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Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals

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Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals[*]

by

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Abstract

The U.S. Food and Drug Administration (FDA) balances risks and benefits before approving pharmaceuticals, as rationality would require. But powerful behavioral biases that lead to the mishandling of uncertainty also influence its approval process. The FDA places inordinate emphasis on errors of commission versus those of omission, a bias that is compounded by the FDA's desire to avoid blame should risks eventuate. Despite extensive testing, uncertainties inevitably remain. We often learn about the risks of drugs after they are on the market. And there are off-label uses of drugs, which are not part of the initial testing.

The FDA shows a strong aversion to ambiguous risks. This is the opposite of what is desirable. For any given initial expected risk level, optimal risk-taking decisions involving uncertainty in a multi-period world should prefer ambiguous risks, and the potential for learning, relative to well-established risks of the same magnitude.

Keywords: pharmaceuticals, drugs, ambiguity, regulation, FDA

JEL Codes: I18, K23, D80

1. INTRODUCTION

The regulation of prescription drugs by the U.S. Food and Drug Administration (FDA) is one of the most well-established areas of government safety regulation. Given that consumers lack the expertise to assess the desirability of drugs, the government preempts their discretion and has the FDA approve drugs for marketing based on their safety risks and health benefits. Despite the rigorous nature of the FDA review process, uncertainties inevitably remain with respect to the risks and efficacy of drugs. The way the agency deals with uncertainties often differs from the way it should. This article examines the strengths and biases of current regulations, and proposes ways the government should deal with the risks and uncertainties associated with prescription drugs.

We should emphasize, notwithstanding our critique below, that pharmaceutical innovation has had a tremendously beneficial effect on health. New drugs have significantly raised life expectancy (Lichtenberg 2011), accounting for at least two-thirds of the 0.6 year increase in life expectancy of elderly Americans from 1996-2003 (Lichtenberg 2013a), and have boosted the quality of life of the elderly on various dimensions (Lichtenberg 2012). Drug innovations have also reduced cancer mortality rates by 8.0% from 2000-2009 (Lichtenberg 2013b). This progress helps to account for the `` pressures, described below, to provide even more rapid access to cancer drugs.

2. THE FDA REVIEW PROCESS

2.1. Review Process Procedures

Prescription drugs pose potential risks. To safeguard the public against risky or ineffective drugs, the FDA must approve a drug before it can be marketed, and the agency regulates the subsequent marketing of the drug.

To be approved, a drug must meet standards of safety and efficacy in its proposed uses. Companies must provide "substantial evidence" of that safety and efficacy, which at the final test stage usually requires at least two adequate and well-controlled Phase III studies. Such studies involve from several hundred to 3,000 adults who have the specified condition or disease. However, the FDA may specify alternative ways in which the criteria can be met.[1]

The FDA's benchmarks for safety and efficacy change over time and differ for drugs targeted at different ailments. To illustrate, the FDA recently proposed loosening the efficacy standards for Alzheimer's drugs. Researchers would not have to demonstrate improved daily, real-world functioning. Rather, the drugs would be subject to a less demanding efficacy standard of subtle improvements in performance on memory and reasoning tests.[2] The desire to strike a balance between safety and efficacy often conflicts with views that safety is the paramount consideration. Moreover, the prospect of setting a lower efficacy standard for Alzheimer's drugs raised the safety concern that potential side effects might not be offset by sufficient efficacy benefits.[3]

The FDA allows the two review tracks made possible by the 1992 Prescription Drug User Fee Act (PDUFA), which established timeline goals for different drugs' reviews and charges drug companies fees to augment the FDA's resources.[4] Drugs offering minor improvements over existing marketed therapies now receive the Standard Review, which has a review goal of about 10 months. Drugs offering major advances in treatment, or therapies where none existed

[1] Federal Food, Drug, and Cosmetic Act (P.L. 75-717, 1938), S505c and (d).
[2] Gina Kolata, "FDA Plans to Loosen Rules on Alzheimer's Drug Approval," *New York Times*, March 14, 2013, and *New England Journal of Medicine*, March 13, 2013, and related article by FDA officials, Kozauer and Katz (2013).
[3] The editorial, "Drugs for Early-Stage Alzheimer's," *New York Times*, March 18, 2013, voiced the following safety-related concerns: "Independent analysts need to look hard at whether the F.D.A. should lower the bar for these drugs – or should demand a very high level of proof of safety and efficacy before exposing still-healthy people to possible harm. Even if drugs are eventually approved under this new approach, it will be imperative to force manufacturers to conduct follow-up studies, as required by law, to see if patients benefit in the long run. This is a task they are often slow to perform once a drug is on the market."
[4] Thaul (2012) provides a review of these various procedures.

before, now receive the Priority Review, which has a review goal of six months. In addition, the FDA can offer either Fast Track or Accelerated Approval to expedite drugs targeted at serious diseases or currently unmet medical needs. None of these review tracks involves any formal alteration of the safety and efficacy criteria applied to new drugs, though some concerns have been raised that safety may be compromised by an excessively hasty review process (Moore and Furberg 2012).

2.2. Drug Lag in the United States

The motivation for many of the changes in the review process that PDUFA implemented was concern about a perceived drug lag in the United States due to the FDA's emphasis on resolving the safety and efficacy issues prior to market approval, and the balance the agency struck between these competing concerns. Many drugs were available in Europe before they became available in the U.S. The U.K. approved the beta blocker Propranolol for treatment of arrhythmias, angina, and hypertension before it was approved in the U.S.; many other drugs experienced a similar history.[5] Two more recent example are Eloxatin (oxaliplatin), an advanced colorectal, head, and neck cancer drug, which was approved in the U.S. in 2002 after being approved by at least 29 other countries,[6] and the veno-occlusive disease drug Defibrotide, which has been approved in the European Union but not the U.S.[7]

Drug lag concerns have diminished, as the FDA has notably accelerated review time due to both PDUFA and administrative decisions, such as the loosening of the standards for Alzheimer's drugs. The median time to approval in 1993 was 22 months for standard drugs and

[5] See Viscusi, Magat, and Scharff (1996) and the U.S. General Accounting Office (1980) for a summary of the approval dates in the U.K. and the subsequent dates in the U.S. for beclomethasone dipropionate, sodium valproate, cimetidine, protirelin, somatotropin, phospholipids, danazol, disopyramide phosphate, and propranolol. These studies also review drugs approved in other countries but not in the U.S. that have been found to be unsafe, where the sedative and morning sickness drug thalidomide is the best known example.
[6] See Trowbridge and Walker (2007).
[7] www.gentium.com/products/defibrotide.

14 months for priority drugs.[8] By 2003, these review times had been cut roughly in half, to approximately 12 months for standard drugs and 6 months for priority drugs.[9] Given these expedited reviews, Downing et al. (2012) concluded that on average the U.S. no longer had a clear cut lag relative to other countries. Reflecting this narrowing gap, Olson (2013) found that the percentage of new U.S. drugs that were first approved in the U.S. rose from 28% pre-PDUFA, to 40% from 1992-1997, to 50% after the passage of the 1997 Food and Drug Administration Modernization Act. Rated in terms of the quantity-weighted fraction of new pharmaceutical products sold in 2009 that were launched after 1990, the U.S. ranked eighth (Lichtenberg 2014). Although the U.S. shortfall is modest, failing to be the international leader is potentially important in that Lichtenberg (2014) found that drug vintage accounts for 73% of the increased life expectancy at birth from 2000-2009.

2.3. Off-Label Uses

Although prescription drugs undergo a rigorous review for specific uses that are indicated in the drug labeling, there are also situations in which doctors can prescribe drugs for uses not specified by the labels and not the subject of the FDA testing. In these instances there is no FDA determination that the efficacy benefits for that use outweigh the safety risks. Neither the safety nor efficacy assessments are directed to the off-label use. Such off-label uses are especially common with anticancer chemotherapy drugs. Approximately half of all usage of such drugs is employed for indications not specified on the label approved by the FDA (American Society of Clinical Oncology 2006). Both the National Cancer Institute and the FDA have recognized that

[8] FDA, FY2001 PDUFA Performance Report, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm116089.htm.

[9] FDA, FY2006 PDUFA Performance Report, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/ucm081893.htm.

there are some circumstances in which off-label uses can be "accepted medical practice" or are part of the "standard of care" for the illness. Cancer and other life-threatening illnesses are particularly subject to off-label drug uses, since the safety-efficacy tradeoff may differ from that for patients with less threatening ailments. A study of off-label prescribing of 160 drugs by office-based physicians in 2001 found 150 million off-label mentions. A drug mention was recorded based on the survey of U.S. office-based physicians whereby a drug therapy was recorded for a patient encounter either in terms of a new prescription or continuation of a previously ordered drug therapy. These mentions were appropriately weighted to reflect national utilization patterns. Within a particular class of drugs, cardiac therapies and anticonvulsants had the highest rate of off-label mentions, 46% for each (Radley, Finkelstein, and Stafford 2006). A quite substantial 73% of all off-label mentions had little or no scientific support, much less a re-visiting of FDA's safety and efficacy requirements. Contrary to usual FDA policies that shun uncertainty and tilt to emphasize safety over efficacy, the agency mostly looks the other way for off-label uses though, as noted below, the U.S. Department of Justice and state attorneys general do not.

