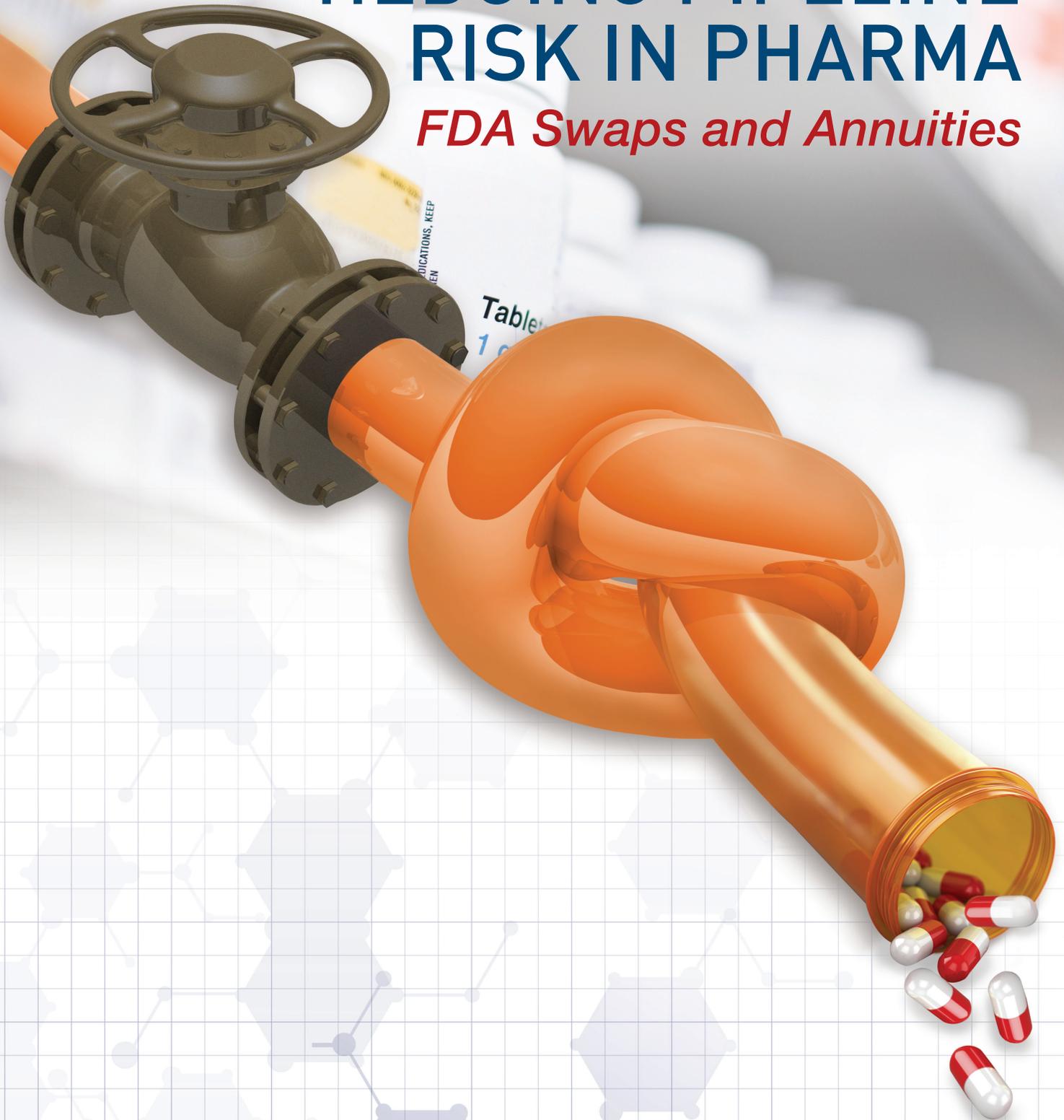# HEDGING PIPELINE RISK IN PHARMA
FDA Swaps and Annuities

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STATEMENT OF PURPOSE

The purpose of this paper, which is part of a broader effort at the Milken Institute, is to define, develop, and conceptualize new financial instruments that allow investors in medical products to share development risks with outside investors. It is the result of discussions with senior fellows and friends of the Milken Institute, and with senior fellows and friends of *FasterCures*. These discussions took place on November 3, 2013, at the Partnering for Cures meeting in New York; on January 16, 2014, at the Milken Institute; April 27, 2014, at the Milken Institute Global Conference in Los Angeles; and September 12, 2014, at the Harvard Club in New York. This project is part of a strategy at the Milken Institute to enlist its community of senior fellows and friends to solve big problems in creative ways using market mechanisms and the tools of finance. This paper was written by Tomas J. Philipson. He is a senior fellow at the Milken Institute, the Daniel Levin Professor of Public Policy at the University of Chicago, health-care program director at the Becker Friedman Institute at the University of Chicago, and a founder of Precision Health Economics LLC.

