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Emerging Life Sciences Companies

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Chapter 16

Risk Management for Drugs and
Biologics in the United States

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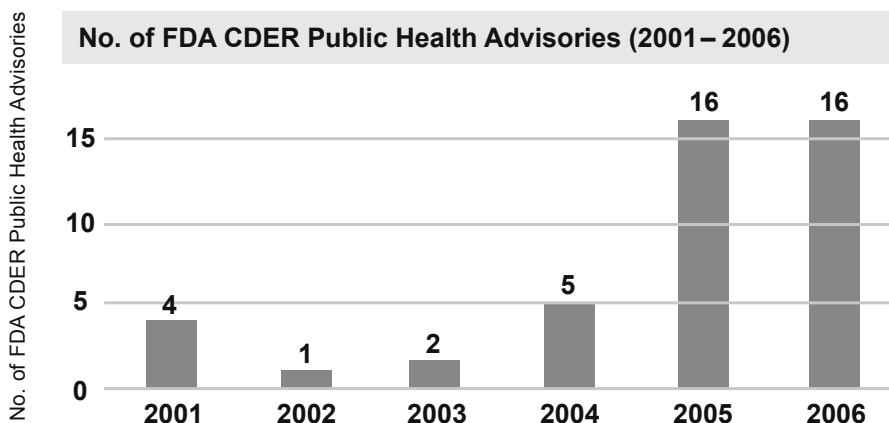
RISK MANAGEMENT FOR DRUGS AND BIOLOGICS IN THE UNITED STATES

Arcoxia, Vioxx, Acomplia, Zelnorm, and Tysabri; Aranesp, Procrit, Avandia, and Lucentis—all of these prominent drugs, and others, have been in the news often over the past year.¹ The concerns raised about them illustrate the unprecedented combined focus on both drug safety and costs, not only by the Food and Drug Administration (FDA), but also by Congress and the Centers for Medicare and Medicaid Services (CMS).

From the enhanced focus on comparative safety by FDA, to the new Food and Drug Administration Amendments Act of 2007 authorizing FDA to impose risk management programs and postmarket studies on applicants as conditions of approval, to increasing interest by CMS in requiring pharmaceutical and biotechnology companies to demonstrate cost and comparative effectiveness, the landscape of drug and biologic development is rapidly and irrevocably changing. These changes will have dramatic consequences on the selection of drug candidates, the scope of clinical studies, and the market valuation of products and companies. This new environment therefore demands development of a new, better-integrated, risk-management strategy by pharmaceutical companies.

FDA's New Safety Focus

FDA's enhanced focus on safety in the drug and biologics approval process and postmarket surveillance is unsurprising given major recent drug safety concerns relating to widely used products, such as Merck's Vioxx and Pfizer's Bextra, leading to highly publicized market withdrawals. There has been a substantial increase in the number of FDA health advisories issued, which provide information on important health issues to the general public, including patients and healthcare professionals.



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FDA's enhanced focus on drug safety is reflected by its actions in both the preapproval process and the postmarket stage, all of which support a key effort by FDA to strengthen the drug safety system at every stage of the product life cycle.