The Medicare Improvements for Patients and Providers Act of 2008 not only permits off-label drug uses but also requires that Medicare cover drugs to treat cancer that have been approved by the FDA for other purposes. To qualify for required reimbursement, the drugs must meet certain specified requirements (Fiegl 2011). In particular, either the off-label use must be supported by one of the compendia for Medicare reimbursement (i.e., American Hospital Formulary Service – Drug Information, Pharmacopeia – National Formulary, and DRUGDEX), or must be medically accepted based on clinical evidence from peer-reviewed journals or other materials approved by the Secretary of Health and Human Services. Medicaid reimbursement of

drugs approved for non-cancer uses and used for non-cancer purposes requires support in a peer-reviewed journal, but does not require compendia approval. However, unlike cancer drugs, the medical acceptance in peer-reviewed journals of non-cancer drugs does not ensure Medicare reimbursement. Companies are permitted to respond to unsolicited requests for information and in response to such requests are allowed to distribute unedited reprints of studies of the off-label drug from peer reviewed journals provided that the company provided no funding for the study. FDA guidelines require that, in responding to requests about a drug, a company should provide truthful and balanced scientific information,[10] and should not include any "misleading" elements.[11]

The penalties associated with off-label uses of drugs have generated substantial costs to pharmaceutical companies. Pfizer was fined $430 million in 2004 for defrauding Medicaid based on Warner-Lambert's (its acquisition in 2000) marketing of Neurontin for a diverse set of ailments such as headaches, bipolar disorder, and alcohol detoxification.[12] AstraZeneca reached a $520 million settlement in 2010 for its off-label promotion of its schizophrenia drug Seroquel.[13] Novartis settled a series of off-label marketing cases for $422.5 million in 2010 for illegal off-label marketing as well as illegal kickbacks to health care professionals for items such as entertainment, travel expenses, and speaker programs.[14] Amgen paid $762 million in 2012 for

[10] U.S. Dept. of Health and Human Services, FDA, Guidance for Industry Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices, Draft Guidance, Dec. 2011, p. 6.
[11] *U.S. v. Caronia*, F.3d (2012) and *Washington Legal Foundation v. Henney*, 202 F.3d 331 (2000). The *Caronia* decision in the Second Circuit gives companies more leeway to provide information.
[12] Julie Schmit, "Drugmaker Admitted Fraud, but Sales Flourish," *USA Today*, Aug. 16, 2004. The marketing activities were those of Warner-Lambert not Pfizer.
[13] Matthew Arnold, "AstraZeneca settles Seroquel off-label suit for $520m, CIA, Medical Marketing and Media," Medical Marketing & Media, April 27, 2010, www.mmm-online.com/astrazeneca-settles-seroquel-off-label-suit-for-520m-cia/printarticle/168794.
[14] Duff Wilson, "Novartis Settles Off-Label Marketing Case Over 6 Drugs for $422.5 Million," *New York Times*, Sept. 30, 2010.

its off-label use of its anemia drug, Aranesp, for cancer patients not undergoing chemotherapy.[15] A suit by 36 attorneys general against Janssen Pharmaceuticals (whose parent company is Johnson & Johnson) led to a $181 million settlement for "deceptive marketing."[16] Off-label uses of the recombinant factor VIIa (rFVIIa) for major hemorrhage, have caused concern due to the absence of adequate safety data. Indeed, some studies have indicated that recombinant factor VIIa did not significantly reduce mortality, but did increase the rate of thromboembolic events. The Fen-Phen combination, an off-label treatment for obesity that caused pulmonary hypertension and heart-valve problems, spawned considerable litigation and led to billions of dollars in damage awards. It was removed from the market in 1997.[17] Such salient negative examples weigh against the benefits for patients and clinical innovations that come from off-label uses (Lipworth et al. 2012; Logan, Yank, and Stafford 2011; Yank et al. 2011).

2.4. Black-Box Warnings, Post-Labeling Changes, and Product Recalls

Even approved drugs may pose potential risks. Some of these risks are known at the time of approval; other risks only become manifested later. Drugs posing risks of serious or life-threatening adverse events receive black-box warnings in which the particular risk warning on the patient packet insert is surrounded in a black box to draw attention to it. A review by Begosh et al. (2006) of new molecular entities submitted to the FDA from May 1981 to February 2006 found that 81 of the 516 such entities received pre-market black-box warnings. Many black-box warnings are required after a drug has been approved and marketed (Murphy and Roberts 2006). From 1975 to 1999, 45 of 548 new chemical entities approved by the FDA acquired black-box warnings after approval (Lasser et al. 2002). From 2004 to 2006, the FDA required 1,569

[15] Andrew Pollack and Mosi Secret, "Amgen Agrees to Pay $762 Million for Marketing Anemia Drug for Off-Label Use," *New York Times*, Dec. 18, 2012.
[16] Lammi (2012).
[17] Kelli Miller, "Off-Label Drug Use: What You Need to Know," WebMD, http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know.

labeling changes, including 174 black-box warning changes; 77 of them were newly imposed black boxes, and 97 were revisions to black-box warnings (Cook, Gurugubelli, and Bero 2009). The remaining 1,395 changes in drug labeling did not involve black-box warnings.

If post-approval risk appearances are grave enough, drugs may be recalled. From 2004 to 2011, there were 91 Class I recalls, which are recalls of products that have the greatest likelihood of causing patient harm (Wang, Gagne, and Choudry 2012). For the 548 new chemical entities approved from 1975 to 1999, 16 were withdrawn altogether (Lasser et al. 2002).

Olson's (2013) recent study of 381 new chemical entities approved by the FDA from 1990-2004 provides evidence of a broad set of drug-related risks and their evolution over time. At the time of approval, 17% of those drugs included a boxed warning, and 3% included a pregnancy contraindication only in the black box. In the two years after approval, there were 308 adverse reactions on average per drug based on the FDA's Adverse Event Reporting System. The distribution of these events is skewed, as the largest concentrations of drugs fall into categories with 80 or fewer serious adverse drug reactions. Drugs on average required183 required hospitalizations and led to 56 deaths. The drugs that were associated with more serious adverse drug reactions disproportionately included novel drugs and drugs with black box warnings. Adverse drug reactions were less common for drugs first launched in the U.S., and those with a long launch lag after being first launched in another country, or with a long FDA review time.

3. RATIONAL REGULATION IN A SINGLE-PERIOD WORLD

To simplify our argument, we will assume that there are only two outcomes, life and death. The drug offers the prospect of reducing the risk of death, but also has the potential to cause the death of someone who takes it.

3.1. Errors of Commission and Omission

Our regulatory policies, and many individuals, regard an "error of commission," taking a drug that causes death, as being much more serious than an "error of omission," not taking a drug that would have saved one's life. The FDA's emphasis on avoiding Type II errors, namely avoiding the approval of unsafe drugs, rather than Type I errors, that is failing to approve beneficial drugs, has been a long standing theme in the literature.[18] The surprisingly modest percentage of FDA-approved drugs that continue to receive their first approvals in the U.S. and the agency's caution with respect to experimental drugs for gravely ill patients reflect this emphasis.[19] One reason for this is that people are subject to reference point effects and may respond in an asymmetric way to changes in risk, as risk increases receive greater weight. Upon reflection, however, one might reframe the decision problem: Abstracting from cost considerations, should one not follow the strategy that maximizes the probability that one stays alive? In what follows, we frame this question by attaching a weight 1 to being saved by a drug, and the weight w to being killed by it. Those who consider errors of commission more serious would have a w value greater than 1. An alternate decision calculus, one that happens to be embraced by the authors, treats the two errors the same and maximizes the probability of staying alive. It thus sets w equal to 1.

Absent the drug, the individual has a probability s of survival. The drug increases the probability of survival by i, reflecting its therapeutic properties, and reduces the probability of

[18] See Viscusi, Magat, and Scharff (1996), and the U.S. General Accounting Office (1980).
[19] See Edwards (2012). The FDA has begun to address these concerns. See U.S. FDA (2009) Expanded Access to Investigational Drugs for Treatment Use, 74 FR 40900-01.

survival by *r* due to possible adverse effects.[20] In terms of safety and efficacy, safety risks would be *r*, and efficacy benefits would be *i*.

3.2. The Individual's Risk Calculation

The individual has an overall probability of surviving of $s + i - r$. To simplify the model, we set aside all cost considerations though we recognize that costs are an important consideration in the efficient allocation of health care resources. Posit that he is a von Neumann-Morgenstern (VN-M) decision maker. However, like our current drug regulatory policies, he incorporates considerations of omission or commission in assessing those end states. Arbitrarily let us assign a utility of 1 to survival and 0 to natural death. If reductions *r* in the probability of survival receive a weight $w > 1$, the expected utility (EU) is thus:

$$EU = s + i - rw.$$

For an individual for whom w = 1.5, he would just accept a drug that offers a 15% chance of saving him if it had a 10% treatment mortality, since

$$s + 0.15 - 0.10(1.5) = s.$$

There are three things to note about this formulation in relation to current FDA policy. First, consistent with that policy, it allows errors of commission to be weighted more heavily than errors of omission. Second, it is at variance with current FDA policy, at least as it applies in most areas, in that it employs a consistent tradeoff rate between saving and costing lives. The safety requirement of FDA policy in most contexts would create a bias against a drug with a significant probability of a highly consequential negative outcome. This reluctance to approve potentially beneficial drugs that involve high risks is reflected in the continuing limitations on

[20] There may be instances where the adverse effect of the drug kills the individual, but otherwise would have saved him. In that instance, we only learn that the drug killed him. In most instances, we will never know whether absent adverse effects the drug would have saved him.

access to experimental drugs for gravely ill patients.[21] This issue received prominence when the family of Abigail Burroughs unsuccessfully sought to secure approval for their daughter to take Erbitux as a treatment for neck and head cancer. The D.C. Circuit upheld the district court's finding that "there is no constitutional right of access to unapproved drugs."[22] Third, if the FDA were to regulate the drug choices available to patients on an individual basis, the drugs made available for people would depend on their preferences. This would clearly lead to significant regulatory complexities, where physicians would be told they could give a drug to a patient, but only after carefully inquiring about that patient's preferences. But the decision to proceed with many treatments already often depends on personal preferences.