Joel Kurtzman
Managing Senior Fellow
Milken Institute

The Innovator's Dilemma

Profit in the global health-care industry is highly concentrated in the United States, the largest market for pharmaceuticals and medical devices in the world. As a result, most health innovators around the globe seek approval from the Food and Drug Administration to sell their products in the U.S. However, the costs and risks inherent in the FDA's approval process are substantial. The average development cost for drugs and biologics, medicines derived from living organisms, is $1.2 billion spread over about 10 years of development, testing, and review. The odds of success are slim. About 13 percent of products starting the process are approved for sale in the U.S.

This rigorous testing is essential to ensure the safety and efficacy of medicines and devices offered to the public. Indeed, until clinical trials are completed, it is uncertain whether a drug or device will work. While the FDA has implemented a number of mechanisms to accelerate product evaluations — including early sharing of data and collaboration to determine clinical benefits[1] — the nature of research and development creates substantial uncertainty for investors. We suggest that the creation of hedging tools similar to those used in other financial sectors would mitigate this risk and attract a larger number of investors to a field that would benefit from an infusion of more private capital.

When attempting to win FDA approval, investors face two risks that are outside their control. First, they may earn nothing if the FDA concludes after its four-phase process that the quality of the product is not high enough for the U.S. market. In terms of the capital invested, failure to win approval is analogous to a default on a bond or loan. Second, the time-consuming process reduces investors' returns because it shortens the length of time a patented product has market exclusivity. This discounts the returns further, because potential early profit cannot be recaptured. These financial risks are outside the control of investors who fund the trials because, until trials are performed, a product's efficacy remains a question mark.

At present, there are no markets that enable investors to share, or hedge against, these exogenous risks. This problem is comparable to the inability of corporate bondholders to hedge default risks before the introduction of the credit default swap (CDS).[2] CDSs were originally developed by lenders to insure their loans against defaults. A similar type of insurance could be designed for medical research and development to protect investors from nonapproval, a result that, in principle, mimics a default.

To lower the uncertainty of product development and increase the amount of capital flowing into medical innovation, this paper proposes financial instruments that allow risk sharing with noninvestors. There are, of course, other forms of risk apart from the FDA approval process, such as reimbursement risks in the U.S. and abroad. These and other postapproval threats to investors' capital will not be addressed here.

