In the wake of the Food and Drug Administration’s (FDA’s) December 2001 rejection of ImClone’s biologics license application (BLA) for Erbitux, ImClone’s stock plummeted, the company’s chief executive officer went to prison, and the future of a highly-touted cancer drug came into doubt. Like Worldcom and Enron, ImClone is maligned not simply for how far it fell, but for the circumstances surrounding its decline.

As ImClone enthusiastically announced trial results, Business Week and others ran glowing stories about Erbitux. In addition to positive test data, Erbitux was credited with the recovery of several cancer patients in “compassionate use” programs. In September 2001, Bristol-Myers Squibb (BMS) signed a $2 billion agreement for a share in Erbitux development and marketing. Less than two weeks before FDA faxed its refusal to file (RTF) letter to the company, ImClone became part of the NASDAQ 100. ImClone’s management may have truly believed it had the next miracle drug, and studies since Erbitux’s rejection bear out the drug’s efficacy, but in December 2001 ImClone failed to prove this to FDA.

Bringing new drugs to market involves efforts to secure FDA approval, with simultaneous attempts to inform investors and consumers of research and development progress. Investors value biotechnology companies based largely on speculation about products in a pipeline, relying on companies to provide accurate and timely information. But the biotechnology industry also relies heavily on secrecy—taking every precaution to protect proprietary information. An inherent tension exists, therefore, between the market’s need-to-know and a company’s need for confidentiality. Connected with this tension are FDA and the Securities and Exchange Commission (SEC).

Because FDA reviews potentially-sensitive information, Congress and the agency itself, limit what may be disclosed to the public concerning the substance of new drug applications. By contrast, the SEC regulates information so as to allow the investing public to properly value companies. The SEC does not require—not could it—disclosure of all of the information that FDA receives about a drug’s development. The result is a regulatory quagmire. In ImClone’s case, FDA officials were aware of the potential for company disclosures to mislead investors well before the issuance of the RTF, but took no action to remedy the problems, while the SEC only became aware of the problems after the fact.

The ImClone incident illustrated many inadequacies in drug development oversight. Resolution of this problem requires interagency cooperation and a pro-active approach by both FDA and the SEC. Preventing a company from making misleading disclosures may be impossible, but it should be possible to identify and address many such disclosures before they cause as much harm as in the ImClone case. Current laws and regulations governing public disclosures may not address the complexities created by the uncertainties of drug development, and reform may be needed. There are limits to government oversight, however, and there also is an inherent need for investors to critically examine information.

The Erbitux BLA

FDA granted Erbitux fast-track status on January 12, 2001, and agreed to review the drug under an accelerated approval protocol on the basis of two Phase II trials. The primary trial, number 9923, tested Erbitux’s efficacy in combination with a standard chemotherapy drug, irinotecan, in refractory colorectal cancer patients. ImClone enlisted 139 patients, and measured the reduction in tumor size over time. In May 2001, ImClone announced that of 120 evaluable patients, 27 patients (22.5%) had a partial response, with a median response duration of 186 days. The second registration study—a condition of fast track designation imposed continued on page 28

Mr. Hron is an Associate in the law firm of Kirkpatrick & Lockhart, Boston, MA.
by FDA—tested Erbitux as a single agent in 57 colorectal cancer patients refractory to irinotecan.\textsuperscript{10} ImClone completed the trial, study 0141, on October 12, 2001, and reported to FDA that six patients (10.5\%) showed partial response.\textsuperscript{11}

FDA reviewers soon discovered several apparent violations of the 9923 study’s eligibility requirements (despite monitoring by a contract research organization (Pharnex)), and noted numerous inconsistencies in dose and administration frequency, and a basic failure to provide adequate documentation for the reported results.\textsuperscript{12} Furthermore, FDA’s analysis of the single-agent study revealed that although only 10.5\% of patients responded—compared to a reported 22.5\% in the combination study—the results from the two trials were not statistically distinguishable.\textsuperscript{13} While the single-agent study supported ImClone’s contention that Erbitux is effective in fighting colorectal cancer, it drew into question the company’s application for use in combination.