The role of personal preferences arises not only with respect to probabilistic outcomes, but also unproven safety. Activist groups for sufferers from various diseases – almost always devastating diseases – have sought to influence FDA policy by expressing their passionate desire to have new drugs be made available, even if their safety was unproven. The most dramatic example was for AIDS sufferers. Two weeks after the AIDS drug protest named "Seize Control of the FDA" took place on October 11, 1988, the FDA announced an expedited drug approval process for HIV drugs.[23] In other instances, the FDA has in effect channeled the preferences of sufferers, and adjusted its rules to allow drugs that otherwise would have been prohibited. The recent situation with unproven drugs being allowed to be administered to sufferers from early symptoms of Alzheimer's is a salient case.

[21] See Edwards (2012).
[22] Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 700 (D.C. Cir. 2007)(quoting *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601, 2004 WL 3777340, at *1 (D.D.C. Aug. 30, 2004)). Also see Stohr (2008) for further discussion of FDA barriers to experimental drugs.
[23] Brier (2009), at 165-166, discusses this chronology and the policy changes.

The insights from common law approaches – that is, following policies that distill the principles from prior decisions – may infuse FDA rulings more in the future.

3.3. Raisin Benefits Versus Watermelon Costs

In some instances, the regulatory process must compare dramatically different benefits and costs, or in effect to compare the economic equivalent of raisins and watermelons. Think, for instance, of a hypothetical new drug that enables people to dramatically reduce the pain of arthritis. Suppose that it is also known that 1 in 100,000 users will have a massive adverse reaction and suffer a fatal heart attack. Should the FDA allow this drug? If not, what if the risk were 1 in 10 million? Decision theory tells us that there is some probability that would make the risk worthwhile. Indeed, that would be true even if the drug merely partly cleared up acne at the expense of a rare heart attack.

In this spirit, a medical panel recently suggested that women might take tamoxifen or raloxifene to lower their risk of breast cancer even though these drugs raise the risks of blood clots and uterine cancer.[24] For a group of 1,000 women, the drugs will prevent seven to nine cases of invasive breast cancer over five years, but lead to blood clots for four to seven women and additional cases of uterine cancer for four women, on average. The desirability of the drugs depends on patient heterogeneity, including their current risk factors such as family history, which would tilt the odds, and preferences relating to side effects and the alternative health outcomes.

3.4. The FDA's Approach to Safety and Efficacy

This discussion of rational regulation roughly captures the spirit of the FDA's actual practices, but the words roughly and spirit should be emphasized. Before the FDA will approve

[24] Denise Grady, "Panel's Report Urges Breast Cancer Drugs for Healthy Higher-Risk Women," *New York Times*, April 16, 2013.

a drug, it must meet tests of both safety and efficacy. Exactly how the FDA strikes this balance is not readily observable. The legislative guidance is quite general, and FDA operations are far from transparent.[25] As a result, we focus on our stylized characterization of FDA policy decisions. Let us return to our spare example where the drug only increases the probability *i* of survival and independently reduces the probability of survival by *r*. For simplicity, suppose that the FDA sets standards of safety and efficacy independently. Assume that the FDA would grant approval if and only if two constraints were met: $r < r^*$, and $i > i^*$, where these values may depend on the seriousness of the disease.

The constraints i^* and r^* should relate to each other. The FDA's enabling legislation calls for a balancing of these concerns but how, and to what extent, there is balancing is not clear. This tradeoff was faced nineteen years ago, when Sally Zeckhauser (wife of Richard) was discovered to have stage-3 breast cancer. One potential treatment was a bone marrow transplant (BMT). Her doctors said: "This procedure has a 4% treatment mortality. We do not like to undertake such procedures." Sally and Richard had consulted the literature, and thus asked the doctors for their best estimate of the gain in survival probability from a BMT. Though reluctant to answer, their guesstimate was 10%. The decision was straightforward. (The 6% expected survival gain made it worthwhile going through the agonizing treatment.) Though the treatment pushed Sally to the edge of death, today she is totally healthy.

Our simplified FDA decision framework requires all drugs to be in the shaded area in Figure 1 denoted by DEFi*. A straight maximization of the probability of survival approach

[25] The 2012 amendment to the Federal Food, Drug, and Cosmetic Act, §. 3187 amended 21 U.S.C. § 355(d), adding: "The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion of regulatory decision making, and the communication of the benefits and risks of new drugs." How the balancing should be done is not articulated except to indicate pertinent factors such as "the seriousness of the disease or condition that is to be treated with the drug."

would require that the drug be to the right of the 45 degree line 0A. If errors of commission were valued at 1.5 times those of omission, an approved drug would have to be to the right of 0B. The hypothesized zone of current acceptable policies leads to rejection of many risk-reducing drugs.

3.5. The FDA and a Conservative Approach to Uncertain Probabilities

The losses generated by FDA policies likely are increased by the way the agency treats uncertainty in its establishment of the safety and efficacy cutoffs.[26] Suppose that the agency does not know the values of r and i with precision, but that there is some error around each of them, which we will denote by e_1 and e_2. If the agency adopts a conservatism principle of focusing on worst-case scenarios, it might view the efficacy or reduced risk due to the drug as being $r - 2e_1$ and the increased risk level $i + 2e_2$. Such a conservatism bias has been documented in the case of U.S. Environmental Protection Agency (EPA) policies, where the extent of the bias varies depending on the worst-case assumptions used. The EPA sometimes uses a series of assumptions in which the upper bound of the 95th percentile is employed for various parameters in the risk calculation. However, when such conservatism is incorporated into numerous parameters that enter the risk calculation multiplicatively, the compounding of the conservatism biases leads to an assessed risk that is beyond the 99th percentile of the actual risk distribution (Hamilton and Viscusi 1999). Although the FDA's conservatism biases with respect to pharmaceuticals are not well documented, the FDA has adopted an explicitly conservatism approach in assessing the risks of seafood after the BP oil spill (Dickey 2012). Biases of this type may be a more general phenomenon in governmental risk assessment (Nichols and Zeckhauser 1986).

[26] In the extreme, the situation may be one of ignorance (Zeckhauser 2010) in which there is no awareness of particular possible states of the world.

The effect of the conservatism bias depends on which tail of the distribution is used and the manner in which conservatism enters. If the FDA bases its policies on the lower-bound value of both the efficacy and safety levels, that will create a powerful bias against new and uncertain drugs. Such a conservative approach to risk would create a bias against drugs that are potentially beneficial but whose performance is less certain. The worst-case scenarios for drugs require conservatism on both safety and efficacy, say 95th percentile lower bounds for each. This approach leads to the rejections of drugs that, on an expected-risk basis, offer beneficial net health effects.[27]

The conservatism bias in risk assessment relates closely to the framing of the precautionary principle that is embodied in the entire FDA regulatory approach. In particular, before a new drug can be approved, the company must show that the drug is safe. To be truly "safe" a drug must be risk-free. However, it is never feasible to prove that any risk is zero as the risk may not have happened in the sample to date. A zero-risk demonstration is not the approach of statistical hypothesis testing. A zero effect would be the null hypothesis. It is feasible to test the hypothesis that a drug's risk cannot be distinguished statistically from zero, but that is quite different from proving that it imposes zero risk.

Fortunately, the FDA's standard for safety is not that there be zero risk. But what level of currently assessed risk the FDA finds too high to approve a drug – i.e., the cutoff level, is not clear. How the FDA selects this cutoff amount also is not clear.

[27] Moreover, the broader the perceived distributions of benefits and costs, the more costly would be this conservatism. To see this, consider a symmetric extremely tight distribution. Then, the 95th percentile is extremely close to the 50th percentile, and virtually nothing is lost by choosing the former rather than the latter. (The 50th percentile, the median and mean, would be the cutoff for a straight maximize expected value criterion.)

3.6. The Role of Heterogeneity in the Single-Period Case

Matters become more complicated if the patient population is heterogeneous. To simplify the analysis, assume that all patients suffer from the same disease. Wholly apart from differences in preferences with respect to risk, longevity, and treatment modes, there may be fundamental differences in the treatment-decision problem, such as a disease progressing to different extents in different patients. Thus, patient A might be gaining an expected r_A from the drug, whereas patient B might be gaining an expected r_B, where $r_A >> r_B$. Posit that A and B have identical preferences. A should accept a much greater risk from side effects of the drug than should B.

Stimulated both by concern over the U.S. drug lag and by the spread of AIDS, the FDA altered its regulations to address situations in which patients face life-threatening ailments.[28] However, these policies have not altered the general safety and efficacy tests for the drugs. Instead, the emphasis became to provide for a more expeditious approval process for the drugs, which is quite different from redrawing the admissible drug-approval regions shown in Figure 1.

4. RISK AMBIGUITY AND RATIONAL REGULATION IN A MULTI-PERIOD WORLD

4.1. Optimal Experimentation with Uncertain Risks

While uncertainty regarding a probability should be a matter of indifference in single-period choices, imprecision in probability assessments of a drug's properties is actually, though perhaps counter-intuitively, a desirable feature. The principle that a certain probability is inferior to a compound lottery offering the same expected value applies in a wide range of situations where a choice can be changed in the future (e.g., a drug on the market can be withdrawn or vice versa, a patient can be put on a drug and then switched to another drug). That is because the

[28] Brier (2009), at 166.

compound lottery offers learning opportunities.[29] We will illustrate the principle with two simple examples, but the result is quite general.