Selected Recent FDA Regulatory Actions Based on Safety Concerns

| Drug (date of action) | FDA regulatory action | Safety reasons |
|--|--|---|
| Advair Diskus (August 8, 2007) | FDA issued a not approvable letter for the application of the higher strength version (500/50) of Advair Diskus, even after an advisory panel had unanimously recommended its approval. | FDA questioned how Advair 500/50 compared to the currently approved lower-strength version (250/50) in order to allow for appropriate dosing recommendations. |
| Acomplia (June 13, 2007) | FDA Endocrinologic and Metabolic Drug Advisory Committee unanimously (14 to 0) voted against the approval of Acomplia. | There was an increase in relative risk of 1.7 for neurological adverse events in four trials supporting the obesity indication. A similar analysis of the diabetes trials showed a relative risk of 3.1. |
| Avandia (May 21, 2007) | FDA issued a safety alert on Avandia because of a potential safety issue related to the drug. In July 2007, FDA's panel called for strengthened warnings for Avandia due to cardiovascular safety concerns. In a related action, the Department of Veterans Affairs, which purchases drugs directly and accounts for 8% of Avandia's sales, decided to significantly limit its purchases based on FDA's safety concerns. | A potentially significant increase in the risk of heart attack and heart-related deaths. |
| Arcoxia (April 12, 2007) | FDA Arthritis Drugs Advisory Committee voted 20 to 1 against the approval of Arcoxia. Subsequently, FDA rejected Merck's request to market Arcoxia. | Arcoxia could cause as many as 30,000 heart attacks annually if widely used. FDA indicated that Merck would need to provide additional data to support the benefit-to-risk profile to gain approval. |
| Zelnorm (March 30, 2007) | FDA requested Novartis to stop selling Zelnorm after reviewing the results of 29 studies. Novartis agreed. In July 2007, FDA began to allow women younger than 55 who meet specific guidelines to have access to Zelnorm under certain conditions. | The results of 29 studies showed that: <ul style="list-style-type: none"> In the Zelnorm group (n=11,614), 13 patients (0.1%) had serious and life-threatening cardiovascular side effects (one died). In the placebo group (n=7,031), only one patient (0.01%) had similar symptoms. |

| Drug (date of action) | FDA regulatory action | Safety reasons |
|--|---|--|
| All sleep disorder drugs (March 14, 2007) | FDA requested all manufacturers of sedative-hypnotic drug products to strengthen their product labeling to include stronger language concerning potential risks. The products include Ambien and Lunesta (a total of 13 drugs). | The risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. After reviewing the available postmarketing adverse events, FDA concluded that labeling changes are necessary. |
| Erythropoiesis-stimulating agents (ESAs) (March 9, 2007) | FDA and the manufacturers (Amgen and Johnson & Johnson) have agreed to change the labeling for Aranesp, Epogen, and Procrit to include a new boxed warning, updated warnings, and a change to the dosage and administration sections for all ESAs. | Analyses of four new studies in patients with cancer found a higher chance of serious and life-threatening side effects and/or death with the use of ESAs. |
| Ketek (February 12, 2007) | FDA announced revisions to the labeling for Ketek, including the removal of two of the three previously approved indications from the drug's label. | An FDA joint advisory committee concluded that based on available data the benefits of Ketek do not outweigh the risks in patients with acute bacterial sinusitis or acute bacterial exacerbation of chronic bronchitis. |
| Tysabri (June 5, 2006) | Tysabri is available only through a RiskMAP (TOUCH Prescribing Programme), which requires the manufacturer to create a mandatory patient registry, provide patient information, mandate a preliminary MRI, and make the product available only through authorized doctors or centers. | Three months after the initial approval of Tysabri in November 2004, three patients were found to have developed progressive multifocal leukoencephalopathy, a serious viral infection of the brain. Tysabri was withdrawn by its manufacturer in February 2005. On June 5, 2006, FDA approved an application for resumed but restricted marketing of Tysabri. |

Preapproval Stage

In the wake of the Vioxx withdrawal, FDA has taken numerous actions at the preapproval stage to strengthen drug safety, including rejecting new drug applications (NDAs) based on safety concerns, and conditioning NDA approval on the applicant's commitment to postmarket studies. The new FDA Amendments Act requirement to post clinical trial results publicly will also significantly strengthen FDA's ability to restrict the scope of approval of drugs, as it will make all of the potential risks of a drug more transparent to the public.

Rejection or Delay of NDAs

FDA's "not approvable" decision regarding Merck's Arcoxia, following the recommendation of its Arthritis Drugs Advisory Committee, is widely perceived as indicating that a new and greater degree of evidentiary support of comparative safety or efficacy will be required for approval where there are other products currently marketed in the therapeutic area.

This more restrictive approach appears to have affected FDA's review of Sanofi-Aventis's Acomplia (which, if approved, will be branded as Zimulti in the United States), which is proposed for obesity management. After issuing an approvable letter, FDA reversed its previous determination that an advisory committee meeting was not needed for approval of the product for an "obesity management" indication. This suggests a more conservative review policy with respect to comparative risk-benefit profiles. FDA's advisory panel later unanimously voted against recommending approval of Acomplia, and Sanofi-Aventis announced a temporary withdrawal of the NDA.