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1. U.S. Food and Drug Administration, "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, http://www.fda.gov/ForPatients/Approvals/Fast/default.htm (accessed February 25, 2015)
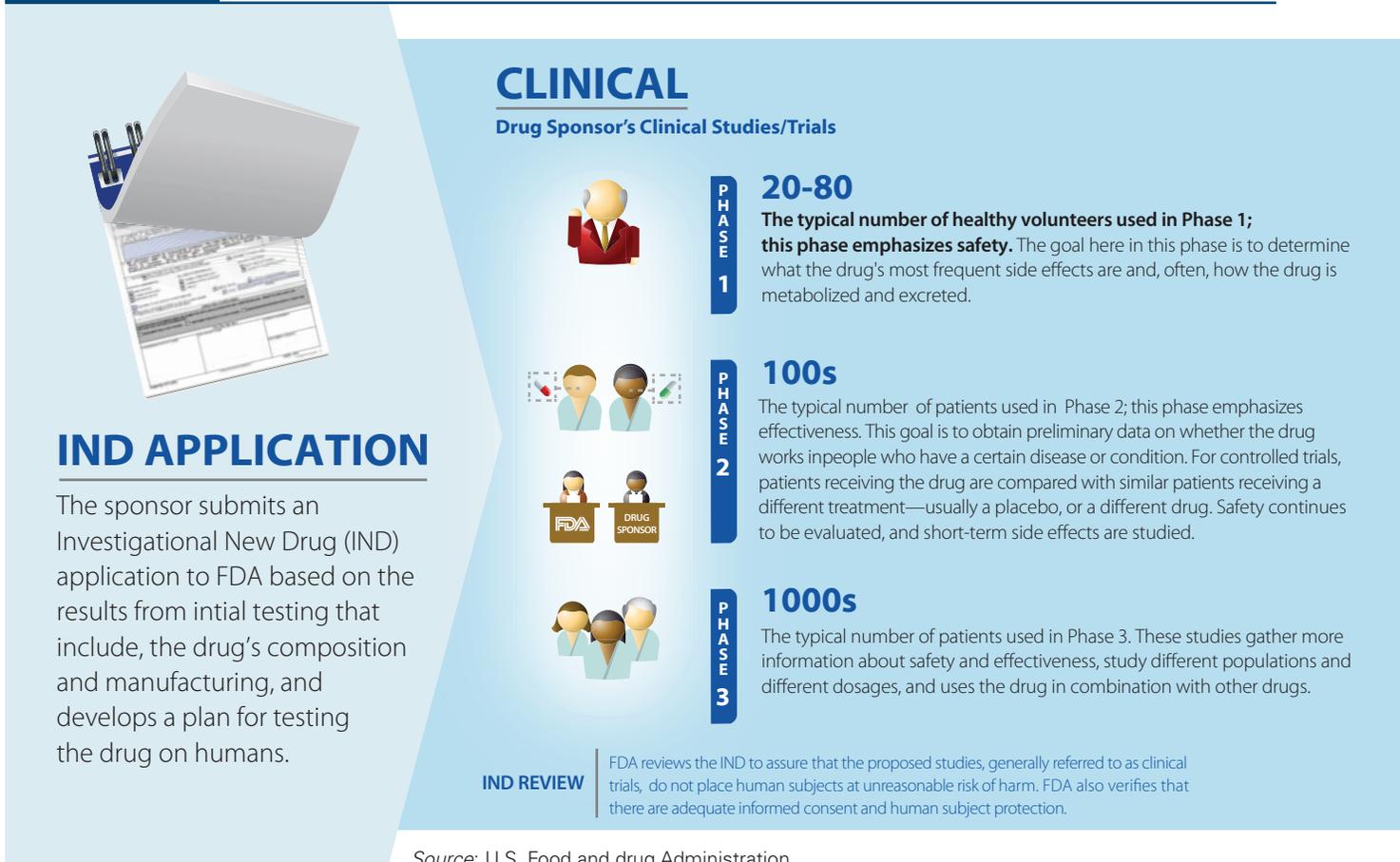
2. A **credit default swap (CDS)** is a financial swap agreement that the seller of the CDS will compensate the buyer in the event of a loan default or other credit event. The buyer of the CDS makes a series of payments (the CDS "fee" or "spread") to the seller and, in exchange, receives a payoff if the loan defaults.

DEFINITIONS AND DESCRIPTIONS

The FDA's approval process involves several important milestones: filing an initial drug application (IND), safety testing in Phase 1, further safety and dosage testing in Phase 2, larger-scale effectiveness testing in Phase 3, and the final approval of the new drug application (NDA), which is filed after all the evidence has been generated and assessed. Similar multiple stages exist for biologics and devices, although there are differences. Figure 1, below, depicts the transition stages for a drug and the multiple forms of defaults or nonapproval that may take place.

FIGURE 1   FDA stages at which nonapproval may occur

CLINICAL
Drug Sponsor's Clinical Studies/Trials

IND APPLICATION

The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from intial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.

PHASE 1

20-80
The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

PHASE 2

100s
The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works inpeople who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

FDA   DRUG SPONSOR

PHASE 3

1000s
The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

IND REVIEW   FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.

Source: U.S. Food and drug Administration

We will consider two major types of instruments that hedge the financial risks associated with this approval process. The first type of instrument is an FDA swap, which in many ways imitates credit default swaps in bond markets. The second is an FDA annuity, which pays the investors in case of a lengthy testing process.

FDA SWAPS

FDA swaps would work as insurance against nonapproval. The basic idea, much as for credit default swaps, is that the buyer of the swap pays a monthly premium to the seller. If the drug is not approved, the buyer is then paid an amount specified by contract.