The first example is stimulated by the classic two-armed bandit problem. Suppose that a patient is faced with two different treatment regimens, which the patient can select in each of the two periods, with associated probabilities of being healthy or sick. Healthy in each period produces a payoff of 1, sick a payoff of 0. There is no discounting. Treatment 1 offers a known probability of 0.5 of making the person healthy in either period. Treatment 2 offers an uncertain probability of 0.5, which we will assume is characterized by a uniform Beta distribution on [0,1]. In particular, assume a Beta distribution characterized by two parameters, α and β. The person has a prior as if having observed α successful outcomes and β unsuccessful outcomes so that the mean perceived risk is $\alpha/(\alpha + \beta)$. With uniform priors, the value of $\alpha = 1$ and $\beta = 1$, and the mean value of the prior is 0.5. The value of $(\alpha + \beta)$ can be viewed as the measure of uncertainty, with lower values of $(\alpha + \beta)$ indicating greater uncertainty. Which treatment option should the patient pick in each period? The expected value of Treatment 1 over the two periods is 0.5*1 + 0.5*1 = 1. In contrast, the roles of learning and adaptive behavior play an important role for Treatment 2. The first period of Treatment 2 offers the same 0.5 expected payoff as that of Treatment 1. If Treatment 2 produces Healthy in the first period, then the updated probability that Treatment 2 produces Healthy in the second period is 0.67.[30] Given its success in period 1, the overall expected payoff to this strategy is 0.5*1 + 0.67*1 = 1.17. This illustrates the stay-on-the-winner rule for two-armed bandit problems.

[29] Unfortunately, there is a strong behavioral bias that leads such learning opportunities to be neglected (Trautmann and Zeckhauser 2013).

[30] With a Beta distribution and uniform prior beliefs, the posterior probability of a healthy outcome after a favorable outcomes in a single trial is (1 + 1)/(2 + 1) = 0.67.

However, if Treatment 2 produces Ill in the first period, the probability that it will produce Healthy in the second period falls to 0.33. It now becomes better to take advantage of learning and switch to Treatment 1, whose probability of producing Healthy stays at 0.5. Given its failure in the first period, the overall expected payoff to this strategy is 0 + 0.5*1 = 0.5.

The expected payoff for starting with Treatment 2 and switching to Treatment 1 if the first period produces Ill is 0.5*1.67 + 0.5*0.5 = 1.085, which is 8.5 percent higher than the payoff to starting with Treatment 1. The more periods there are, holding other factors equal, the greater is the per-period advantage of the dynamic learning strategy.[31]

In some contexts, individuals need success in multiple periods to come out okay. Think of an individual who will receive two periods of treatment, with a life or death outcome in each period. If he survives for two periods, he will also enjoy a third period of life for sure. Survival each period provides utility 1, and death 0, as before. If he dies in either period 1 or period 2, he does not proceed to the next period. With Treatment 1, his expected utility is 0.5*1 + 0.25*1 + 0.25*1 = 1, where 0.25 = 0.5*0.5 is his probability of living through the second period. Treatment 2, likewise, offers a first-period probability of survival of 0.5. However, if the patient survives, the probability of surviving period 2 rises to 0.67. As a result, the expected payoff over two periods from Treatment 2 is 0.5*1 + 0.5*0.67*1 + 0.5*0.67*1 = 1.17, which is 17% greater than the expected rewards from Treatment 1.These results are quite general both for situations of experimentation and adaptive behavior and for situations in which there is a sequence of lotteries on life and death (Berry and Viscusi 1981).

This preference-for-uncertainty result is apparent from a simple example. Suppose that the prior beliefs were based on a great deal of information, such as being equivalent to having

[31] Two-armed bandit problems can become highly complex in multi-period settings, particularly if both "arms" offer learning possibilities. In our example, if there were many periods, it would be worthwhile sticking with Treatment 2 for a while even if it looked inferior, given the benefit should it turn out to be superior.

observed 200 trials, of which 100 had seen success. In that instance, for Treatment 2 the posterior probability of success in the second period after a successful outcome in the first period would only be 101/201 = 0.502. The uncertain treatment consequently would offer a negligible advantage over Treatment 1, whether or not the problem was one of costless learning and experimentation, or a sequence of lotteries on life and death. If, however, there are many periods to the choice problem, the role of learning with the uncertain Treatment 2 could potentially play an important role even with fairly tight prior risk beliefs. In situations of experimentation and information acquisition, one would expect the uncertainty regarding the properties of a drug to be positively correlated with the degree to which it is possible to learn about the risks before the drug is on the market.

Drugs that are first adopted in other countries offer extensive foreign experience in addition to the informational base of the U.S. drug review procedures, thus suggesting that these drugs should be safer. However, contrary to expectations, the opposite result has proven true in practice. Drugs approved elsewhere before marketing in the U.S. have higher rates of adverse drug reactions than those first approved by the FDA (Olson 2013). This result is consistent with non-random sorting, in which drugs of uncertain riskiness get marketed elsewhere first.[32] Moreover, drugs posing few risks could receive accelerated approval by the FDA, also giving a lower adverse reaction rate to drugs getting first approval in the U.S. Other determinants of drug riskiness with respect to adverse drug reactions, hospitalizations, and deaths accord with

[32] Thus, it is the baseline rate of risk of drugs approved elsewhere first, not FDA review practices that produces this higher risk. This could be because drug companies disproportionately submit risky drugs first elsewhere. A second explanation would be that the FDA stretches matters out more than foreign countries when a drug looks risky, and risk appearance makes a drug riskier even if approved. Still, a third explanation would be that the FDA simply counts the same level of foreign evidence of safety as being more compelling than its own evidence; that seems implausible.

expectations. For example, lengthier review periods decrease risks, and accelerated approvals increase risks.[33]

5. RISK AMBIGUITY AND BEHAVIORAL ANOMALIES THAT UNDERCUT RATIONAL CHOICE

A number of behavioral anomalies come into play when choices of drugs with uncertain properties are involved. These anomalies may be enshrined in government policies, both because government regulators and legislators are human and subject to behavioral biases, and because the general public, which is subject to such behavioral phenomena, pressures the direction of government policy.

5.1. Ambiguity Aversion[34]

Our analysis in this section has assumed that the FDA knew the risks associated with a drug. However, probabilities are often highly uncertain. That is, there is ambiguity in the probability.[35]

Uncertain probabilities come from what is called a compound lottery. Thus, in effect, the FDA has to cast its vision forward and ask what are the possible probabilities that it will believe in the future, and what is the likelihood of each? To illustrate numerically, it might think that the possible future probabilities assessments for this side effect are 10%, 5%, 1% and 0.1%. Each of these would be associated with a particular set of future evidence. The FDA thinks these probabilities will come up respectively with likelihoods 0.05, 0.05, 0.178, and 0.722. To get the expected probability, we compute the weighted average, where each probability is weighted by its likelihood. For this example, 0.05*10% + 0.05*5% + 0.178*1% + 0.722*0.1% = 1.002%.

[33] These results would surely apply if there were no selection associated with the length of the review process. However, if drugs thought more risky got longer reviews, and those perceived as less risky got speedier approvals, we would expect a selection effect that pushed in the opposite direction from the observed pattern.
[34] See Trautmann and van de Kuilen (forthcoming) for a broad discussion of ambiguity aversion.
[35] See Trautmann and van de Kuilen (forthcoming).

Rational decision theory – see e.g., Raiffa (1968) – would prescribe that an individual facing a single period choice between a drug with a certain 1% chance of side effect A should also be indifferent to taking the drug with this unknown risk of the side effect, but where the expected value was 1%, in a single period decision. His chance of suffering from the side effect would be 1% in either case.

A particularly germane starting point for how people respond to ambiguity is the Ellsberg Paradox (Ellsberg 1961). In an experimental task involving the chance to win a prize based on draws from an urn, subjects prefer to make a choice from an urn presenting a known probability of success rather than from an urn involving an equivalent but uncertain probability of success, generating a phenomenon known as ambiguity aversion.

There has long been speculation as to why we observe ambiguity aversion rather than neutrality with respect to uncertainty in single-period trials such as this. One possibility is that blame (including self-blame), recrimination, and regret may be greater when the subject fails to win the prize by making an unsuccessful choice from the uncertain urn after passing up a guaranteed 50% chance of success with the known probability.[36] There also may be the fear that the experimenter could be manipulating the contents of the uncertain urn strategically to undermine the person's chance of success, but this risk can be neutralized by flipping a fair coin so that the uncertain option can always be transformed to being characterized by hard probabilities (Raiffa 1961).

The ambiguity situation involving drugs is somewhat different since there is an ambiguous chance of losses rather than only gains as in the Ellsberg Paradox study and most of its sequels. Evidence does exist that people often exhibit ambiguity aversion with respect to

[36] Heath and Tversky (1991).

losses, but the level of ambiguity aversion appears to be less pronounced for losses than for gains (Camerer and Weber 1992).[37]

The power of ambiguity aversion for real world decision makers was manifested by the responses of state judges to a product-liability scenario involving a drug with uncertain properties. The study asked 91 state court judges to choose between two different contrast agents then in use for CAT scans (Viscusi 1999), though the probabilities presented to the judges were hypothetical. The judges considered the following text:

> You are running a pharmaceutical company and must choose only one of two variants of a drug to market as a contrast agent for CAT scans. Your company has been selling *Old Drug* for decades. *Old Drug* works well, but there is a well-established 1/100,000 chance that the patient will suffer an adverse reaction and die. Your research team has already developed *New Drug* that performs identically and will have the same price and manufacturing costs, but *New Drug* poses uncertain risks. Based on the clinical trials the best estimate of the expected level of risk is that it is 1/150,000, but the risk is not known for sure. Some scientists believe the risk from *New Drug* is zero and some believe the risk could be as high as 1/50,000. Which drug would you choose to market? You must pick one. Circle your choice below.