In August 2007, FDA declined to approve a higher-strength version of GlaxoSmithKline's (GSK's) inhaled Advair Diskus for chronic obstructive pulmonary disease, even after an advisory panel had unanimously recommended its approval. FDA questioned how the higher-strength Advair compared with the lower-strength version "in order to allow for appropriate dosing recommendations." Similarly, FDA rejected Wyeth's new schizophrenia drug bifeprunox, and requested more efficacy data, as well as information on a patient who died while taking the drug, and declined to approve Wyeth's Pristiq, requesting additional data regarding the potential for serious adverse cardiovascular and hepatic effects. FDA also declined to approve Pozen's migraine drug Trexima, and required more information from preclinical studies or animal studies, and issued a "not approvable" letter to Novartis for use of its drug Prexige for patients suffering from osteoarthritis pain.

Conditioning NDA Approvals on Postmarket Trials

FDA has increasingly required drug developers to agree, as a condition of receiving approval for NDAs, to undertake postmarket clinical studies, generally referred to as Phase IV studies. The effectiveness of this requirement, and FDA's oversight of such trials, has been widely criticized. The new FDA Amendments Act provides greater authority to require postmarket trials.

A recent survey of 61 postmarket drug studies found that 45% of the 61 trials did not meet their projected completion date and that, of the delayed studies, 56% took at least a year longer to complete than their original deadline.

Postmarket Stage

At the postmarket stage, FDA has acted to ensure drug safety through various mechanisms, including the following:

Safety Alerts

In response to outside scientific and Congressional concerns, FDA has evaluated the need for additional safety warnings for currently marketed products, including GSK's Avandia and Takeda's

Actos diabetes drugs, Cephalon's Fentora (a narcotic medicine for treating pain in cancer patients) and Provigil (indicated to improve wakefulness), and AstraZeneca's Prilosec and Nexium:

- FDA's Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees suggested in July 2007 that Avandia should remain on the market but carry additional warnings about cardiac risks, and FDA is urging that a black box safety warning be added to Avandia's labeling.
- Takeda notified healthcare professionals in March 2007 of recent safety data, suggesting that healthcare professionals consider the risk of fracture when treating female patients with type 2 diabetes.
- In August 2007, FDA issued an early communication about the ongoing review of new safety data for Prilosec and Nexium. The new safety data raised concerns that long-term use of Prilosec or Nexium may have increased the risk of heart attacks, heart failure, and heart-related sudden death in certain patients with severe gastroesophageal reflux disease.
- In September 2007, FDA issued a public health advisory to alert patients, caregivers, and healthcare professionals to important information (particularly dosage information) on the safe use of Cephalon's Fentora, after receiving reports of death and life-threatening side effects in patients who have taken Fentora. FDA also has been monitoring cases of serious skin reactions associated with the use of Cephalon's Provigil, which will carry warnings of life-threatening rashes and psychiatric symptoms.

Label Revisions

FDA and the manufacturers of erythropoiesis-stimulating agents (ESAs, for example, Aranesp, Epogen, and Procrit), Amgen and Johnson & Johnson, have agreed on a revised product label that includes updated warnings, a new boxed warning, and modifications to the dosing instructions. These restrictions followed findings of "an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure" when ESAs were administered at higher-than-recommended doses.

In addition, more rapid tumor growth was reported in patients with head and neck cancer who received these higher doses.

In March 2007, FDA sent letters to manufacturers of sleep disorder products, requesting that the whole class of drugs revise their product labels to include warnings about potential adverse events, including anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling), and complex sleep-related behaviors, including sleep-driving, making phone calls, and preparing and eating food while asleep.

Eli Lilly announced in October 2007 that, as part of ongoing discussions with FDA, the company is updating labeling to include new side effects warnings for its antipsychotic drugs Zyprexa and Symbyax. FDA also has requested that Bristol-Myers Squibb and GE Healthcare add a black box warning to their ultrasound-contrast drugs Definity and Optison.

