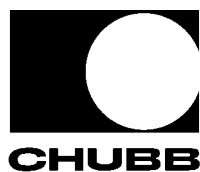


# **A Panoramic View: What Life Sciences Firms Can Learn from Insurance Carriers that Take a Holistic Approach to Underwriting**

**Philip W. Fiscus**





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## ABSTRACT

An insurance underwriter's job is to evaluate risk and determine how much of a particular risk the insurance company should assume and at what price. To really understand the risk profile of a specific biotech, underwriters must take a long-term view of the company and the exposures associated with different stages of product development. A biotechnology company can learn a lot by how its insurance carrier views the business.

## INTRODUCTION

There's no question that biotechnology is risky business. This is apparent in the numerous lawsuits filed because drugs and medical devices that once offered great promise have gone awry. But to the trained eye of a life sciences insurance underwriter, danger also lurks in the mundane: a power failure at a research facility, a poorly worded consent form in a clinical trial, or overzealous marketing in the doctor's office or on TV.

An insurance underwriter's job is to evaluate risk and determine how much of a particular risk the insurance company should assume and at what price. Given the potential for multibillion-dollar class-action settlements, it's a serious gamble. The underwriters who make the best bets know the industry inside and out and have a keen eye on the changing regulatory landscape and product liability litigation trends. But to really understand the risk profile of a specific biotech, top-flight underwriters take a long-term view of the company and the exposures associated with different stages of product development. To get the full picture, underwriters have to put the biotech's business practices under the proverbial microscope.

A biotechnology company can learn a lot by how its insurance carrier views the business. As with any business, it's always good to hear an independent opinion, especially from a carrier that takes a holistic approach to underwriting.

The stakes are high for the biotech as well as the insurance carrier. According to 2005 data from Jury Verdict Research, medical products liability compensatory verdict awards for single claimants averaged \$3.2 million. In more

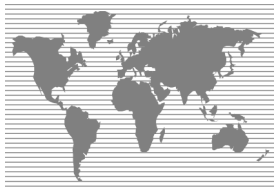
than half of the cases, the award topped \$1 million. This data does not include the cost to defend lawsuits or punitive damages that might be awarded, in some instances. Class-action lawsuits, which are not included in these figures, have been on the upswing over the past decade.

Companies that do a good job of identifying exposures and managing risk may qualify for lower rates and less restrictive terms in their insurance policies. A few years ago, insurers were engaged in fierce competition for new business, courting even high-risk life science businesses with relatively low premiums. When the insurance landscape shifted after the terrorist attacks in 2001, carriers without a long-term commitment to the drug and device industry walked away from the challenges the market presents. As a result, drug and device firms that fail to demonstrate an ability to effectively assess and manage their risks may find it harder to get adequate or affordable insurance coverage to meet their specialized needs.

The implications of good risk management extend far beyond insurance pricing. A life sciences underwriter's evaluation process can help uncover the very problems that could prove devastating to a drug or device firm, its balance sheet, and its customer or vendor relationships down the road.

Insurance underwriters work closely with loss prevention experts to examine technical safety and security issues in the early, middle and late stages of product development. But those underwriters who know this industry well also consider philosophical issues. Is the commitment to safety and security so pervasive in the culture of the organization that it's as apparent in the most senior managers as it is to hourly maintenance personnel? Is the sales and marketing

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culture so aggressive that a voice counseling caution is silenced?

If there is one overarching principle that applies throughout the spectrum—from the earliest stages of research to monitoring side effects after the product is widely used—it is this: The drug or device companies that will get the most favorable risk rating are those that incorporate “best practices” into their standard operating procedures instead of just following the letter of the law. Compliance with U.S. Food and Drug Administration rules and regulations will not be enough to protect a company in court, where it is often judged against the industry’s highest standards. FDA regulations should be viewed as minimum requirements rather than the goal.

## EARLY STAGE: RESEARCH AND DEVELOPMENT (R&D)

For many younger firms, clinical testing and product manufacturing are still a far off dream. To them, a delay in an R&D project is the worst possible risk. The loss of a building and equipment to a fire won’t cause most companies to self-destruct, but it could result in lost funding for a research project and ultimately delay that critical market launch. In one case, the FDA shut down a biotechnology research facility for six months because a microorganism was found in the purified water.

Each day of downtime in the product development cycle could cost a company up to \$1 million in product sales. An even greater risk: A competitor could beat the company to market with its own blockbuster.

Businesses in the midst of drug research and development may spend years conducting chemical or microbiological analyses to identify an agent or compound for use in a potential product. During this process, a master cell line of unique, temperature-sensitive biological material may be developed. If, because of a power failure, the temperature changes significantly and the materials are destroyed, the R&D disruption could be devastating.