More precisely, an FDA swap would be a derivative contract between two counterparties. It would be defined through a reference medical product (the drug or device covered by the swap), a maturity date, and a payment amount conditional on nonapproval. The seller of the swap would compensate the buyer if the product was not approved within the maturity date.

In other words, the buyer of the swap would make monthly payments to the seller and, in exchange, receive a payment if the product did not get approved or was not resubmitted for consideration to the next stage in the approval process. The "spread" of a swap is the annual amount the buyer must pay the seller during the length of the contract, expressed as a percentage of the notional amount. For example, if the notional amount (total dollars upon which the swap is based) were $120 million, and the spread were 100 basis points, then the annual payment would be $1.2 million, or $100,000 a month. These payments would continue until either the maturity date was reached or there was a nonapproval decision, as specified by the contract.

The swap contract should also specify what would happen if there were a change in ownership of the product, conditional upon default, and whether the seller of the swap would receive the intellectual property (IP) in case of nonapproval. Contracts must, of course, precisely define and specify nonapproval. They also must establish how much is paid if the drug testing is prolonged. For example, an FDA decision to require more trials before granting an approval would be analogous to a debt restructuring for a traditional credit default swap.

NDA APPLICATION
FDA's New Drug Application (NDA)Review

The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

FDA

DRUG APPROVAL

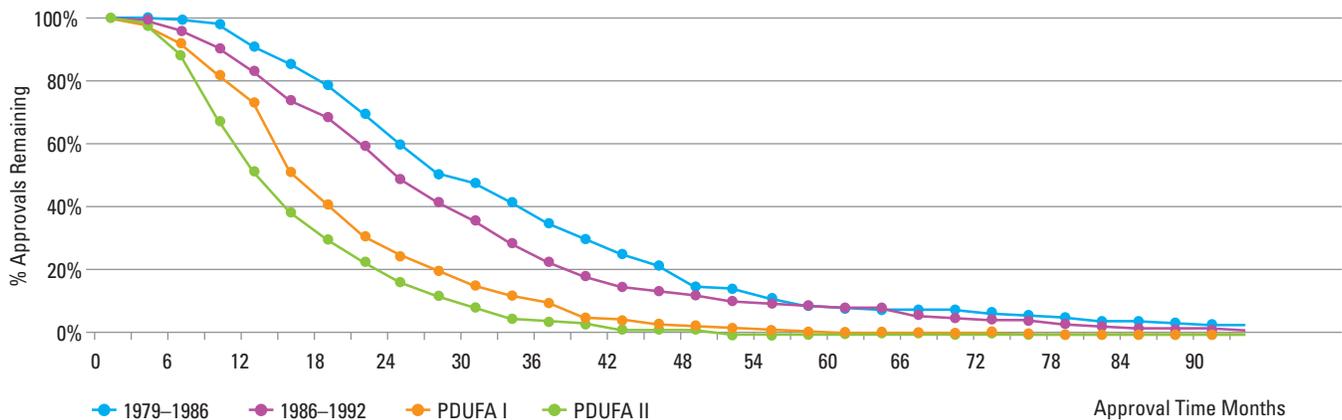FDA reviewers approve the application or issue a response letter.

In addition, other terms need to be defined before this product can be put into general use. These include frequency of premium payments, the period during which the contract is active, the nonapproval payment, the definition of a nonapproval or default, and the exact payment rules conditional on such defined nonapproval events.