Additional Required Safety Trials

FDA noted that questions about the safety of sleep disorder drugs “could warrant additional clinical trials” to further assess the complex sleep-related behaviors associated with the drugs.

FDA convened its Oncologic Drugs Advisory Committee in May 2007 to reassess the risk-benefit profile of ESAs to address new safety concerns associated with their use in cancer patients. The Committee unanimously recommended that additional safety studies be conducted to support continued marketing of the drugs in the oncology setting.

Similarly, in September 2007, FDA’s Cardiovascular and Renal Drugs Advisory Committee recommended postmarketing safety studies of Bayer’s Trasyolol.

Restricted Distribution Programs

In June 2006, FDA approved an application for resumed marketing of Tysabri, a monoclonal antibody used for the treatment of patients with relapsing forms of multiple sclerosis. The drug was withdrawn by the manufacturers, Biogen-Idec and Elan, three months following FDA approval, after three patients developed progressive multifocal leukoencephalopathy, a serious viral infection of the brain. Tysabri is now available only through a risk minimization action plan (RiskMAP), which includes requirements that the manufacturers create a mandatory patient registry, provide patient information, mandate a preliminary MRI, and make the product available only through authorized doctors or centers.

Removal of Previously Approved Indications

In February 2007, FDA announced revisions to the labeling for the antibiotic Ketek, which included removing two of the three previously approved indications—acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis—because FDA has determined that the risk-benefit profile of Ketek no longer supports approval for them.

Market Withdrawal

FDA’s current restrictive review policy is also reflected in Novartis’s recent suspension of sales for Zelnorm at FDA’s request, following a post-hoc analysis of clinical trials that showed an increased risk of cardiovascular events.

FDA made the request even though its data analysis showed that only 0.1% (a total of 13) patients had serious events, out of 29 studies reviewed covering 11,614 patients treated with Zelnorm. In July 2007, FDA began to permit restricted use of Zelnorm by allowing women younger than 55 who meet specific guidelines to have access to Zelnorm under certain conditions.

Postmarket Risk Management

RiskMAPs

FDA has reacted to the increasing concerns about the safety of marketed drugs in part through imposing RiskMAPs, which are intended to minimize product risks and provide specific objectives to ensure the safe use of the drugs subject to them.

FDA issued guidance documents in March 2005 concerning the development and use of RiskMAPs, which can be far-reaching and effectively limit the scope of distribution and sale of the affected products (such as Tysabri).

Risk Evaluation and Mitigation Strategy

The new FDA Amendments Act requires that a drug have a Risk Evaluation and Mitigation Strategy (REMS) if serious risks are found in its pre- or postmarketing studies.

Drug Safety Board

In March 2007, FDA established the Drug Safety Board (DSB), which is intended to provide independent oversight and advice on managing important drug safety issues and dissemination of certain safety information through FDA's website to healthcare professionals and patients. Any organizational unit in FDA's Center for Drug Evaluation and Research (CDER) can refer a drug safety issue to the DSB for assessment by submitting a request.

FDA has also recently established, within each of its 17 drug review divisions, associate directors for safety and safety-regulatory program managers, to coordinate postmarket safety issues.

Postmarket Surveillance and Risk Communication

Under a pilot program, FDA will prepare safety profiles for several new molecular entities, using data from the first year of postmarket experience. The pilot program will help determine the impact on drug safety by closely monitoring a drug's use and adverse events.

FDA has also reacted to the criticisms of its drug safety processes by the Institute of Medicine in its 2006 report by establishing a new Risk Communication Advisory Committee to assist it in communicating risks and benefits of FDA-regulated products to the public.

The growing importance of communicating risks to the public is further illustrated by FDA's new requirement that manufacturers of attention deficit/hyperactivity drugs develop patient medication guides. This was announced in response to spontaneous reports of sudden, unexplained death and psychotic symptoms in patients with no previous illness.

In September 2007, the inaugural issue of the FDA Drug Safety Newsletter was published. According to FDA, the purpose of the newsletter is to provide postmarketing information to healthcare professionals to "enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting."