One biotech firm’s cell culture, representing an accumulated investment of \$1.7 million over 22 months, spoiled after a power outage cut electricity to the facility and the backup diesel generator failed. The company lost both the critical cell line and the opportunity to earn a \$1 million milestone payment from a sponsor. With 25 percent of U.S. biotech firms in California, the state’s energy crisis in 2001 ruined experiments and damaged costly equipment at the many organizations that lacked sufficient backup power. Last summer’s heat waves again put pressure on the power grid with usage as much as five times greater than during the 2001 electricity crisis. The question is: are drug and device firms better equipped to weather brown outs or power interruptions today as a result of risk management improvements since 2001?

Drug and device companies can’t eliminate physical threats to an R&D facility, but they can minimize the damaging consequences. Underwriters look for safety measures that help protect not just the building and the expensive equipment inside, but research, documents, lab animals and other property that is difficult to replace. A “good risk,” in an underwriter’s view, will have effective duplication procedures—for lab books, electronic data, samples, cell lines and cultures—and see that the duplicates are securely stored off-site. Underwriters will also look to see that a firm has a prudent facility protection philosophy that includes proper storage and use of flammable chemicals; controls to protect clean rooms from potential breaches; alarms and a backup supply of electricity or refrigeration; systems that detect both heat and smoke; and sprinkler systems designed to reduce the chance of water contamination in a lab.

Highly sensitive lab apparatus—such as gas chromatographs; nuclear magnetic resonance spectrometers; and protein, DNA and peptide synthesis equipment—are particularly susceptible to smoke damage. In one example, a contract manufacturer sustained smoke damage from a small oven fire. It took five weeks of round-the-clock work for specialist cleaning contractors to get clean rooms back to the required standard, and only then could the process

of revalidating the rooms by regulatory authorities begin. In many such cases, a fire or other damage will invalidate equipment warranties and service contracts, making the cost to obtain a third-party warranty and service contracts a factor in the claim adjustment.

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Another risk in the early stages of product development is the potential theft of research data and other proprietary R&D information. Drug and device firms can reduce this risk, too, by conducting thorough background checks on employees and contractors, requiring non-disclosure agreements and restricting access to facilities and sensitive information to those who need it. For labs that do animal research, security systems are also critical to address the rising threat of domestic terrorism from extremists. According to the Foundation for Biomedical Research, animal rights extremists have committed almost 500 illegal acts against biomedical research facilities since 1981, two-thirds of them since 2000. The acts range from vandalism to arson and include destruction of research equipment and data, theft of lab animals, bombings and the harassment of researchers, their families and business partners.

Drug and device firms that have thought through their vulnerabilities—including their dependence on valuable research data—and how they would get back in business are much more likely to minimize losses and recover quickly from a disaster. Even when companies heed advice to create business continuity and recovery plans, it’s not enough to focus just on getting facilities back in action. For

a company, especially at the R&D stage, putting together an effective business continuity plan requires a team with knowledge of not just facilities but finance, science and information technology.

## CLINICAL TRIALS

As companies enter the clinical trials stage they face greater risks, especially as advancing trials involve greater numbers of human research subjects. At this critical milestone, life sciences underwriters evaluate a company's commitment to patient safety. Committing to patient safety sounds obvious, but it's amazing how many drug and device companies, crunched for time and money and bent on success, end up compromising patient safety with no deliberate intent to do so. Lawsuits following patient injuries often uncover evidence that the clinical trial was subtly—or not so subtly—tainted by the interests of the investigators or the sponsors. When it's hard mustering the required number of volunteers who fit the exact profile in the protocol, aggressive recruiting tactics can cross the line and consent forms may understate risks.

In the past few years, litigation arising from clinical trials has increased sharply as trials have grown in number and complexity. The targets are usually the clinical investigators and research institutions that conduct the trials, but companies that sponsor trials are vulnerable, too. In 2005, the family of a Massachusetts woman who died of a rare nervous system disorder after participating in a clinical trial of multiple sclerosis drugs sued the manufacturers, Biogen Idec and Elan Pharmaceuticals. Among the issues raised by the lawsuit was the enrollment of research subjects who have mild or no symptoms. The woman whose family is suing, it turns out, didn't even have MS. The doctor who misdiagnosed the weakness in her legs was an investigator in the trial, and the woman agreed to enroll, according to news reports, because she could get the medication with which she was being treated for free.