FDA ANNUITY

FDA swaps would insure investors against the risk of nonapproval, while FDA annuities would operate as insurance against a lengthy but successful approval process represented by a long lifetime at FDA. For small-molecule drugs, the first three FDA phases of clinical development are estimated to take on average about 24 months, 30 months, and 42 months, respectively, with the final NDA approval taking an additional year, on average. However, as illustrated in Figure 2, there is a large variance among these average approval times.[3] The figure depicts approval rates and the length of the process between 1979 and 1992. The graph includes the share of products that had not yet been decided upon by the FDA for various cohorts or review periods, around the implementation of the Prescription Drug User Fee Act. The act permits the FDA to charge fees that pay for additional resources to speed the review process.
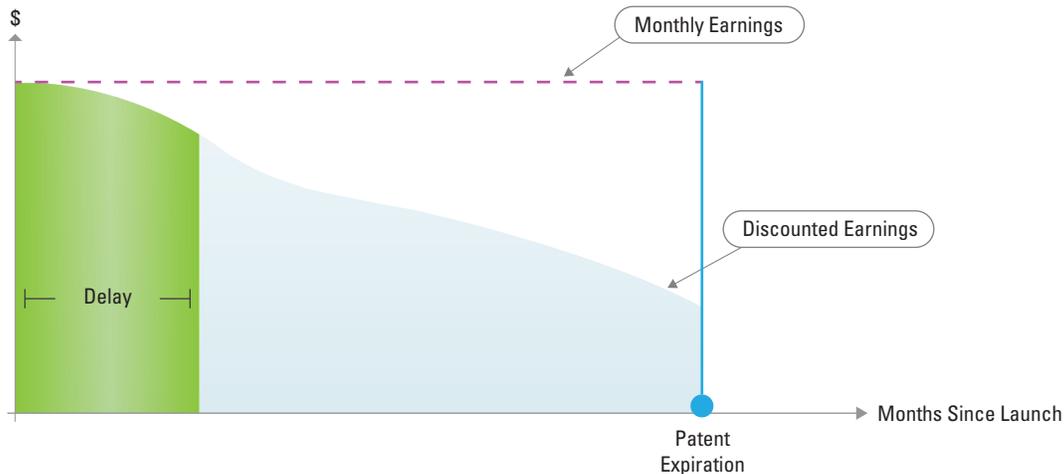
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3. Philipson, Tomas, Ernst R. Berndt, Adrian H.B. Gottschalk, et al. Cost-Benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts. *Journal of Public Economics*, 92(5-6): 1306-1325, June 2008.

FIGURE 2   Variance in NDA Approval Times

The risk inherent in these regulatory survival curves may be insured by annuity-like instruments, just as human survival times are. Even when the product ultimately gains FDA approval, the tails of long approval times add a measure of risk for the developer. To illustrate the cost of delays, consider Figure 3, below, which depicts the relatively large impact a delay has on the overall present value of a return.

FIGURE 3   Innovative Returns and Front-Loaded FDA Delays

Consider a delay of, say, six months for a blockbuster drug with monthly earnings, as indicated in Figure 3, of $100 million. For the sake of illustration, consider that the earnings start directly at launch without a buildup period. The discounted earnings are indicated by the declining curve below these monthly earnings, so that the area under that curve makes up the total present value of the innovation. In this case, about $600 million in earnings discounted over six months is lost because of the delay. This is because the patent time is eaten up by a longer approval time, while the patent expiration date remains unchanged. As a result, sales are not pushed into the future. Instead, the exclusivity of a 10-year-remaining patent is shortened to 9.5 years as a result of the six-month delay, since the date that the patent expires does not change. In addition, what is lost is current revenue as opposed to future revenue, which is more harmful to returns. This is because losing early earnings amounts to losing undiscounted earnings, making up a larger share of the overall return. The bottom line is that a given reduction in market exclusivity time induced by FDA delays of, let's say, 10 percent implies an even larger reduction in the present value of earnings. Of course, sales typically ramp up at launch, and this ramp up is delayed by FDA. Even so, approval delays cause huge reductions in returns, because they eliminate short-term profits that are minimally discounted by time.

FDA annuities will insure a buyer for delays in the approval process, assuming the product ultimately receives approval. The seller of the annuity agrees to compensate the buyer for his or her losses as long as the delay at FDA continues. The contract could have an accumulation period, likely being the period leading up to an FDA submission. After this accumulation period, the annuity would start in the same manner as a standard annuity. The buyer of the annuity would make monthly payments to the seller until the accumulation period ends, which could be a single payment as in a single premium annuity. After the accumulation period, cash flows turn from the buyer to the seller. For example, for an NDA approval duration contract with an accumulation period of one year, the buyer pays 12 monthly premiums, after which the seller starts paying the buyer monthly payments in the 13th month until the product is approved.

The "spread" of an FDA annuity is the annual amount the buyer must pay the seller until the accumulation period ends, expressed as a percentage of the payment amount after the accumulation period. For example, if the notional amount were $100 million, paid monthly after a submission, and the spread were 100 basis points, then the annual payment would be $1 million in the accumulation phase.

If the reference product did not get approved, the contract could specify the flow of funds in various ways. Payments might terminate upon nonapproval or the annuity might be converted into a swap. Naturally, the spread on the contract paid in the accumulation phase would adjust to the way the market values the exact definition and payout structure of the contract conditional on nonapproval.