As part of the industry's response regarding drug safety, seven pharmaceutical companies announced in September 2007 the formation of a new alliance, the International Serious Adverse

Events Consortium. The consortium, with scientific and strategic input from FDA, will sponsor two initial research programs designed to identify genetic markers to predict which people are at risk for serious drug-related adverse events.

FDA's focus on drug safety has substantial implications in a variety of areas, including selection of drug candidates, scope of clinical trials, and market valuation of products and companies.

Selection of Drug Candidates

"Me-too" Products

FDA officials have noted that the Agency often holds "me-too" products (drugs that are structurally very similar to already known drugs) to a higher approval standard because of the evolving regulatory landscape relating to the approval of additional agents in a therapeutic class. FDA reviewers must apply the new information obtained on the safety of existing drugs, according to FDA officials, to their applications as science advances.

It is therefore not completely surprising that the FDA Advisory Committee for Arcoxia concluded that "approval of an additional NSAID [a class of drugs that reduce inflammation and pain] is only warranted if a compound can demonstrate a unique therapeutic value."

Medical Needs May Affect the Standard for NDAs

FDA's Anti-Infective Advisory Committee recommended in 2003 that clinical trials for acute bacterial sinusitis be designed to show superiority to placebo. However, FDA recently decided not to seek superiority trials if there were no safety concerns. One reason for FDA's position is that the number of anti-infective applications submitted to FDA is declining "at a very alarming pace," and the failure to develop new anti-infectives comes at a time when bacterial resistance to existing drugs is rising, raising concerns that "more companies may withdraw from anti-infective development at a time when new antibiotics are urgently needed."

Replacing an Existing Drug

If an existing drug offers the same benefit as new products, but is found to be more toxic, FDA can request the market withdrawal of the existing drug. This occurred with Pfizer's Rezulin, which FDA requested that the company stop marketing after safer alternatives, GSK's Avandia and Takeda's Actos, became available. The new FDA Amendments Act strengthens FDA's authority to further restrict distribution of drugs in the postmarket context.

Continuous Assessment of Risk/Benefit Profiles

The advancement of biomedical sciences makes it possible to detect trends of adverse events that were previously undetectable. At the same time, demands are rising for safer and more effective drugs and biologics, which drive manufacturers to develop better alternatives to existing therapies.

At the time Rezulin was withdrawn at FDA's request and replaced by Avandia and Actos, FDA was confident that patients were being provided with safer alternatives. However, recent safety alerts issued for Avandia and Actos illustrate the constantly changing views as to what might be con-

sidered safer alternatives. As a result, there will be a focus by FDA on continuous assessment of the risk/benefit profiles of marketed drugs.

Scope of Clinical Trials

FDA's recent safety actions, such as the requested market withdrawal of Zelnorm, may indicate that future clinical trials will have to evaluate whether to enroll more patients to address potential safety issues.

Effects on Market Valuation

FDA actions based on safety concerns could have an impact on the market valuation of the affected product and company.

Effect of FDA Safety Actions on Market Valuations

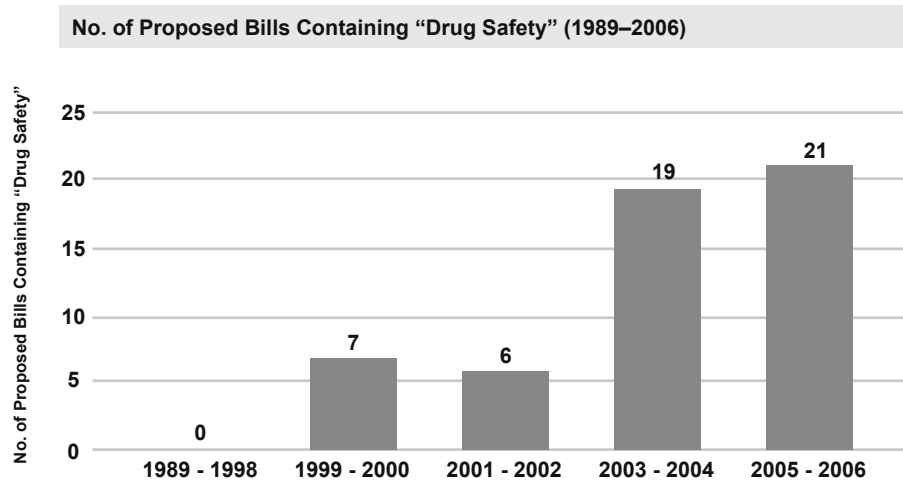
| Product | Company | Product sales and effect of FDA safety actions (if any) |
|---------------------------|-------------------|--|
| Zelnorm | Novartis | U.S. Zelnorm sales were \$488 million (about €360 million) in 2006. Due to the FDA suspension, the loss in sales on a budgeted 2007 basis is estimated to be more than \$600 million (about €439 million). |
| Aranesp and Epogen | Amgen | In the third quarter of 2007, sales of Aranesp decreased 23% to \$818 million (about €599 million), while sales of Epogen dropped 5% to \$602 million (about €441 million). Amgen's Chief Executive stated that sales of Aranesp and Epogen "were adversely affected by regulatory and reimbursement changes." The two products account for almost 40% of Amgen's revenue. |
| Procrit | Johnson & Johnson | Sales for the third quarter of 2007 were expected to decrease 8% to \$482 million (about €353 million). |
| Avandia | GlaxoSmithKline | A lawsuit was filed in June 2007 claiming GSK failed to warn of the drug's heart risks. |

