance of each payor segment?
- Will the product be self administered or office administered, and how will it impact reimbursement?
- Will your product require a new code to maximize reimbursement?

Step II: Examine current treatment options and characterize unmet medical needs

More often than not, health plans will compare your product to existing treatments regardless of the mechanism of action. They will compare efficacy, safety and cost as a package rather than addressing individual factors.

Many payers will need to see a “value” proposition relative to the current standard of care.

Demonstrating that the product meets and exceeds the value differential is key. First, a novel product that meets a previously unmet medical need will gain the attention of health plans. Second, if the product has sufficient benefits over other therapeutic alternatives — ideally some health

or economic benefit — payers will be more compelled to provide attractive formulary positioning.

How can you assess the merits of your product? Through a series of primary and secondary market research with both payers and providers, a partner such as Reimbursement Intelligence can help address these types of questions:

- How will payers perceive your product's “value proposition” compared to existing or future products?
- What health outcomes or medical cost offsets are critical to disease management for payors?
- What payer trends in this category could have an impact on the product's success?
- Do you understand the issues and obstacles that payers could pose to the commercial success of the product?

Step III: Provide payers with a product profile and clinical trial protocol for evaluation

It is never too early in the product development process to give payers a clinical profile to evaluate, including “likely” and “best case” clinical results and key product attributes with commercial value.

The product profile includes key attributes such as product efficacy, safety, mechanism of action, tolerability, dosing and administration, and projected health outcomes and medical cost offsets.

This evaluation offers insights about objectives that need to be achieved, so that the product can be commercially viable. Ideally, if this step is completed at Phase II, then Phase III clinical studies can focus on gaining data for key attributes that will impact commercial success. Key questions that can be answered include:

- What clinical attributes will have a positive influence on formulary acceptance?
- How can we design health outcomes to demonstrate our cost effectiveness?
- What information gaps exist that will improve our “value” proposition to payers?



Understanding the challenges

In order to raise capital, investors are asking emerging biotech companies tough reimbursement questions. There are many reimbursement issues that are not obvious and need to be considered before investing.

FDA Proposal from page 1

including those discussing off-label uses — it proposes new guidelines that would limit the publications that can be cited. Specifically, articles should be drawn from peer-reviewed publications with independent editorial boards that offer demonstrated expertise in the subject matter. Publishers are also required to clearly disclose any bias or conflicts of interest.

The guidelines specifically exclude supplements (advertorials) that are funded in whole or part by the manufacturers of the product under discussion.

Prevalence of off-label usage

According to a 2006 study from the Archives of Internal Medicine, approximately 20% of all prescriptions are currently written for off-label uses. With numbers like this, the new guidelines could be interpreted as an acknowledgment that off-label use is widespread and shows no signs of slowing down.

It is especially true in cancer treatment where over 60% of oncologists use therapies off-label.

To put the matter in perspective, manufacturers need look no further than the FDA draft guideline summary, which seems to acknowledge the importance of off-label use:

“The FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products. Accordingly, if a manufacturer follows the recommendations described... FDA does not intend to use the distribution of such medical and scientific information as evidence of an intent by the manufacturer that the product be used for an unapproved use.”

What appears to be a product with tremendous market potential to life science executives and investors may not be to payers. Every management team should be sure they have addressed reimbursement and understand the challenges in order to accurately forecast revenue. ■

Weighing the risks

So, how might these new guidelines impact players in the biotech, pharmaceutical, and medical device arenas? Currently, we can only speculate, but we believe there will be both a positive and negative impact to managed care. On the negative side, because some medical and political stakeholders are already dubious about distributing reprints to doctors, the FDA draft guidelines have already drawn concern and brought renewed attention to the practice.

Further, since the guidelines essentially roll back more onerous restrictions on the practice of distributing reprints, managed care companies could begin to scrutinize off-label use of products more closely, resulting in denial of coverage or tougher requirements:

- Diagnosis or prior authorization
- More detailed medical histories
- Limiting the off-label usage to specialists

The positives are that the revised guidelines no longer require that drug and device makers provide studies to the FDA beforehand or promise to seek approval for the described use.