MATCHING DERIVATIVES TO APPROVAL STAGES

Given the many phases of the FDA process at which defaults or delays can take place, there may be different types of swaps and annuities that are of value to both sides of the trade. First, there may be swaps written for only the phase the product is currently entering, or there may be swaps written on any default for all remaining phases until approval.[4] For example, there may be a swap for only the Phase 3 results or a swap that pays for nonapproval from Phase 3 all the way through the NDA.

Second, swaps may be created for baskets, or groups, of compounds investigated by the FDA—batches containing more than a single new drug.[5] For example, the entire pipeline of a given manufacturer may be hedged. The CDS analogs are contracts based on indices or baskets of bonds.[6] Thus, if there were a notional amount of $100 million on a pipeline of 10 compounds, of which one was rejected, the notional amount would be $1 million for that failed compound.[7] In addition, securitized default obligations, similar to credit default obligations (CDOs), could be created for these baskets of products.

MARKET ACCEPTANCE AND LIQUIDITY

Credit default swaps (CDSs) were introduced in the early 1990s, and their use has expanded greatly since then. In 2012, their reported aggregate notional value reached $25.5 trillion worldwide. CDSs are nonstandardized contracts in the over-the-counter market, and thus are not traded on exchanges. FDA swaps and annuities for medical investments may be liquid due to the same market forces that create liquidity for CDSs issued for nonmedical investments.

One also would presume that the same type of stakeholders that participate in CDS markets for outside of medical R&D firms would have an appetite for FDA risk instruments, including portfolio managers, hedge funds, pension funds, speculators, and manufacturers of the original reference medical products.

These instruments would initially be traded bilaterally through over-the-counter markets but, similar to interest-rate swaps or other instruments, they may become more standardized and more transparently traded through clearinghouses or exchanges after maturing.

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4. Different phases will carry different probabilities of failure; e.g., strong results in Phase 2 bodes well for a successful Phase 3.

5. Within the basket, different compounds may carry different biological risks as well as different lab-to-market risks that will in part depend upon the reputation of the developers and their historic success rates.

6. Mimicking a typical CDS contract, the definition of default, or nonapproval, of an individual compound would remain the same, but the notional amount paid would be the basket amount divided by the number of compounds in the basket.

7. The products in the basket could be weighted equally or differently but, for ease of market acceptance, should follow established CDS structures.

Acquisitions completed in recent years provide some insight into the potential value and liquidity of hedging contracts for medical products submitted to the FDA. In deal structures involving so-called contingent value rights (CVRs), buyers make additional payments once an acquired company hits a future regulatory benchmark. For example, Celgene's $3 billion deal for Abraxis BioScience in 2010 included a CVR provision, conditioned upon regulatory approval of the cancer drug Abraxane for various uses. In addition, in the 2011 sale of Genzyme Corp. to Sanofi-Aventis SA for $20.1 billion, the CVR provision was largely tied to the performance of Campath, another cancer medication. These types of CVRs are essentially an "earn-out" structure of a sale, but specific to the development risk of a product rather than overall company performance. Like earn-outs, regulatory CVRs can be used when buyers and sellers can't agree on a purchase price; they provide additional sales proceeds that kick in after an acquired company meets a regulatory target, such as FDA approval of its compounds. The interesting aspect of these CVRs is that they were listed separately on exchanges and traded upon with great liquidity.

Because of asymmetric information between issuers and the market, regulations to ensure transparency will be required for both over-the-counter and exchange-traded hedging instruments. There are already firms emerging in the marketplace, such as Claravant, that rate the risks associated with pipeline medical products in a manner similar to the way Moody's rates the bonds underlying CDS contracts. In addition, many financial institutions conduct their own surveys of external experts to better assess development-related FDA risk. It is important to keep in mind that many markets do exhibit substantial liquidity despite the presence of what appears to be asymmetric information, casting doubt on the general argument of asymmetric information in eliminating trading volume. Indeed, issuers in regular equity and bond markets often have superior information about the value of these securities than outside market participants, yet substantial liquidity exists in new offerings.