Due to the suspension of Zelnorm, Novartis estimated the loss in sales for the 2007 budget year to be more than \$600 million (about €439 million).

Credit Suisse forecasted an 8% decrease (compared to the year-earlier quarter) for the third quarter of 2007 for Johnson & Johnson's Procrit (an ESA), following revisions of product labels and CMS's proposed restriction on coverage. Meanwhile, sales of Amgen's Aranesp and Epogen, both ESAs, fell 23% to \$818 million (about €599 million), and 5% to \$602 million (about €441 million), respectively. The sales of these two drugs account for almost 40% of Amgen's revenue.

Congressional Activities

The increasing concerns regarding drug safety, efficacy, and costs have stimulated the most intense level of involvement by Congress in these areas in several years. Congress passed new legislation enhancing FDA's drug safety authority, and has undertaken hearings on safety issues affecting specific drugs. Congressional concern is illustrated by the substantial increase of proposed legislation relating to drug safety in recent years.



New Legislation

Against this background of enhanced safety concern, new legislation, the Food and Drug Administration Amendments Act of 2007, was enacted on September 27, 2007. It includes several significant provisions relating to drug safety:

- New FDA powers to require changes to labeling.
- The requirement that FDA create an active postmarket drug surveillance system.
- The requirement for a drug to have an REMS if serious risks are found during its clinical trials or postapproval studies, or through FDA's adverse event reporting system or outside studies.
- The requirement that manufacturers post certain information in a public clinical trials data registry book.
- Significant civil penalties for companies for certain violations, of up to \$10 million (about €7.3 million).

The former head of both FDA and CMS, Dr Mark McClellan, has commented that the legislation "is going to be the biggest set of changes in post-market drug regulations since at least 1962," with FDA "doing no less than entering a new era of post-market drug regulation." McClellan

has observed that the new drug safety legislation can be expected to create new interactions between FDA, CMS, and private payers regarding the use of drugs. This is part of the development of cost containment mechanisms by the government in the wake of the substantial use of drugs following the introduction of the new Medicare prescription drug benefit in 2006.

In this regard, legislation has been introduced in the House of Representatives to give the Agency for Healthcare Research and Quality (AHRQ) additional funding to compare the effectiveness and cost of the treatments available for a particular condition.

Hearings and Inquiries

The House of Representatives has held hearings on, for example, the potential risk of Avandia, following the release of an analysis by an academic cardiologist linking the drug to a potential risk of heart attacks. In addition to exploring concerns about this specific drug, broader issues also were raised as to whether FDA is properly safeguarding the public, and whether changes in FDA's authority, resources, or leadership might be necessary.