**FDA Oversight**

The failures of the Erbitux BLA tell only one side of the story—it is less evident why FDA took so long to confront these failures, and then allowed the positive publicity surrounding Erbitux to continue unchecked. At the congressional hearings, FDA officials admitted having concerns about the 9923 trial in August 2000, when they first met with ImClone to discuss Erbitux.\textsuperscript{14} After consideration of the completed BLA began in November 2001, reviewers realized the clinical data was “severely deficient and could not meet the legal requirement of an adequate and well-controlled clinical trial.”\textsuperscript{15} FDA knew of the media attention surrounding Erbitux’s clinical results, but did not suggest that the company retract, or qualify, earlier statements. By November 30, 2001, FDA reviewers had decided to recommend refusal of the Erbitux application, but did not mention this during a December 4 meeting with ImClone, or suggest the company warn investors that rejection remained a possibility. FDA waited more than three weeks from that meeting to notify ImClone—ample time for the information to leak.\textsuperscript{16}

Prior to a product coming under its review, FDA has no authority to regulate public disclosures and no means of determining if information reaching the public is accurate. Once actual review of an application begins, the agency still may not have sufficient information to detect problems. Dr. Patricia Keegan of FDA’s Center for Biologics Evaluation and Research (CBER) pointed out during the congressional hearings that “[FDA is] often hampered in the pre-marketing setting by … not having the facts and the raw data, and not being able to tell how far off the mark they are … “\textsuperscript{17}

Perhaps FDA should have recognized in August 2000 the inadequacies of the 9923 trial protocol, but the agency had no cause to doubt the veracity or good faith of ImClone’s contentions about Erbitux’s efficacy. ImClone’s statements concerning the 9923 trial results, and results from other trials, were typical of a biotechnology company and in keeping with the information available to the agency.

Once review begins, FDA may need to decide quickly if any problems with an application necessitate warning the public. FDA is prevented from voluntarily disclosing information contained in a BLA, either through a press release or in response to a request under the Freedom of Information Act (FOIA).\textsuperscript{18} 21 C.F.R. § 601.51 states that, even when the existence of a BLA is public knowledge, “no data or information contained in the file is available for public disclosure before such license is issued.” Although the D.C. Circuit has determined that section 601.51 does not prevent FDA from responding to a FOIA request,\textsuperscript{19} the Act itself generally allows administrative agencies to refuse to disclose such information under an exception pertaining to “trade secrets and commercial or financial information obtained from a person and privileged or confidential,” and much of the information in a licensing application meets these criteria.\textsuperscript{20}

Despite these constraints, FDA may address perceived misbehavior by drug sponsors under 21 U.S.C. § 336, by issuing written notices to companies and instructing them to cease any offending activity,\textsuperscript{21} and if necessary may take further action, including suspending review of a drug application.\textsuperscript{22} FDA could have communicated its concerns to ImClone and recommended that the company withdraw the application or caution investors, but there is no guarantee this would have prevented insider trading and shareholder losses. Alternatively, the agency could have chosen to issue a press release in November 2001, stating simply that its preliminary assessment of the Erbitux application raised concerns about the results previously disseminated by ImClone.

FDA recently adopted this tactic when it issued a public warning in March 2003 about misrepresentations in a press release by SuperGen, Inc. concerning that company’s cancer drug, Mitozytrex.\textsuperscript{23} The announcement pointed to several inaccuracies, including that the company “exaggerates the efficacy of Mitozytrex and fails to include the significant risks associated with the use of the drug,” and noted that “[n]o data submitted by the company provided evidence that Mitozytrex is superior to existing marketed formulations of
Such announcements could cause investor confusion if not used sparingly, and phrased carefully, but all of the media hype suggests an announcement probably was warranted in November 2001 when FDA realized the considerable problems with the Erbitux BLA.

SEC Oversight

Even to the extent that FDA can regulate disclosures, the agency has no authority prior to commencement of a licensing application. Under FDA regulations, however, the agency may disclose some nonpublic information to other government agencies, if certain conditions are met. Although FDA is prohibited from sharing “trade secret” information outside the Department of Health and Human Services, in the context of FOIA, courts have characterized clinical trial protocols and data as “commercial information” rather than trade secret information. Thus, FDA could have supplied SEC with concrete evidence concerning the problems with ImClone’s 9923 trial or recommended an investigation.