Swaps and annuities are likely to be of more value for products in late-phase development. This is because the mergers and acquisitions between companies with pipeline products and larger companies essentially serve the role of enabling nonapproval insurance for smaller acquired biotech companies. On the sell side, the small biotech gets a fixed payment at sale even if it fails later. Thus, the small biotech purchases insurance as it gives up part of its upside to the big pharma buyer in exchange for a limited downside in case of nonapproval. On the buy side, the big pharma company holds a portfolio of which one in ten or so compounds succeeds. This acts like a small insurance company, with more certain odds than the separate sellers. Therefore, the fact that early phases of development already have this type of de facto insurance mechanism suggests that the value of these instruments will be focused on products that are in the later stages in development, such as Phase 3 or NDA approval.

In a liquid market, the trading price serves an important informative role. Speculation may arise because of differences in opinion about scientific or regulatory risk affecting the value of an instrument. In addition, if public pricing of the instruments discussed becomes available, it will be useful for understanding how the market assesses regulatory risks, in much the same way that corporate-debt yields relative to treasury yields are informative about corporate defaults. FDA swap prices should be predictive of future FDA nonapproval rates for the same reason corporate yields predict defaults.

The liquidity of these instruments may be enhanced by the infusion of capital from third parties, such as nonprofit patient groups or foundations, which increasingly are taking on the role of equity investors rather than mere donors in the development of new drugs and devices. Like any nonprofits, such organizations may make very profitable investments. They differ from for-profit firms in that they cannot distribute the earnings but must reinvest them into the mission of the organization. For example, the Cystic Fibrosis Foundation's $3.3 billion sale of rights to its drugs, including Kalydeco, was from an investment of $150 million. Since the foundation does not have shareholders, these earnings cannot be distributed as dividends but mainly serve to further fight cystic fibrosis. Indeed, a useful role of third parties would be to make an otherwise illiquid market liquid by providing funding and eliminating any potential negative bid-ask spreads. In other words, third parties may subsidize part of the swap or annuity purchase, thereby making a market viable even though bids may be below asks. Such third-party subsidies may even come from more unusual capital sources within the biopharmaceutical industry. For example, new regulations may allow for the return of untaxed earnings abroad by biopharmaceutical companies for the purpose of closing negative bid-ask spreads.

VALUE PROPOSITION

The attractiveness of the pricing of these instruments will depend on the aggregate variability of FDA approval behavior and delays over time. The less variation over time in aggregate FDA approval behavior, the less risk issuers bear from insuring individual companies. Life insurance offers a useful analogy. A policy has value for individual customers because it removes the financial uncertainty of their own mortality. This is true even though aggregate mortality rates may be certain and may not change greatly year to year. In particular, it is unlikely that aggregate approval behavior of the FDA, driven largely by the results of human testing, varies with aggregate economic behavior, such as the business cycle or aggregate market risks. This zero-beta risk nature of FDA securities may be attractive to both issuers of FDA swaps and annuities as well as others seeking diversification in their financial portfolios. As growth of the credit default swap market demonstrates, these are powerful tools for attracting capital. In the world of medical innovation, the use of hedging mechanisms would accomplish more than offer protection for investors. By invigorating the financial climate, they also would help accelerate the development of new medicines and devices that improve individual lives and ease the broader economic and financial burdens of disease.

About the Author

Tomas J. Philipson is a senior fellow at the Milken Institute and is the Daniel Levin Professor of Public Policy Studies in the Irving B. Harris Graduate School of Public Policy Studies at the University of Chicago and an associate member of the Department of Economics. His research focus is health economics.

Before joining the University of Chicago as a postdoctoral fellow in 1989, he was a visiting faculty member at Yale University and a visiting fellow at the World Bank. Philipson was a senior health-care advisor for Sen. John McCain's 2008 presidential campaign and served in the Bush administration as the senior economic advisor to the head of the Food and Drug Administration and later to the head of the Centers for Medicare and Medicaid Services.

He is the recipient of numerous international and national research awards, including the highest honor of his field: the Kenneth Arrow Award of the International Health Economics Association (for best paper in the field of health economics) in 2000 and 2006.

Philipson is a co-editor of the journal *Forums for Health Economics & Policy* of Berkeley Electronic Press and sits on the editorial board of *Health Economics and the European Journal of Health Economics*. His research has been published in leading academic journals of economics and appears and is frequently quoted in the media. Philipson received an undergraduate degree in mathematics at Sweden's Uppsala University and an M.A. and Ph.D. in economics from the Wharton School of the University of Pennsylvania.

About the Milken Institute

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