Although the new drug offered a lower expected risk level, 57% of the judges selected the old drug. After the survey, the judges were asked why they had selected the old drug. The dominant response was that a drug with known properties posed fewer liability risks and that they didn't want to gamble with the uncertain drug as that would lead to greater potential liability if a patient died.[38] In effect, their comments suggest that ambiguity aversion on the part of jurors will lead the courts to make adverse rulings against uncertain drugs when products posing precisely known risks are compared with those whose risk levels are uncertain. This could be because errors of commission count much more than errors of omission. In addition, if the new

[37] Though the phenomena are different, this seems to complement the finding of Prospect Theory (Kahneman and Tversky 1979) that individuals are risk taking in the loss domain.
[38] Note the similarity to the attitudes of the rational drug company in the example just considered.

drug is never tried, there is no way to know whether losses have been incurred, but with a switch to the new drug, any losses will be evident. Decision maker preferences may stick with the well chronicled preference for the status quo (Samuelson and Zeckhauser 1988). While most decision theorists would label this irrational, it is consistent with more general fears as to whether novel products incur greater expected liability costs than risky products posing more familiar, well-known hazards.

Consideration of the product-risk case illuminates another potential source of the aversion to ambiguous risks. For a product posing well-known risks, an adverse experience does not alter risk beliefs. For an uncertain product, however, an adverse event will increase the assessed risk. To the extent that people exhibit reference-point effects regarding risk levels, there will be an exaggerated response to adverse events that raise the assessed risk level.[39] The anticipation of such an exaggerated response in combination with the threat of liability will promote caution on the part of both companies seeking to market drugs and regulators who determine whether they can come on the market.

There is an important almost philosophical question as to whether the FDA should embrace this non-rational attitude. If it does not, it is effectively overruling consumer sovereignty. If it does, over the long run it will be accepting drug x that incurs a risk of *k*, but turning down drug y that offers the same benefits but incurs a risk of *k* - *d*, where d is a positive number.

For now, let us posit that the FDA followed the rational prescription, and regulated on the basis of the expected value of risks. Additional considerations come into play. Consider the standpoint of consumers, and then the standpoint of drug companies, both assumed to be rational

[39] There is, for example, a considerable asymmetry between consumers' willingness to pay for risk reductions and their willingness to accept amounts that they require for increases in risk (Viscusi, Magat, and Huber 1987).

for this analysis. Posit further that after the risks become known, the drug would be allowed to continue on the market if its side effect risk is 1% or 0.1%, but not if it is 10% or 5%. The *a priori* probabilities of the 10% and 5% risk were each 0.05. Thus, there is a 10% chance that the drug will be withdrawn from the market.

Up to the time when the risk becomes known, consumers are experiencing expected risk 1%, so they are unaffected. But once the future information comes in and the continuation-withdrawal decision is made, they are better off than they would be with a certain 1% risk. To see this, consider what would happen if the FDA merely ignored the updated assessment. Consumers would then face a 1% expected risk forever, just the equal of the certain 1% risk. But the FDA does the analysis and determines that consumers are better off not taking this drug with 10% or 5% side effect risks. Thus, consumer welfare is improved. Another way to see this is to observe that 90% of the time when the drug is left on the market, the consumer is better off, since more than 4/5 of the time the side effect risk is only 0.1%, and the other 1/5 of the time it is 1% as before.

What about the well-being of the companies? They would be better off with the certain 1% risk. First, their drug will stay on the market for sure. Second, they may be subject to liability if the side effect risk is great enough that they are required to withdraw the drug from the market. Thus, there is not the danger that drug companies – positing they are rational – would favor the uncertain drug. The regulators, from a purely parochial standpoint assuming that they are blame averse, would be better off with the certain risk. There is no chance of the embarrassment or criticism that comes from approving a drug and then removing or having the drug company remove it from the market because its risk was excessive.

Until a drug's performance is known for sure, there is always a positive informational externality going from current to future users. For example, consider a two-person world. A and B both suffer from a condition for which drug 1 is known to perform at level 70, where the score balances efficacy and safety to produce a VN-M utility. Drug 2 has been tested, but its performance is ambiguous. The current analysis is that its VN-M value is equally likely to be either 58 or 80 after one trial, implying an expected utility of 69. After one person takes it, its future VN-M value will be known. A and B have two strategies to compare. They could each take drug 1, and each receive a VN-M value of 70. Alternatively, they could flip a coin to decide who goes first. That individual would get a VN-M value of 68. The second person would stick with drug 2, if the first person had a success, and otherwise switch to drug 1. His VN-M would thus be (1/2)80 + (1/2)70 = 75. Following this second strategy, the expected VN-M value for A and B would be (68+75)/2 = 71.5, which represents an improvement.

This positive informational externality has been widely discussed, notably by those concerned with ethics. Individuals do not flip to decide who comes first. The first sufferer is the first to take the drug. Having one person accept an expected loss so another, or thousands of others, can reap expected gains, is contrary to contemporary medical ethics, which prescribe that the treatment be given that is best for this patient. Compensation, financial or other, could be employed to benefit the first taker. But this approach too, though welcomed by some, has generally been rejected.

At various points in history, drug trials have been undertaken with some form of compensation. For example, prisoners have been given time off in exchange for taking a drug that could be expected to hurt them. One of the most infamous and disgraceful clinical experiments in history was the Tuskegee syphilis study, whereby rural black men were left with

untreated syphilis presumably because they were being given free medical care by the government. The compensation was clearly woefully inadequate. The Tuskegee patients were neither fully informed nor in any sense made better off by participating in the trial.

Our current drug regulatory system on occasion allows drugs with highly uncertain risks on the market, but that happens only when the condition the drug addresses is extremely debilitating or strongly life threatening. To be sure, if the compound lottery associated with an uncertain risk could be resolved in a day or a month, it would be worthwhile waiting. But often additional testing would be extremely expensive, and the only realistic way to know of the existence of risks, particularly low probability risks, and the levels they impose, is to allow the use of the drug and engage in post-marketing surveillance. It is sometimes said that if none of your bridges is falling down, you are building them too strong. Similarly, if none (or indeed very few) of the drugs the FDA has approved are being withdrawn from the market, it is almost certainly regulating them too tightly.[40] Drug performance is highly uncertain. If our regulatory processes are avoiding all losses, then they are surely sacrificing significant gains.

We should note, however, that post marketing surveillance is far from a perfectly rational process. Posit a drug already on the market that has proved more dangerous than expected, and that would not have been allowed on the market in the first place given its currently assessed levels of efficacy and safety. In theory, it should be removed from the market. (We are leaving aside the consideration that patients should not quickly be taken off of drugs, or might not replace a drug with another that is superior.) However, the FDA, like any agency, is hesitant to admit to past errors. Moreover, patients currently taking the drug may favor its continuation

[40] See the Appendix for a discussion of how uncertainty in the testing regimen should combine with the FDA's prior distribution on the risk level to determine what cutoff in the drug trials should be used before market approval. Surprisingly, if the prior on safety is favorable (i.e., the likelihood is great that a drug is safe), the more uncertainty in the testing, the higher the cutoff – the less convincing the results – should be for allowing market approval.

because status quo bias triumphs. Note the continued permission to use the diabetes drug Avandia in the United States despite considerable evidence, and thousands of successful lawsuits deriving from its alleged association with a vast increase in heart attacks. [41]

Just over three decades ago, the authors conducted a decision analysis training program for FDA officials. When the participants were asked why they did not want to base decisions on subjectively assessed risk levels where there was some uncertainty about the potential adverse effects of the drug, the dominant response was that they did not want to be responsible for the next Thalidomide, a drug which led to severe birth defects among children born to mothers in Europe who had taken the drug for morning sickness. Interestingly, the morning-sickness drug Thalidomide had never been approved by the FDA, but it remained one of the most salient cases in the regulatory literature. More interesting still, it has since been approved by the FDA and is currently marketed by Celgene as an anti-cancer treatment known as Thalomid.

5.2. Ambiguity-Seeking Behavior

Responses to uncertain probabilities may depend on the level of the probabilities. There could be manifestations of ambiguity aversion, ambiguity neutrality, and ambiguity-seeking behavior for the same type of risk, depending on the particular levels of risk involved. Ambiguity-seeking behavior is possible in lotteries involving low probabilities for gains and high probabilities for losses (Camerer and Weber 1992).

