SUCCESS in the pharmaceutical industry is all about playing the odds: At each stage in a compound's development, companies place a bet worth millions of research dollars on whether the compound will reach the market. Any molecule's chances are so minuscule that drug companies might be better off trying their luck in Las Vegas.

With the odds stacked against them, companies are ready to embrace any tools that can improve their luck. It's therefore no surprise that, 10 years ago, Christopher A. Lipinski sent ripples through the industry with a chapter in the journal *Advanced Drug Delivery Reviews* laying out parameters—dubbed "The Rule of Five"—for when an interesting compound is likely to make a good, orally available drug.

Lipinski formulated the rules two years earlier when, as supervisor of Pfizer's medicinal chemistry drug discovery labs in Groton, Conn., he decided to take a closer look at the compounds that survived to midstage clinical studies. He knew that solubility, a predictor for safety and metabolic activity, was a major stumbling block in drug development, and he was curious to find patterns in the physical and chemical properties of successful drugs.

"I noticed the vast majority of the compounds in Phase II had properties lying in a certain range," Lipinski says. Curiously, the upper limit of the values for "druggable" compounds seemed to be multiples of five.

His rules, which do not apply to natural products, go as follows: A compound must have fewer than five hydrogen-bond donors, estimated by adding up its -OH and -NH groups; its molecular weight must be under 500; its log P, a measure of lipophilicity, which signals the ability to cross a cell membrane, must be less than five; and it must have fewer than 10 hydrogen-bond acceptors, determined
by tallying up its nitrogen and oxygen atoms.

Lipinski had the engineers at Pfizer rig the firm's computer system so that when a chemist registered a compound for testing, it would automatically be evaluated by the rules. If the compound violated them, a bright blue screen would pop up, "like the Windows screen of death," Lipinski recalls.

Though scofflaw compounds were not automatically shelved, they were likely to be downgraded on Pfizer's priority list. Furthermore, the compounds' files were flagged to let everyone know that challenges likely lay ahead.

When the paper came out in 1997, it quickly became apparent to Lipinski just how much interest his guidelines would generate. "All of a sudden, I started getting invitations from the outside to speak at conferences," he says.

A decade later, the rules have been adopted throughout the industry, particularly at big pharmaceutical companies where scientists have wrestled with the glut of information generated by high-throughput screening.

Although Lipinski retired as a senior research fellow at Pfizer in 2002, he is still active on the speaking circuit and on scientific advisory boards of companies developing drugs for underserved diseases. Since the rules were published, he notes, a flood of research papers has shown the relationship between a compound's physical chemical properties and its chances for success in the clinic.

Lipinski acknowledges that the rules have encountered some criticism over the years. Academic scientists, in particular, cringe at the idea of guidelines that could box them in. He responds that academics aren't operating under the same profit motive that drug companies are. "In the pharma industry, you're trying to discover medicines that will make your company money, so there's a need to be practical and play to the probabilities," he says.

**Yet even** in industry, some scientists are wary of the rules. On balance, the application of the Rule of Five has done more harm than good, contends Julian Adams, president and chief scientific officer of Infinity Pharmaceuticals, a Cambridge, Mass.-based biotech company. Earlier in his career, Adams discovered Velcade, a cancer treatment that disproved the common wisdom that boronic acids could not be drugs.

"I think the Rule of Five has had an oppressive effect on creative thinking in the industry," Adams says. While the rules were conceived as guidelines, many companies treat them as set in stone. Meanwhile, Adams points out, nearly half the drugs we take are derived from or inspired by natural products, compounds that universally break the rules. "When the exception is 50% of the time, how useful is a rule?" he asks.

Moreover, Adams argues, innovation in drug formulation and delivery has changed the parameters of what is druggable.

Adams agrees that it's critical to assess safety and metabolism issues throughout the drug discovery and development process. However, examining those issues "on a rules-based basis, when we have such little understanding of how the body handles drugs, is reductionist and anti-intellectual."

Lipinski himself stresses that any rules should be applied with common sense and that there will always be exceptions. "There's a natural priority order in decision-making," he says, "and the most important thing is what happens in humans." However, in the absence of that information, "you rely on rules and filters because they're better than nothing."

Besides, Lipinski can back up his rules with some pretty compelling data. As he points out, three of Pfizer's newest drugs, Sutent, Chantix, and Selzentry (with a minor molecular-weight violation in the last one), all follow the rules.