Perhaps the best-known suit involving a clinical trial was filed against the University of Pennsylvania by the family of Jesse Gelsinger, an 18-year-old who died after participating in a gene therapy trial in 1999. The investigator running the trial was the majority owner in a biotech firm that had a strong financial stake in the success of the experiments. The conflict of interest introduced serious questions about whether Gelsinger received unbiased medical information. Gelsinger's family claimed that the consent form underestimated the risk and excluded information about liver damage suffered by earlier volunteers.

Although complying with regulatory standards helps to shield companies engaged in clinical trials from lawsuits, it does not eliminate the drug or device firms' responsibility

to properly manufacture products, prevent contamination or adulteration or to warn of foreseeable problems. When clinical trials fail to adhere to strict protocols and the highest ethical standards, lawsuits can breach the traditional immunities that protect researchers and their sponsors. Legal damages may arise from negligence of the physicians and staff conducting the trial as well as defects in the products used. Under case law, particularly the California case *Brown v. Superior Court*, a product manufacturer is not ordinarily strictly liable for failure to warn of dangers that it neither knew nor could have known, given the state of the art at the time the drug was manufactured. But the law does not absolve manufacturers from their responsibility to disclose all known and reasonably knowable risks to potential trial participants.

The hepatitis B drug Fialuridine prompted several multi-million-dollar lawsuits after five patients died of liver toxicity during a trial. Even though the patients signed medical waivers before treatment began, several suits alleged negligence, suggesting the scientists could have predicted its toxicity and the probability of serious adverse reactions. Since the consent forms didn't warn of possible death or permanent injury, attorneys argued that the consent documents were inadequate.

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As the public's perception of clinical trial safety has deteriorated, it is getting more difficult to find willing participants. This opens the door to aggressive recruiting and a host of problems that could put research volunteers at risk and invite litigation. To

determine if a company sponsoring or conducting a trial is a good risk, life sciences underwriters examine its policies and practices regarding the development of protocols; the financial interests of investigators and their research team; the qualifications of principal investigators and the Institutional Review Boards that provide oversight; how volunteers are recruited; the informed consent process; and how the trial is monitored for safety problems.

Protocols, informed consent, financial interests and recruiting seem like separate issues, but often they are intertwined. If, for example, investigators receive financial incentives to recruit patients quickly, they may misrepresent the nature or risks of the research or enroll patients who, for one reason or another, should be excluded.

The protocol provides a roadmap for any clinical trial and a mechanism to maintain the integrity of the research project. Insurance underwriters can read quite a lot into the risk profile of a company by the care it takes in developing protocols and monitoring systems to ensure investigators adhere to them. Before beginning a clinical trial, a company must establish proper protocols so that the information emerging from the trial is not only well documented but also reflects the goals set before the initial research and development stage. The protocol describes what types of

people can participate in the trial, the schedule of tests, procedures, medications and dosages, and the length of the study. It also should show how the company intends to explore all possible drug interactions.

Developing realistic informed consent documents requires a crucial but delicate balancing act. The consent process must disclose all known and reasonably foreseeable risks to potential trial participants without using a lot of incomprehensible scientific jargon.

Even with a well-constructed consent document, the practice of obtaining informed consent is rife with landmines. When investigators target their own patients as potential subjects or pay referral fees to physicians, patients may participate without considering all the risks because they trust their doctor. Some clinical trials offer payments to participants, but payments might induce someone to sign on to a risky experiment that they otherwise would not. For people who are economically deprived, access to basic health care may be an inducement to overlook the risks of a clinical trial. When people are desperately ill, the stakes are even higher.

The recent TeGenero/Paraxel case in the United Kingdom is a case in point. The trial involved a monoclonal antibody drug, called TGN1412, for leukemia. In March 2006, six healthy volunteers for a P-I trial had severe organ failure.

Two placebo patients did not experience an adverse reaction. Ethicists who reviewed the consent form indicated the document didn't adequately inform participants of the therapy's dangers or depict the treatment of the novel drug as having an effect that would disrupt the body's immune system. They accused Paraxel of hiding the risks from the volunteers. Bioethicists also question why the drug was administered by Paraxel simultaneously rather than one at a time to watch for adverse effects. The protocol is said to have exploited the subjects' need for money, threatening to withhold payment if the subject left the trial early. Preliminary reports suggest that neither manufacturing nor dosing issues were to blame for the adverse reactions. It is reported that TeGenero only carried insurance coverage in the amount of 2 million Euros. The case and adverse publicity ultimately resulted in the suspension of business by TeGenero.

The explosive growth of international trials—especially in poor and developing nations—exacerbates all of these risks. Drug and device companies conduct trials overseas for many legitimate reasons. The treatment may target an ailment or condition that is more prevalent in a particular country or region, or it may be necessary to find a pool of people who are not receiving other forms of treatment for a disease. While most researchers apply high ethical standards, underwriters know that some have questionable motives and may employ controversial practices. Trials may be conducted in a particular country simply because

it's perceived as having favorable regulation and less litigation. Perhaps the trial will be completed more quickly with less red tape, but deliberately avoiding oversight is a risky strategy.