In the Viscusi and Chesson (1999) survey of 266 business owners and business managers in coastal North Carolina, the authors elicited preferences for locating a business where the choice involved either an area where the experts were in agreement about a precise risk or an

[41] An FDA panel refused to recommend that Avandia be withdrawn from the market, contrary to the recommendations of some of its reviewers. The *New York Times* reported its association with an increase of 83,000 heart attacks. Gardiner Harris, "Controversial Diabetes Drug Harms Heart, U.S. Concludes," *New York Times,* Feb. 19, 2010. The use of Avandia is down substantially since this risk information became known. The drug has been taken off the market in Europe.

area with experts in disagreement and thus holding different risk estimates. For low levels of average risk, subjects exhibited ambiguity aversion. At about a risk of 0.5, they exhibited ambiguity neutrality, and for higher risk levels they exhibited ambiguity-seeking behavior. Thus, risk ambiguity appeared to generate fear of the worst-case outcome at low probabilities and hope for the more favorable outcome at high probabilities. [42]

An analogous situation often arises in medical contexts. Consider two different scenarios for a doctor's visit. In Scenario 1, a patient is told that there is a 10% chance she suffers from a fatal form of cancer, whereas in Scenario 2, the patient is told that the chance could be as low as 5% or as high as 15%. The patient, reflecting ambiguity aversion for low-level risks, would prefer the known risk with Scenario 1. If, however, Scenario 1 posed a well-established 80% risk of a fatal form of cancer, whereas Scenario 2 posed a risk that ranged from 70% to 90%, the same patients might find the medical uncertainty to be a hopeful sign of a better chance of survival.

5.3. Ambiguity and Risk Debates

How people react to ambiguous medical choices depends also on the source of the information that generates the ambiguity. Usually, there is some disagreement either across studies or among different experts. For breast implants, the plaintiffs' bar and many medical experts, including the head of the FDA, either sounded the alarm or expressed caution, whereas plastic surgeons stood by the controversial technology. How do people react to situations in which there is conflicting information? In situations in which there are two conflicting studies of risk levels in the ambiguity averse range by a common entity, such as two government studies, people tend to average the risk assessments but with some modest additional premium that reflects ambiguity aversion. The ambiguity-aversion premium becomes more prominent if the

[42] This would seem consistent with risk taking on losses.

studies are performed by different parties, such as a government entity and an industry group that has a vested interest in the research (Viscusi 1997). Whenever there is such a difference of opinion by different types of groups, people tend to gravitate to the upper-bound risk assessment value, irrespective of whether it is the industry or the government that argues for the high end of the range, leading to a larger ambiguity aversion premium.

Alarmist reactions of this type may contribute to the very strong market response to many risk controversies in the medical field, whether the controversies pertain to medical devices such as breast implants or to Avandia. Such controversies are fueled in addition if they call people's attention to a novel risk not formerly associated with the product. The role of accustomed reference points in thinking about risks makes the perceived changes in risk levels associated with such debates a particular source of concern.

6. CONCLUSION

The FDA's regulatory approach to pharmaceuticals embodies many concerns that are clearly pertinent to a sound drug policy such as focusing on the reduced risk attributable to the drug, the increase in risk caused by the drug, and a balancing of these competing consequences. There is considerable evidence that pharmaceutical innovation has had a significantly beneficial effect on health. However, despite this record of success, unexploited opportunities remain. Even when the pertinent probabilities are known with precision, there is policy controversy as to the appropriate balance between safety and efficacy. Behavioral biases against errors of commission and asymmetric attitudes with respect to increases and decreases in risk will lead to inordinate attention to possible increases in risk.

The policy task becomes much more challenging when the risk properties of drugs are not well known. Despite the FDA's extensive testing requirements, the risks posed by a drug

often cannot be well understood until the drug is put on the market, as evidenced by the frequency of recalls, labeling changes, and off-label uses of drugs for purposes for which the FDA has not assessed safety and efficacy. In addition, the presence of uncertainty may prevent potentially effective markets from reaching the market. The aversion to ambiguity, which is a fairly deep-seated phenomenon for low probabilities of loss, will disadvantage uncertain drugs as compared to drugs with similar, but more precisely understood risks. But this bias against uncertainty is the opposite of what is optimal from the standpoint of promoting public health. Uncertainty offers the greatest chance for learning about favorable properties of drugs, and for promoting long-term survival and quality of life when facing a sequence of risky decisions over time.

References

American Society of Clinical Oncology. 2006. Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications. *Journal of Clinical Oncology* 24:1–3.

Begosh, Allan, John Goldsmith, Ed Hass, Randall W. Lutter, Clark Nardinelli, and John A. Vernon. 2006. Black Box Warnings and Drug Safety: Examining the Determinants and Timing of FDA Warning Labels. NBER Working Paper No. 12803.

Berry, Donald, and W. Kip Viscusi. 1981. Bernoulli Two-Armed Bandits with Geometric Termination. *Stochastic Processes and Their Applications* 11:35–45.

Brier, Jennifer. 2009. *Infectious Ideas: U.S. Political Responses to the AIDS Crisis*. Chapel Hill, NC: University of North Carolina Press.

Camerer, Colin, and Martin Weber. 1992. Recent Developments in Modeling Preferences: Uncertainty and Ambiguity. *Journal of Risk and Uncertainty* 5:325–370.

Cook, Daniel M., Rama K. Gurugubelli, and Lisa A. Bero. 2009. Risk Management Policy and Black-Box Warnings: A Qualitative Analysis of U.S. FDA Proceedings. *Drug Safety* 32: 1057−1066.

Dickey, Robert W. 2012. FDA Risk Assessment of Seafood Contamination after the BP Oil Spill. *Environmental Health Perspectives* 120:a54–a55.

Downing, Nicholas S., Jenerius A. Aminawung, Nilay D. Shah, Joel B. Braunstein, Harlan M. Krumholz, and Joseph S. Ross. 2012. Regulatory Review of Novel Therapeutics – Comparison of Three Regulatory Agencies. *New England Journal of Medicine* 366:2284–2293.

Edwards, Hayes. 2012. Risky Business: How the FDA Overstepped Its Bounds by Limiting Patient Access to Experimental Drugs. *George Mason University Civil Rights Law Journal* 22:389–426.

Ellsberg, Daniel. 1961. Risk, Ambiguity, and the Savage Axioms. *Quarterly Journal of Economics* 75:643–669.

Fiegl, Charles. 2011. Medicare Ordered to Pay for Off-Label Drugs. Amednews.com, March 18. http://www.ama-assn.org/amednews/2011/03/14/gvse0318.htm.

Hamilton, James T., and W. Kip Viscusi. 1999. *Calculating Risks?: The Spatial and Political Dimensions of Hazardous Waste Policy*. Regulation of Economic Activity Series No. 21. Cambridge, MA: MIT Press.

Heath, Chip, and Amos Tversky. 1991. Preference and Belief: Ambiguity and Competence in Choice under Uncertainty. *Journal of Risk and Uncertainty* 4:5–28.

Kahneman, Daniel, and Amos Tversky. 1979. Prospect Theory: An Analysis of Decision under Risk. *Econometrica* 47:263–291.

Kozauer, Nicholas, and Russell Katz. 2013. Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease. *New England Journal of Medicine* 368:1169–1171.

Lammi, Glenn G. 2012. State Attorneys General Step to the Fore on Off-Label Drug 'Promotion.' Forbes.com, September 7. http://www.forbes.com/sites/wlf/2012/09/07/state-attorneys-general-step-to-the-fore-on-off-label-drug-promotion/.

Lasser, Karen E., Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe, and David H. Bor. 2002. Timing of New Black Box Warnings and Withdrawals for Prescription Medications. *Journal of American Medical Association* 287:2215–2220.

Lichtenberg, Frank R. 2011. The Quality of Medical Care, Behavioral Risk Factors, and Longevity Growth. *International Journal of Health Care Finance and Economics* 11:1–34.

Lichtenberg, Frank R. 2012. The Effect of Pharmaceutical Innovation on the Functional Limitations of Elderly Americans: Evidence from the 2004 National Nursing Home Survey. *Advances in Health Economics and Health Services Research* 23:73–101.

Lichtenberg, Frank R. 2013a. The Effect of Pharmaceutical Innovation on Longevity: Patient Level Evidence from the 1996-2002 Medical Expenditure Panel Survey and Linked Mortality Public-use Files. *Forum for Health Economics and Policy* 16:1–33.

Lichtenberg, Frank R. 2013b. Has Medical Innovation Reduced Cancer Mortality? *CESifo Economic Studies doi: 10.1093/cesifo/ift014.*

Lichtenberg, Frank R. 2014. Pharmaceutical Innovation and Longevity Growth in 30 Developing and High-Income Countries, 2000-2009. *Health Policy and Technology* 3:36–58.

Lipworth, Wendy, Ian Kerridge, Miles Little, and Richard Day. 2012. Evidence and Desperation in Off-Label Prescribing: Recombinant Factor VIIa. *British Medical Journal* 344:26–28.

Logan, Aaron C., Veronica Yank, and Randall S. Stafford. 2011. Off-Label Use of Recombinant Factor VIIa in U.S. Hospitals: Analysis of Hospital Records. *Annals of Internal Medicine* 154:516–522.

Moore, Thomas J., and Curt Furberg. 2012. The Safety Risks of Innovation: The FDA's Expedited Drug Development Pathway. *Journal of the American Medical Association* 380:869–870.

Murphy, Shirley, and Rosemary Roberts. 2006. “Black Box” 101: How the Food and Drug Administration Evaluates, Communicates, and Manages Drug Benefit/Risk. *Journal of Allergy and Clinical Immunology* 117:34–39.

Nichols, Albert L., and Richard J. Zeckhauser. 1986. The Perils of Prudence: How Conservative Risk Assessments Distort Regulation. *Regulation* 10:13–24.

Olson, Mary K. 2013. Eliminating the U.S. Drug Lag: Implications for Drug Safety. *Journal of Risk and Uncertainty* 47:1–30.

Radley, David C., Stan K. Finkelstein, and Randall S. Stafford. 2006. Off-label Prescribing Among Office-Based Physicians. *Archives of Internal Medicine* 166:1021–1026.