While the SEC can only seek to correct company statements once they are made, its ability to police information like that contained in ImClone’s press releases may suffer from more fundamental problems. The SEC likely lacks the scientific expertise to evaluate the accuracy of many of the disclosures made by biotech and pharmaceutical companies, so the agency may not know a problem exists until it is too late. Also, because SEC disclosure rules were not written with drug development in mind, even arguably misleading statements and omissions by ImClone may not have violated the securities laws.

One commentator notes several areas where disclosures made in the course of drug development may be problematic under the securities laws, the most relevant of which are statements about communications with FDA, especially concerning the chances of approval and the disclosure of clinical test results. Each of these may give rise to civil liability and SEC litigation. Over the course of several years, ImClone released information on a regular basis concerning the ongoing progress of Erbitux development, including specific references to preclinical and clinical trials purporting to demonstrate the drug’s safety and efficacy, and to the status of FDA review.

Congress and the courts have created a high threshold for establishing corporate liability for predictions of future events. In addition to the requirement under Rule 10b-5 of the Securities Exchange Act of 1934 (SEA) that plaintiff’s prove the company had “actual knowledge” that the prediction was false or misleading, the Private Securities Litigation Reform Act (PSLRA) further provides a safe harbor from private actions where a qualifying forward-looking statement is accompanied by “meaningful” cautionary language identifying important factors that could cause variations from the predicted result.

ImClone was careful to qualify statements made with respect to FDA by consistently including standard warnings about product approval and marketability in its press releases, SEC filings, and annual reports. Nevertheless, the Southern District of New York denied ImClone’s June 2003 motion to dismiss a class action alleging that the company and several officers violated Rule 10b-5 from March 27, 2001 through January 25, 2002. In finding the cautionary language in ImClone’s public statements insufficient to bring the statements within the PSLRA safe harbor provision, the court stated, “[I]ndividuals commonly ignore such boiler-plate warnings … merely warning investors that FDA may not approve the drug does not warn investors about some of the specific shortcomings of the … trials …” In Amylin, plaintiffs pointed to a meeting between defendant and FDA, prior to the making of the allegedly false and misleading statements, in which FDA expressed concerns about the company’s drug development plan. The court concluded that Amylin’s failure to make these concerns known, while continuing to make positive statements about its product’s development and prospects for FDA approval, was sufficient evidence to survive a motion to dismiss.

Biotechnology and pharmaceutical companies also have the problem of relying on trial data to support many of their disclosures. To make trial results accessible to the masses, companies may prefer to simply comment on data, without presenting actual numbers that could be misconstrued. In doing so, however, the company risks making statements that could be misinterpreted and could render the disclosure misleading. Alternatively, a company may decide to present only raw numbers, but this risks providing insufficient context to allow investors to accurately interpret the data.

The use of data is not necessarily problematic, but there may be a tendency to take statistics at face value, and fail to question the assumptions behind the numbers. A risk also exists that later trials, or even later analysis of the same trial, will render the original disclosure inaccurate. William Fisher emphasizes that courts must remember that results are open to interpretation; even though FDA finds the data inadequate, the company still may have interpreted, announced, and submitted the results in good faith. Revealing trial results is a balanc-
ing act between providing investors enough information and simplifying the analysis to avoid confusion. ImClone sought to accomplish this by supplementing the announcement of trial results with some data, and often a simplified version of the trial protocol. In addition, ImClone consistently disclosed the level of patient response, explained how response levels differed, and provided data for baseline comparisons. This information helps, but may not always suffice.

In hindsight, the information ImClone omitted from its press releases appears more essential to understanding why the public had such inflated expectations for Erbitux. In its RTF letter, FDA noted a failure by ImClone to abide by standard scientific protocol in the design and implementation of and data analysis for the 9923 study, but ImClone did not release study protocols, except in the most basic form, so investors had no way of discovering this problem. Also, ImClone provided no information about the statistical significance of the study data, making it impossible to evaluate the scientific validity of results. The company frequently used words such as “significant” to describe study results, but made no attempt to define what it meant.

Even clearly announcing and explaining trial results, however, will not avoid confusion if later revelations affect the interpretation of earlier studies. Once a company has released some information, changing circumstances may obligate it to update or change its interpretation of the data. The importance of company announcements is commercialized…. There is no guarantee that the FDA will approve the drug [and the] agency often asks for more data, adding many months to the process.”