What's more, some advocates for rare illness have expressed positive reaction to the guidelines, because off-label use offers new hope to patients with limited treatment options

Finally, since the new guidelines would effectively convey approval on the more widespread distribution of reprints, it could also offer greater levels of credibility to such articles and encourage more widespread use of off-label prescriptions.

While there is little doubt that manufacturers need to proceed cautiously whenever they promote a product's off-label use, it would appear that, barring any serious challenge to the draft guidelines, the climate for doing so is about to become a bit more favorable. ■

The Winning Launch Plan: How P&T Committees Evaluate New Therapies

Health plan drug coverage decisions are made by the Pharmacy & Therapeutics (P&T) Committee, which generally includes the health plan pharmacy director, a medical director, and sometimes community-based physician consultants. The primary role of the P&T Committee is to review new products and make recommendations on formulary inclusion, tier placement, and utilization restrictions.

Reimbursement Intelligence recently interviewed Robert LoNigro, MD, MS, Medical Director at Tufts Health Plan, which was rated by *U.S. World & News Report* as one of the top two U.S. health plans based on quality of care. Dr. LoNigro, who has served on P&T committees for more than 13 years, was able to shed some light on the most pressing questions facing early-stage manufacturers and their investors.

Q: How has the P&T process changed over the years?

A: The emergence of costly biologic therapies, many with multiple indications, has caused a greater scrutiny of the value that new products bring to the marketplace. Plans are implementing tighter controls via a variety of utilization management and cost sharing methodologies, and a shift to preferred agents in the biologic space (see *chart below*).

Drug Management Methods	
Formularies	Prioritized lists of prescription medications (generic and brand) indicating plan's preference and level of financial coverage
Co-pay, co-insurance	A fixed amount (co-pay) or percent (co-insurance) that the member will pay for a prescription medication; level of co-pay or co-insurance often reflects drug's placement on plan's formulary
Prior Authorization	Health plan must provide additional coverage approval of the prescription before drug is dispensed; usually based on patient's clinical status
Step Therapy	Other (typically cheaper) drugs must be tried and fail first
Generics First	If a generic option is available, it must be tried first
Quantity Limits	Limit on the number units (e.g., pills) approved for coverage within a period of time (e.g., each month)
Hard Blocks	Drug, procedure and facility are not a covered benefit and patient pays full fee for service

Q: When should a manufacturer start the P&T process with a health plan?

A: P&T planning should begin at least three years before the anticipated product launch. Understanding the current state of the therapeutic space, including unmet clinical and

financial needs and the value that a new drug can offer to a health plan are the two key drivers that can make drug coverage more likely. Understanding these issues and gathering data during the R&D process helps ensure that there will be no coverage delays at launch.

A drug may offer value in novel ways, such as reducing the need for nurse monitoring or demonstrating safety in checking blood levels once a month rather than bi-weekly. These examples can save health plan dollars, partially offsetting any increased drug cost.

“Successfully understanding the P&T process is critical to achieving overall commercial success.”

Q: Is the economic story the only thing a P&T Committee looks at?

A: No, although health economics is important, there are other equally important aspects to the P&T Committee evaluation, including: the product's potential for better clinical efficacy; better safety and tolerability; meeting a previously unmet medical need; meeting the clinical needs of a specific patient sub-segment that previously didn't respond to therapy; and improvement in quality of life.

Q: What are the key steps in the P&T process?

A: The process varies by health plan, but the main steps are as follows:

Clinical specialists within the health plan review all the product information and supporting data provided by the manufacturer, and issue a report to the P&T Committee prior to the meeting/review date. The plan will generally apply their population to a financial model – either developed by the manufacturer (e.g., a budget impact model, a cost offset model, etc.), or an internally developed model to estimate the cost of adopting the new product onto the formulary.

The P&T Committee then meets to review this report/recommendation from both a clinical and financial perspective. They may adopt the recommendation in full, make modifications to it, or ask the manufacturer for more information. (Many plans will not allow a manufacturer to be present during the meeting). Formulary inclusion can



take place immediately or the product may be phased in during the course of a set formulary update schedule.