Raiffa, Howard. 1961. Risk, Ambiguity, and the Savage Axioms: Comment. *Quarterly Journal of Economics* 75:690–694.

Raiffa, Howard. 1968. *Decision Analysis*. Reading, MA: Addison-Wesley.

Samuelson, William, and Richard Zeckhauser. 1988. Status Quo Bias in Decision Making. *Journal of Risk and Uncertainty* 1:7–59.

Stohr, Greg. 2008. U.S. Supreme Court Refuses to Expand Experimental-Drug Access. Bloomberg, January 14. http://www.bloomberg.com/apps/news?pid=newsarchive&sid=atnVIGEgRQt4.

Thaul, Susan. 2012. How FDA Approves Drugs and Regulates Their Safety and Effectiveness. Congressional Research Services Report for Congress 7-5700 (June).

Trautmann, Stefan T., and Gijs van de Kuilen. Forthcoming. Ambiguity Attitudes. In *Blackwell Handbook of Judgment and Decision Making*, edited by Gideon Keren and George Wu.

Trautmann, Stefan T., and Richard J. Zeckhauser. 2013. Shunning Uncertainty: The Neglect of Learning Opportunities. *Games and Economic Behavior* 79:44–55.

Trowbridge, Ronald L., and Steven Walker. 2007. The FDA's Deadly Track Record. *Wall Street Journal*, August 14.

U.S. Food and Drug Administration. 2009. Expanded Access to Investigational Drugs for Treatment Use. *Federal Register* 74: 40900–40945.

U.S. General Accounting Office. 1980. *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*. Washington D.C.: U.S. General Accounting Office, May 28: HRD-80-64.

Viscusi, W. Kip. 1997. Alarmist Decisions with Divergent Risk Information. *Economic Journal* 107:1657–1670.

Viscusi, W. Kip. 1999. How Do Judges Think About Risk? *American Law and Economics Review* 1:26–62.

Viscusi, W. Kip, and Harrell Chesson. 1999. Hopes and Fears: The Conflicting Effects of Risk Ambiguity. *Theory and Decision* 47:153–178.

Viscusi, W. Kip, Wesley Magat, and Joel Huber. 1987. An Investigation of the Rationality of Consumer Valuations of Multiple Health Risks. *RAND Journal of Economics* 18:465–479.

Viscusi, W. Kip, Wesley A. Magat, and Robert Scharff. 1996. Asymmetric Assessments in Valuing Pharmaceutical Risks. *Medical Care* 34:DS34-DS47.

Wang, Bo, Joshua J. Gagne, and Niteesh K. Choudry. 2012. The Epidemiology of Drug Recalls in the United States. *Archives of Internal Medicine* 172:1109−1110.

Yank, Veronica, C. Vaughan Tuohy, Aaron C. Logan, Dena M. Bravata, Kristan Staudenmayer, and et al. 2011. Systematic Review: Benefits and Harms of In-Hospital Use of

Recombinant Factor VIIa for Off-Label Indications. *Annals of Internal Medicine* 154:529–540.

Zeckhauser, Richard J. 2010. Investing in the Unknown and Unknowable. Pp. 304–346 in *The Known, the Unknown, and the Unknowable in Financial Risk Management: Measurement and Theory Advancing Practice*, edited by Francis X. Diebold, Neil A. Doherty, and Richard J. Herring. Princeton, NJ: Princeton University Press.

Appendix
Drug Safety

1. MODEL

Consider the public policy question of deciding how to set safety standards for drugs to be released on the market. We assume that there is one salient feature when deciding whether or not to release a drug: the probability that a patient experiences side effects when using the drug. Denote the threshold at which a drug will be released by p_{thresh}; if you believe the drug has a probability of side effects $p \leq p_{thresh}$, you will release the drug to market, and you will reject the drug otherwise.

Your belief about p (the unknown probability that the drug being considered will cause a side effect in a particular patient) depends on two things. First, based on observing previous drugs, you have a prior distribution P_{prior} over p; this is your prior belief about the likelihood of any randomly-selected drug having a particular side effect rate. Second, you will perform a clinical trial of the drug on a group of C people, and observe the percentage of people that experience side effects. Based on this clinical trial, you update your prior belief to your posterior belief P_{post}, your belief about the likelihood that this particular drug will have a particular side effect rate. Finally, if P_{post} has a mean greater than p_{thresh}, you will reject the drug, and accept it otherwise.

2. BETA DISTRIBUTION

To model P_{prior}, we will use the Beta distribution. The Beta distribution is a suitable choice because it is the conjugate prior of the binomial distribution. This family of distributions has several nice properties.

1. Given a binary experiment with an unknown p probability of success, a prior distribution over p of $Beta(\alpha, \beta)$, and an observation of s successes and f failures, the

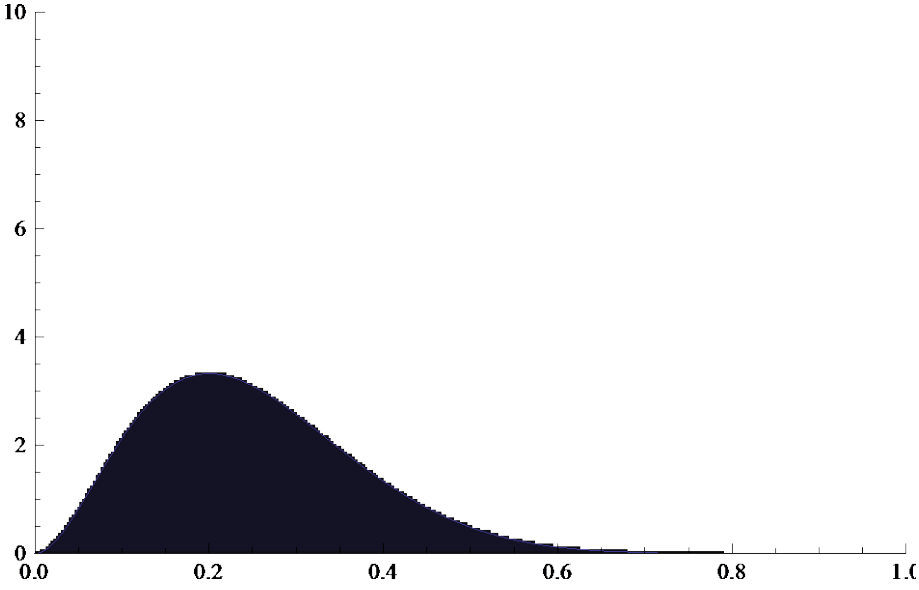
posterior distribution on p is $Beta(\alpha + s, \beta + f)$. This is what is meant when we say that the Beta distribution is the conjugate prior of the binomial distribution.

2. Since $Beta(1,1)$ is just the uniform distribution between $[0,1]$, we can interpret $Beta(\alpha, \beta)$ as the correct posterior distribution after observing $\alpha - 1$ successes and $\beta - 1$ failures, given a uniform prior distribution.
3. $Beta(\alpha, \beta)$ has a mean of $\frac{\alpha}{\alpha+\beta}$.
4. $Beta(\alpha, \beta)$ has a mode of $\frac{\alpha-1}{(\alpha-1)+(\beta-1)}$

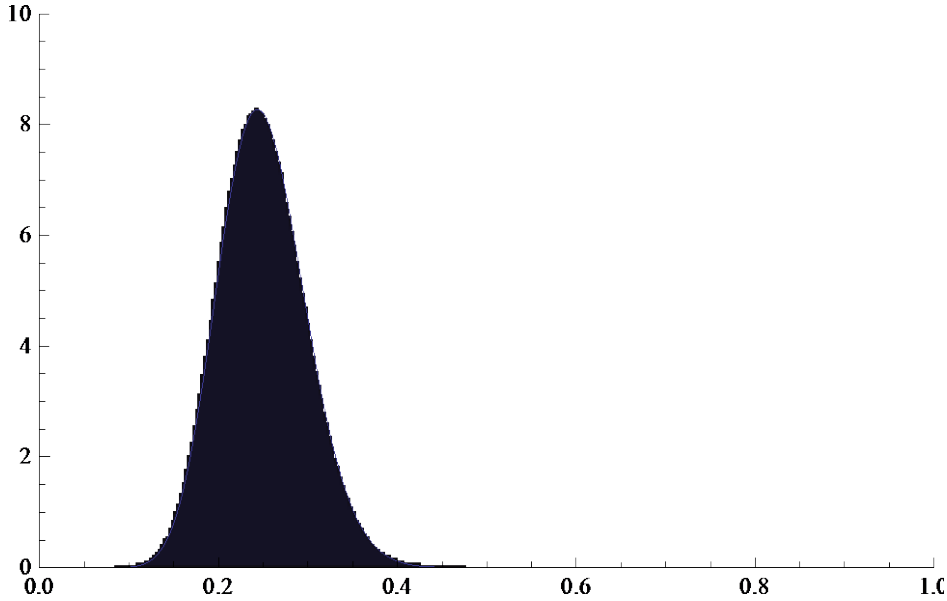
Finally, we note that given facts 2 and 4, for two Beta distributions $Beta(\alpha_1, \beta_1)$ and $Beta(\alpha_2, \beta_2)$ where

$$\frac{\alpha_1}{\alpha_1+\beta_1} = \frac{\alpha_2}{\alpha_2+\beta_2}$$

but $\alpha_1 + \beta_1 < \alpha_2 + \beta_2$, both Beta distributions have the same mean, but the latter distribution expresses more confidence about that mean. For example, $Beta(3,9)$ is



and $Beta(20, 60)$ is:



In other words, since we can interpret the sum $\alpha + \beta - 2$ as number of observations we have made of our experiment, the higher this sum, the more confident we are about the value of p, the rate of success. (A parallel analysis would apply for the mode.)