Clinical trial information announced by ImClone, and some information withheld by the company, could have contributed to investor misconceptions, but many investors would not take the time and effort to parse the details of trial data. A more noticeable—and arguably more credible—signal to investors was BMS’s $2 billion investment in Erbitux in the fall of 2001.

Investors were unaware, however, of the serious concerns BMS had about the Erbitux BLA—a problem compounded by ImClone’s press releases. Internal BMS communications, revealed during the course of congressional investigations, indicate that the company perceived several potential problems with the BLA. At the time it invested, BMS lacked data from the single-agent 0141 study, but knew that FDA had never approved a fast-track drug based solely on data in combination studies. Furthermore, a BMS radiology review of 27 alleged responders in the 9923 study concluded the initial analysis may have overstated the response rate, which BMS concluded could be lower than the 15% belief necessary for approval in a combination study. BMS also determined the number of eligible patients in the 9923 study might be below 100, making it unlikely the study could serve as the basis for an accelerated approval application.

BMS had no obligation to disclose any of this information to the public, nor should such an obligation be im-

The Big Deal

In its cover story on Erbitux, Business Week pointed out that “a rule of thumb in the pharmaceutical industry is that only one out of 5,000 drug candidates discovered in laboratories is commercialized….” There is no guarantee that the FDA will approve the drug [and the] agency often asks for more data, adding many months to the process.”

Clinical trial information announced by ImClone, and some information withheld by the company, could have contributed to investor misconceptions, but many investors would not take the time and effort to parse the details of trial data. A more noticeable—and arguably more credible—signal to investors was BMS’s $2 billion investment in Erbitux in the fall of 2001.

Investors were unaware, however, of the serious concerns BMS had about the Erbitux BLA—a problem compounded by ImClone’s press releases. Internal BMS communications, revealed during the course of congressional investigations, indicate that the company perceived several potential problems with the BLA. At the time it invested, BMS lacked data from the single-agent 0141 study, but knew that FDA had never approved a fast-track drug based solely on data in combination studies. Furthermore, a BMS radiology review of 27 alleged responders in the 9923 study concluded the initial analysis may have overstated the response rate, which BMS concluded could be lower than the 15% belief necessary for approval in a combination study. BMS also determined the number of eligible patients in the 9923 study might be below 100, making it unlikely the study could serve as the basis for an accelerated approval application.

BMS had no obligation to disclose any of this information to the public, nor should such an obligation be im-
posed, but if investors relied on the BMS deal in evaluating ImClone’s worth, and if BMS overvalued ImClone, then investors were harmed. Unlike investors, however, after FDA rejected the Erbitux BLA, BMS was able to compel ImClone to return some of its investment.

Improving Regulatory Oversight

FDA has undertaken several reforms in response to the ImClone affair. These changes do not alter the basic authority of the agency, however, and do little to prevent future Erbitux-like disasters.

The problems presented by the BMS agreement are probably impossible to police. The decision to enter into a licensing agreement is purely the company’s; inadequate due diligence and poor business judgment are not in the purview of the SEC—absent breach of management’s duty of care—much less that of FDA. The SEC does require that companies reveal some information about such transactions, but it cannot require disclosure of every internal memo expressing doubt or concern. To do so would deter companies from sharing confidential information in the first place, and add even more uncertainty to collaborative agreements.

Problems presented by the announcement of clinical trial results may be easier to address, although they cannot be eliminated. A company choosing to present clinical data could be required to provide other information to put those results in context (e.g., basic statistical analysis, including the significance of all results, along with an explanatory note about the uncertainties of such analysis and of data interpretation). Requiring certain contextual information about related therapies—whether part of the study or not—would give investors a basis of comparison, and putting each study in the context of prior studies could allay confusion. Rather than rewriting its regulations, the SEC might accomplish this by publishing an industry guidance specifying what sort of information should be disclosed to make disclosures informative and not misleading. At least, this should reduce uncertainty.

The SEC seems the more natural choice for enforcing such restrictions, in part because disclosures made prior to the initiation of FDA review of a licensing application will be difficult, if not impossible for that agency to police. The SEC cannot, however, be expected to pass on the scientific accuracy of many disclosures. A compromise might give SEC primary authority to monitor disclosures, but require companies to simultaneously submit data to FDA in support of any clinical trial results the company chooses to announce. All of this data eventually will be disclosed if the company seeks marketing approval, and FDA need not review the information when received, but could access it if necessary.