Some researchers have gone to developing countries to conduct research on human volunteers that would not pass muster in the United States. In just one example, the U.S. Office for Human Research Protections found that some of the asthma research conducted by a Harvard professor subjected families in China to risks even though they were unlikely to benefit from the study. Consent forms were too hard to understand and didn't list the risks and discomfort associated with some tests.

## PRODUCTION AND MARKETING

Human clinical trials represent one of the most challenging exposures for life sciences underwriters, but they are equally concerned about risks that drug and device firms face as they move from the research stage to production and marketing.

Underwriters look carefully at the design process. Do the company's design engineers engage in systematic and thorough analyses to try to anticipate how the product will

be used as well as how it might be misused? Have they built controls to prevent inappropriate uses? Companies dedicated to human design engineering are less likely to face product liability problems.

Even if no lives are endangered, such firms risk losing millions of dollars in revenue if a key supplier experiences a fire or other disaster and cannot provide critical materials. Underwriters that provide insurance against lost business income want to know that the drug or device firm has thoroughly analyzed their supply chain dependencies and identified alternative suppliers where possible.

In this day of skyrocketing drug development costs, Wall Street pressures, fierce competition and direct-to-consumer advertising, it can be difficult for firms to resist the temptation to overstate a product's benefits or minimize its risks in marketing to doctors and to consumers.

In a growing number of product liability cases, plaintiffs are arguing successfully that an advertisement's message about a drug's benefits outweighed physicians' warnings about its risks, eroding one of the most potent defenses in product liability lawsuits. Under the widely accepted "learned intermediary rule," manufacturers have a duty to warn medical professionals—not the patient—about the risk of most prescription drugs. But in a case involving the contraceptive Norplant, the New Jersey Supreme Court determined that an onslaught of consumer advertising alters the doctor-patient relationship by encouraging patients to ask for specific products by name. In those

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cases, manufacturers should not automatically be freed of their duty to properly warn consumers of dangers or side effects. Though limited to one state, the decision has influenced litigation in other jurisdictions, giving insurers pause when companies aggressively market to consumers. Prudent underwriters will consider whether the process for developing and reviewing promotional materials includes representatives from legal affairs, medical affairs and safety surveillance departments.


Every health application created by a drug or device firm has risks, and before a product reaches the market, companies must do their best to identify risks and demonstrate that its benefits outweigh them. Even with thorough clinical trials, undiscovered side effects may not appear until long after the product has been used by large numbers of people over long periods of time. Underwriters also want to ensure that the drug and device firms they insure have a very robust safety surveillance team that has the autonomy, clout and resources to collect and analyze data concerning the use of its product and take remedial action, from minor labeling or dosage changes to product withdrawal.

In a landmark guilty plea several years ago, Endovascular Technologies paid \$92.4 million to settle criminal and civil charges that it concealed from authorities thousands of incidents—including 12 deaths and dozens of invasive surgeries—in which a device used to treat aneurysms in the aorta malfunctioned. Under federal law, a company is required to report to the FDA any incident in which its device may have caused or contributed to death or serious injury or if the device malfunctioned, causing the potential for death or injury.

Off-label use is another source of exposure to lawsuits. The use of a drug or device for purposes other than for which it was approved is not uncommon or illegal, but it increases a manufacturer's vulnerability in a product liability lawsuit. Underwriters will scrutinize how a company reacts when it becomes aware of pervasive off-label use. Companies are not allowed to actively market off-label uses, but some turn a blind eye to sales representatives who do. The wide use of a drug product without clinical testing for safety and effectiveness would put a drug or device company at risk. If a company sees that an off-label use grows, it should give serious consideration to conducting clinical trials for that use.

## SUMMARY

Although many of the largest pharmaceutical firms have become household names, it's important to recognize that 90 percent of medical technology firms have fewer than 100 employees, according to AdvaMed, the trade association for medical technology firms. Many of these smaller businesses lack the sophisticated risk management and safety surveillance systems found in the largest drug and device companies. But their risks are just as great, and perhaps greater. When it comes to physical threats to their facilities, they may lack the capital to stay in business through a prolonged shut-down. If, because of their risk profile, underwriters won't offer high limits of insurance at a price they can afford, one major lawsuit could put them out of business.

In many ways, the scrutiny that life sciences underwriters give to these firms is like a dose of preventive medicine. You may not like the taste of it, but it's good for you. 



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