Members of Congress also have been demanding information on drug safety issues. In a June 8, 2007 letter to the then Acting Commissioner of FDA, the Chairman of the Senate Committee on Finance asked FDA to explain what it "is doing to inform parents about the safety concerns surrounding pediatric trials of the Ketek antibiotic." The Chairman's inquiry was his second in six weeks: The first inquiry was based on an internal review of safety reports by FDA that found 110 cases of liver failure and serious liver injury, while the second inquiry was prompted by a newspaper report revealing FDA's decision to allow pediatric trials of Ketek to proceed, despite the risk of fatal liver failure and questions from one of its own officials in its Office of Drug Safety.

CMS Activities

Perhaps most surprisingly, in view of its traditional lack of involvement in the area, CMS has begun to consider a role in drug safety and effectiveness matters. The driving force is the strong impetus to develop cost-containment mechanisms following the introduction of the Medicare prescription drug benefit. Recently, CMS has become actively involved in the preapproval and postmarket contexts, using its control over coverage and reimbursement, as well as undertaking initiatives to stimulate the use of comparative effectiveness studies.

Preapproval Stage

In view of CMS's increasing focus on costs, it is important for a drug manufacturer to communicate with CMS at the preapproval stage to clarify the position of clinical trial designs and proposed medications in relation to coverage and likely reimbursement categorization.

Drug manufacturers seeking parallel consideration by FDA and CMS must take care to avoid "endless loops of information requirements," because, in making coverage and reimbursement determinations, CMS often requires different data from that required by FDA for product approvals.

Postmarket Stage

Restriction of Coverage and Reimbursement

CMS has proposed restrictions on coverage and reimbursement for antianemia drugs (that is, ESAs), such as Aranesp and Procrit, for certain cancer patients in view of FDA's imposition of a new black box label warning for this therapeutic class. CMS also is reviewing its coverage policy for these drugs when used in kidney disease patients.

According to its Acting Administrator, CMS pays "close attention" to such black box warnings because the safety of Medicare beneficiaries is "paramount." The cost of these drugs to Medicare was \$2 billion (about €1.46 billion) in 2006, making them the single largest expenditure for Medicare. A Wall Street securities analyst, commenting on the unprecedented involvement by CMS with respect to these drugs, observed that "we could never have anticipated that the extent of the regulatory and reimbursement threat could reach these levels."

In July 2007, CMS, under pressure from patient advocacy groups, medical societies, and legislators, issued new rules on its coverage of ESAs that are substantially less stringent than what it had originally planned. One difference between the new guidelines and proposed rules is that CMS will pay for treatment with ESAs when hemoglobin is less than 10 g/dl of blood, rather than below 9 g/dl as proposed. Nonetheless, CMS's action represents the first time it has restricted coverage based on FDA safety concerns. In October 2007, FDA responded to Congress stating that CMS's decision is "generally consistent" with available scientific data. Private health insurers, such as Aetna, have altered their coverage of ESAs to mirror the restrictions imposed by CMS.

Comparative Effectiveness Studies

There is currently substantial interest in research on the comparative effectiveness of drugs and biologics. For example, the head of CMS's predecessor agency, Dr. Gail Wilensky, has proposed a new, quasi-governmental entity to oversee comparative research, linked to an existing federal entity, such as AHRQ.

The Medicare Payment Advisory Commissions recommended, in June 2007, that Congress create an independent agency to sponsor and disseminate information on comparative effectiveness.

According to a Congressional Research Service report released on October 15, 2007, proponents of comparative effectiveness research emphasize the potential of such research to "increase the efficiency and coordination of research, boost the perceived independence and scientific integrity of the research, or generate [new] research." They maintain that information derived from such studies would help in "using limited resources effectively and efficiently." However, the report also noted concerns expressed by some about such government-sponsored prescription drug research, including "poor study design, lack of access to full study results, and bias in interpreting the results."

Insurer groups have supported the establishment of such an entity to develop comparative effectiveness and cost-effectiveness data for coverage and reimbursement decisions, similar to the UK's National Institute for Health and Clinical Excellence. This new melding of comparative effectiveness

and cost issues with clinical safety and efficacy is illustrated by the February 2007 announcement of the first comparative effectiveness trial ever undertaken of a pioneer drug by the U.S. government, by the National Institutes of Health. The trial will compare two Genentech drugs, Lucentis (which costs \$2,000, or about €1,460, per dose) and Avastin (which costs \$40, or about €29.30, per dose). Both are variations of an ocular vascular endothelial growth factor inhibitor, and are approved for different applications. The potential Medicare savings if the less expensive drug could be used for both indications are estimated to be as much as \$1 billion (about €732 million) to \$3 billion (about €2.2 billion) per year. In October 2007, Genentech announced it will stop making Avastin available to certain pharmacies in an effort to limit its off-label use in treating eye disease, the indication of use of its drug Lucentis.