No matter how much information investors are provided with, however, they still must rely on the company to a point, and no matter how much FDA regulates clinical trials, it cannot guarantee protocol always is followed, and data always properly documented. The lesson of the ImClone affair may be that investors must recognize the considerable uncertainty and complexity inherent in drug development. Biotechnology stocks are not for the faint of heart, and risk-averse investors must take adequate precautions by diversifying their portfolios, or simply avoiding the biotech sector all together.

Epilogue

On October 10, 2003, ImClone announced that FDA had accepted for filing its second BLA application for Erbitux. As with the first application, ImClone sought review of Erbitux for use in combination with irinotecan in refractory colorectal cancer patients. With results from a major clinical trial by ImClone’s European partner, Merck KgaA, nearly identical to those of studies 9923 and 0141, it appears the primary failure with ImClone’s first BLA turned out to be poor documentation and procedure, rather than an inadequate response rate. This makes the nearly two-year delay all the more tragic. Nevertheless, the fact that the results from ImClone’s initially-troubled clinical trials may be vindicated must not be used as a reason to lower FDA’s standard of review. Rather, it should serve as a warning to investors that FDA’s review process is thorough and demanding, and will not be compromised by a few promising results and glowing news stories.

This article is an abbreviated version of a paper that was awarded Honorable Mention in FDLI’s 2002-2003 H. Thomas Ausrten Writing Award Competition for law students.

1 Erbitux™ is the trademark name for a drug referred to by ImClone as IMC-C225 (or C225). The generic name for Erbitux™ is Cetuximab.
3 “Compassionate use” gives patients with no other options access to experimental therapies in some circumstances.

Refractory means the cancer progressed despite adequate prior treatment with the relevant drug—irinotecan. Irinotecan is a chemotherapy drug also known as Campto-and CPT-11.

Raymond B. Weiss, Report to House Committee on Energy and Commerce [herein-after Weiss Report], available at http://energycommerce.house.gov/107/Hearings/06132002/hearing587/hearing.htm (last visited Nov. 17, 2003) (this testimony is part of the ImClone hearings, but is not part of the transcript available on the House committee’s website). Of these 139 patients, 121 had progressive cancer after initial irinotecan treatment. Only 120 patients are rated in the final results, there is no information as to what happened to the 121st patient.


Hearings, supra note 6, at 40-41 (citing Jan. 19, 2001 letter from FDA to ImClone).

Id. at 41.

Weiss Report, supra note 8.

FDA Says ImClone Data Insufficient to Evaluate Colorectal Cancer Drug C225, 28(1) The Cancer Letter, Jan. 4, 2002 (reporting the 95% confidence intervals as 15.4%, 30.5% for the combination and 4%, 21% for single-agent studies). See also Gardiner Harris, ImClone Shares Fall Amid FDA Concerns, Wall St. J., Jan. 9, 2002, at B14; Hearings, supra note 6, at 209 (testimony of Dr. Richard Pazdur, Center for Drug Evaluation and Research, FDA); Press Release, ImClone Systems, Inc., Data Presented on Study of ERBITUX® (cetuximab) Combined with Docetaxel in Patients with Advanced Non-Small Cell Lung Cancer (May 19, 2002), available at http://www.imclone.com/news.

Hearings, supra note 6, at 39, 197-98.

Id. at 41-42 (preliminary Committee Staff Report).

Id. at 42 (preliminary Committee Staff Report).

Id. at 202 (testimony of Dr. Patricia Keegan, Center for Biologics Evaluation and Research, FDA).


§ 5 U.S.C. § 552. Information that is “instrumental in gaining marketing approval” is clearly commercial for purposes of the FOIA exception. See Public Citizen Health Research Group v. FDA, 704 F.2d 1280, 1290 (D.C. Cir. 1983). The D.C. Circuit also acknowledged that “a drug manufacturer which has submitted an NDA has a competitive interest in seeing that the information contained in its NDA is not prematurely released to the public.” Webb v. Dep’t of Health and Human Servs., 696 F.2d 101, 102-03 (D.C. Cir. 1982).