Medicare health plans must give the product a formal review within six months of launch. Depending on the product therapeutic category, it can take up to 12 months for a formal review in private health plans.

Q: Do all products get reviewed equally?

A: Invariably the most costly therapies (for example, specialty biologics) and/or those products that impact the biggest population get more attention and analysis by the P&T Committee, because they have a bigger impact on overall plan costs and can affect access to other products. ■

Oncology and Off-Label Use: Trends in Management by Health Plans

Up to recently, oncology treatment decisions were exempt from health plan interference. With the newer products having high costs and with multiple products entering the same category, there is increasing management as well as cost shifting for oncology patients.

With product such as Avastin costing \$8,100 and Vectibix \$14,000, there is a need to better monitor utilization as appropriate and on label.

What are the methods used by health plans to managed IV chemotherapy agents in the physician’s office?

Prior authorization

This requires that the physician provide clinical information to get approval for use. These requirements can be statement of medical necessity from the physician, specific lab or diagnostic values, and prior therapies. The list below indicates the rate of prior authorization in some recognized “wonder drugs” that are seen as highly effective.

Avastin	38%
Campath	25%
Erbixut	37%
Herceptin	30%
Velcade	30%
Rituxan	36%

Plans also monitor these products to ensure that they are used “on label” and in patients who are appropriate candidates for these therapies.

Off-label use restrictions

Plans that are more aggressive in managing oncology drugs can exclude “experimental” or “investigational” treatments. However, this is usually a judgment call by the plan’s Medical and Pharmacy team.

The plan uses all or some of the following factors in deciding to cover an “off-label” indication.

- Number of studies and patients in whom the drug has been used
- Rigor of the studies in which it has been used
- Cure or response rate in these studies
- Current state of treatment in type of cancer in which the drug is used
- Whether or not the drug and/or indication has been approved by the FDA

Generally, the rule of thumb is to require two peer-reviewed publications.

Formulary evaluation for cancer agents

The FDA is looking closely at overall survival as an endpoint that is critical to approval. Managed Care also is looking at whether it is “worth it” to provide access to a product that will only increase survival five months or less.

It will become more of an issue as more and more drugs reach the market. The freedom of choice for oncologists will be decreasing and oncology management increasing.

Cancer patients do need to have special consideration when treatment decisions are made. Health plan are looking at what is the “value” of this product in improving the patients health outcomes and quality of life.

Oncology is a focus of many emerging biotech and specialty pharmacy companies. It is critical to understand the reimbursement landscape based on physician and payer reimbursement and management.

It is also important to understand how your product can influence oncologist revenue stream and how payers will perceive its value.

Reimbursement Intelligence is a consulting firm helping investors and emerging biotech with due diligence and business planning. Our sole focus is to help our clients understand the implications of reimbursement and formulary access on the commercial success of their product. Let us know how we can help your organization.

For more information, contact Rhonda Greenapple at rgreenapple@reimbursementintelligence.com or 973.805.2301. ■

REIMBURSEMENT READINESS CHECKLIST

Great medical innovations don't always result in blockbuster products. Without an effective access and reimbursement strategy, even the best science can fail in the marketplace. As new technologies enter the marketplace, government and commercial payers seek to contain costs and utilization of expensive products. Managed care access and reimbursement is critical to effective business forecasting.

Use this checklist to help you during the development and development and due diligence process for your product:

- Have you considered the role of reimbursement analysis and planning as part of your overall product evaluation or due diligence?
- Have you spoken with managed care decision-makers to determine how they will respond to your product's clinical profile?
- Does senior management understand the issues and obstacles that commercial and government payers could pose to the commercial success of this product?
- Are you aware of the payer trends in the disease state, therapeutic category, or technology that could affect the bottom line?
- Will payers think your product is "worth it" when compared to the current standard of care?
- How can you structure your "value story" to ensure that your clinical and economic messages will maximize product uptake and access?
- What does competitive intelligence say about current or potential competitors' positions from the perspective of managed care decision-makers?
- Has your current revenue projection included payer contracting discounts and rebates or the net-net price?
- Is there a long-term reimbursement plan that outlines important timelines, budgets, and resources necessary for successful launch?

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