While CMS asserts that comparative effectiveness research is part of CMS's mandate, and that evidence derived from the research is "essential" for helping doctors and patients choose the best quality care, Janet Woodcock, FDA's deputy Commissioner, cautioned that such research is "not a panacea," because people are different, and thus "[s]omething that is good for some people is bad for others."

Data Sharing

A January 2005 Department of Health and Human Services report suggested that FDA and CMS initiate several pilot projects allowing FDA to use drug safety information collected by CMS. Subsequently, data sharing between FDA and CMS has progressed despite the "very distinct missions" of FDA and CMS, and the "institutional resistance" to integrating a payer's considerations into regulatory decisions that FDA makes. The new FDA Amendments Act requires the creation of a national database on adverse events, with many government agencies participating.

As part of the effort to significantly expand its access to safety information, FDA has entered into a data use agreement with AHRQ to use data from CMS to conduct "a collaborative research project to develop data structures and methodologies for identifying and analyzing adverse drug events." The study will include three projects involving the use of four drugs in the Medicare beneficiary population. FDA and AHRQ also have collaborated in an investigation of the risk of angiotensin-converting enzyme inhibitors in pregnancy, with the results of the collaboration expected by the end of 2008.

In August 2007, FDA and the Department of Defense announced a partnership to share data and expertise related to the review of use of FDA-regulated drugs, biologics, and medical devices. The partnership is part of FDA's Sentinel Network, a medical product safety initiative that is intended to explore linking private sector and public sector information to create an integrated, electronic network.

New Risk-Management Strategy

The unprecedented interest of Congress, FDA, and CMS in safety, comparative effectiveness, and cost issues makes it imperative for pharmaceutical and biotechnology companies to develop a more sophisticated, integrated risk-management strategy.

The effects of the various activities and initiatives discussed in this chapter are likely to be substantial, including:

- More and earlier information on clinical trials, resulting in earlier, and perhaps premature, risk-benefit assessments.
- More restricted distribution, and consequently sales, for some drug and biologic products.
- Development of institutional entities to produce comparative effectiveness and, potentially, cost-effectiveness studies, which can be expected to lead to reductions in coverage and reimbursement by the government and private payers.
- Resulting effects on market valuation of products and companies, which may affect negotiations and decisions on collaboration agreements, mergers, and acquisitions.

Traditionally, the focus of drug developers during clinical trials has been narrow, on the generation of sufficient safety and efficacy data to obtain NDA approval from FDA as quickly as possible. Pricing and reimbursement issues were rarely, if at all, addressed as of the preapproval stage. Indeed, they rarely needed to be addressed at all, since virtually every approved drug was reimbursed at whatever price level was set by the manufacturer.

That system no longer exists. Major changes in this new era of greater focus on safety and cost can be expected, including the following:

- Manufacturers of drugs and biologics must develop a new risk-management strategy that incorporates, during the clinical trial phases, tests designed to establish comparative safety and effectiveness and cost-effectiveness.
- It will no longer be adequate to ignore the need to have such evidence available at the time of approval to meet potential challenges by the government and private payers.
- Clinical testing and communications strategies to respond to the results of institutional comparative or other studies will also be necessary, as well as consideration of the implications of making supporting data more publicly available at an earlier stage in a product's life cycle.

- It is prudent to prepare action plans to address questionably supported calls for market restrictions or imposition of REMS, or nonapproval or market withdrawal of products, and the potential for class action challenges that will inevitably follow.

Establishing the safety and efficacy of new drugs and biologics is only the beginning. Successful marketing of drugs and biologics in the future will depend on drug developers adjusting to these new safety and cost-containment demands by developing improved, better-integrated risk-management strategies.