Untitled letters and warning letters are available under FOIA, and some are available on FDA’s website, but no public announcement is made when they are issued. Examples of FDA enforcement actions—as supplied at the hearing—provide limited insight into the ImClone situation because they all deal with efforts to revoke approval based upon false or misleading information provided to the agency, not to the public. Hearings, supra note 6, at 243, 245 (testimony of Dr. Lester Crawford, Deputy Director, FDA).

Hearings, supra note 6, at 231-32 (testimony of Dr. Lester Crawford, Deputy Director, FDA).


Id.


§ 20.85; 21 U.S.C. § 331(j) (FDCA § 301(j)).

Public Citizen, 704 F.2d at 1280. FDA adopted the Public Citizen distinction between “trade secret” and “confidential commercial” information at 21 C.F.R. § 20.61. Before that, FDA applied a much broader definition of “trade secret” that encompassed clinical trial information. The Public Citizen court explicitly stated that the definition it adopted applied only in the context of Exemption 4 of FOIA (704 F.2d at 1290 n.27). FDA could argue that section 331(j) prohibits disclosure of clinical trial information under a broader definition of “trade secret”; however, because the agency’s definitions of “trade secret” and “commercial information” are found in the same part of its regulations as the rules permitting disclosure to other agencies, this seems unlikely.

William O. Fisher, Key Disclosures Issues for Life Sciences Companies: FDA Product Approval, Clinical Test Results, and Government Inspections, 8 MENS. TELECOM.

& TECH. L. REV. 115, 116-17 (2002). Although Fisher does not discuss ImClone, much of this section borrows from his article.


James D. Cox et al., Securities Regulation: Cases and Materials 74 (3d ed. 2001). Fisher argues, that although not explicitly included in the PSLRA’s definition of “forward-looking statement,” projections of FDA approval “could certainly be phrased as an ‘objective of management,’ and could also be disclosed as an assumption underlying predicted future financial performance.” Fisher, supra note 28, at 119 n.10. See also In re PLC Systems, Inc. Sec. Litig., 41 F. Supp. 2d 106, 117-18 (D. Mass. 1999) (finding no cause of action where statements of possible FDA approval were qualified using words such as “believe” and “expect”).


Id. at *5 (Quoting in re Amlynz Pharmns, Inc. Sec. Litig., 2002 U.S. Dist. LEXIS 19481 (S.D. Cal. Oct. 9, 2002)).


The possibility for data to be misused, or at least misleading, is exemplified by two ImClone press releases dated March 26, 2001. In one release ImClone announced results from a recent study, and in the other the company cites to those results as authoritative. The study results are contradicted by statistics from the American Cancer Society, which ImClone fails to mention. Press releases available at http://www.imclone.com/news.

Fisher, supra note 28, at 143-44. One court noted, the securities laws do not impose a requirement that companies report only information from optimal studies, even if scientists could agree on what is optimal. Nor do they require that companies who report information from imperfect studies include exhaustive disclosures of procedures used, including alternatives that were not utilized and various opinions with respect to the effects of these choices on the interpretation of the outcome data.


Fisher, supra note 28, at 162-63. In this context, courts have equated the test for materiality of the information to investors with determinations of the statistical significance of the result. Id. 161-62.

Weiss Report, supra note 8. Independent review of study data by the study investigators, BMS, and an Independent Response Assessment Committee (IRAC) assembled by ImClone, revealed numerous disagreements. Overall, the investigators reported 23 partial responses (greater than 50% regression), the IRAC reported 27 partial responses, and BMS recategorized as “stable disease” 8 patients the IRAC had labeled as partial response. The IRAC and the investigators agreed only on 20 patients with partial response; the IRAC and BMS agreed only on 16 patients with partial response. The IRAC and investigators disagreed about the category of the disease status prior to study entry (i.e., progressive or stable) for 38 patients.


For example, in announcing the results of the 9923 study, ImClone stated that all patients in the trial “had failed irinotecan therapy prior to joining the study,” but later review concluded the refractory status of many patients was not adequately documented. ImClone Press Release of May 12, 2001, supra note 9.

Id. See also Weiss Report, supra note 8.


Hearings, supra note 6, at 45 (preliminary Committee Staff Report).

See ImClone Press Release of June 1, 2003, supra note 4. The study found a 22.9% response rate in patients receiving Erbitux and irinotecan in combination, and a 10.8% response rate in patients receiving only Erbitux.