3. ANALYSIS

Given this model of approving drugs, we wish to determine the cutoff k you should set for your clinical trial. Specifically, given a prior distribution $P_{prior} = Beta(\alpha, \beta)$ and clinical trial of size C, we wish to determine the maximum percentage of patients in the trial who experience side effects (k) that will still lead to a posterior distribution P_{post} with a mean less than or equal to p_{thresh}. In other words, given our method for deciding whether or not to accept a drug as described above, we wish to determine what rates of side effects in our clinical trial are acceptable. We examine three different cases.

3.1. $\boldsymbol{P_{prior}}$ has mean equal to $\boldsymbol{p_{thresh}}$

In this case, $k = p_{thresh}$. To see this, we note that our prior $P_{prior} = Beta(\alpha, \beta)$ has the property that:

$$\frac{\alpha}{\alpha+\beta} = p_{thresh}$$

Given a clinical trial with xC patients with side effects and $(1-x)C$ patients with no side effects, our posterior $P_{post} = Beta(\alpha + xC, \beta + (1-x)C)$. Now, consider the following:

$$Mean(P_{post}) = \frac{\alpha+xC}{\alpha+\beta+C} \leq p_{thresh}$$

$$\alpha + xC \leq p_{thresh}(\alpha + \beta + C)$$

$$\alpha + xC \leq \alpha + p_{thresh}C$$

$$x \leq p_{thresh}$$

In other words, the mean of our posterior is less than p_{thresh} if and only if $x \leq p_{thresh}$. Accordingly we should set $k = p_{thresh}$.

3.2. $\boldsymbol{P_{prior}}$ has mean less than $\boldsymbol{p_{thresh}}$

In this case, $k > p_{thresh}$. To see this, we note that our prior $P_{prior} = Beta(\alpha, \beta)$ has the property that:

$$\frac{\alpha}{\alpha+\beta} < p_{thresh}$$

For convenience, we will set $d = p_{thresh} - \frac{\alpha}{\alpha+\beta}$.

Given a clinical trial with xC patients with side effects and $(1-x)C$ patients with no side effects, our posterior $P_{post} = Beta(\alpha + xC, \beta + (1-x)C)$. Now, consider the following:

$$Mean(P_{post}) = \frac{\alpha+xC}{\alpha+\beta+C} \leq p_{thresh}$$

$$\alpha + xC \leq p_{thresh}(\alpha + \beta + C)$$

$$\alpha + xC \leq \alpha + d(\alpha + \beta) + p_{thresh}C$$

$$x \leq p_{thresh} + \frac{d(\alpha+\beta)}{C}$$

In other words, the mean of our posterior is less than p_{thresh} if and only if $x \leq p_{thresh} + \frac{d(\alpha+\beta)}{C}$. Accordingly we set should $k = p_{thresh} + \frac{d(\alpha+\beta)}{C}$. Furthermore, since $d, C, \alpha, \beta > 0$, we have that $k > p_{thresh}$, as desired.

In addition, we can make two observations about k. The more skewed to the right of p_{thresh} our prior distribution is, and the larger $are\ d$ and $\alpha + \beta$, the larger is the difference between k and p_{thresh}. Furthermore, as $C \to \infty$, $k \to p_{thresh}$; the larger our clinical trial, the closer we should set k to p_{thresh}.

3.3. $\boldsymbol{P_{prior}}$ has mean greater than $\boldsymbol{p_{thresh}}$

In this case, $k < p_{thresh}$. To see this, we note that our prior $P_{prior} = Beta(\alpha, \beta)$ has the property that:

$$\frac{\alpha}{\alpha+\beta} > p_{thresh}$$

For convenience, we will set $d = \frac{\alpha}{\alpha+\beta} - p_{thresh}$.

Given a clinical trial with xC patients with side effects and $(1-x)C$ patients with no side effects, our posterior $P_{post} = Beta(\alpha + xC, \beta + (1-x)C)$. Now, consider the following:

$$Mean(P_{post}) = \frac{\alpha+xC}{\alpha+\beta+C} \leq p_{thresh}$$

$$\alpha + xC \leq p_{thresh}(\alpha + \beta + C)$$

$$\alpha + xC \leq \alpha - d(\alpha + \beta) + p_{thresh}C$$

$$x \leq p_{thresh} - \frac{d(\alpha+\beta)}{C}$$

In other words, the mean of our posterior is less than p_{thresh} if and only if $x \leq p_{thresh} - \frac{d(\alpha+\beta)}{C}$. Accordingly we set should $k = p_{thresh} - \frac{d(\alpha+\beta)}{C}$. Furthermore, since $d, C, \alpha, \beta > 0$, we have that $k < p_{thresh}$, as desired.

In addition, we can make two observations about k. The more skewed to the left of p_{thresh} our prior distribution is, and the larger $are\ d$ and $\alpha + \beta$, the larger is the difference between k and p_{thresh}. Furthermore, as $C \to \infty$, $k \to p_{thresh}$; the larger our clinical trial, the closer we should set k to p_{thresh}.

4. MODELING ERROR

Up to this point, we have assumed that our clinical trial is completely error free. However, in practice, there is some uncertainty to the observed results of a clinical trial; the true number of patients in the study who experienced side effects may be higher or lower than the observed quantity. We will model this situation as follows. Given a clinical trial of size C with xC observed side effects, we have some probability distribution over the true number of side effects. The only requirement we have about this distribution is that it is symmetric around xC. By symmetric, we mean the following. Let e_i denote the probability that the true number of side effects was $xC + i$. Then we have that

$$e_i = 0 \text{ for all } i < -xC, i \geq (1 - x)C$$

$$e_i = e_{-i}$$

It turns out that that given a prior distribution of $P_{prior} = Beta(\alpha, \beta)$, the mean of our posterior distribution P_{post} does not change after accounting for error; it is still

$$\frac{\alpha + xC}{\alpha + \beta + C}$$

This means that our analysis about k - the maximum acceptable percentage of observed side effects in a clinical trial - from the previous section does not change even after accounting for error. Regardless of the error distribution around the observed side effect frequency, as long as it is symmetric, you choose the same k given the same prior, clinical trial size, and p_{thresh}.

To see why the mean of the posterior distribution does not change, consider the following. We will denote the probability density function (PDF) of a $Beta(x, y)$ distribution by $b_{x,y}$. Furthermore, we will denote the PDF of our posterior distribution given a clinical trial of size C with xC observed side effects, and a prior of $Beta(\alpha, \beta)$ by f_{post}.

$$f_{post}(p) = \sum_{i=-xC}^{(1-x)C} e_i b_{(\alpha+xC+i),(\beta+(1-x)C-i)}$$

$$\begin{aligned} Mean(P_{post}) &= \int_0^1 p f_{post}(p) dp \\ &= \int_0^1 p \sum_{i=-xC}^{(1-x)C} e_i b_{(\alpha+xC+i),(\beta+(1-x)C-i)} dp \\ &= \sum_{i=-xC}^{(1-x)C} e_i \int_0^1 p b_{(\alpha+xC+i),(\beta+(1-x)C-i)} dp \\ &= \sum_{i=-xC}^{(1-x)C} e_i Mean(Beta(\alpha + xC + i, \beta + (1-x)C - i)) \\ &= \sum_{i=-xC}^{(1-x)C} e_i \frac{\alpha+xC+i}{\alpha+\beta+C} \end{aligned}$$

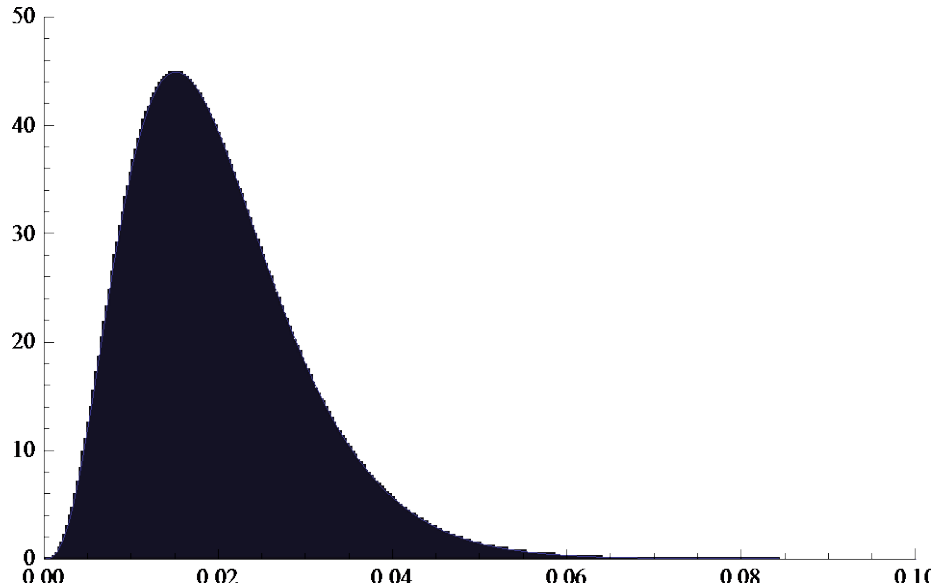
However, since $e_i = e_{-i}$, we have that

$$Mean(P_{post}) = \frac{\alpha+xC}{\alpha+\beta+C}$$

as desired.

5. AN EXAMPLE

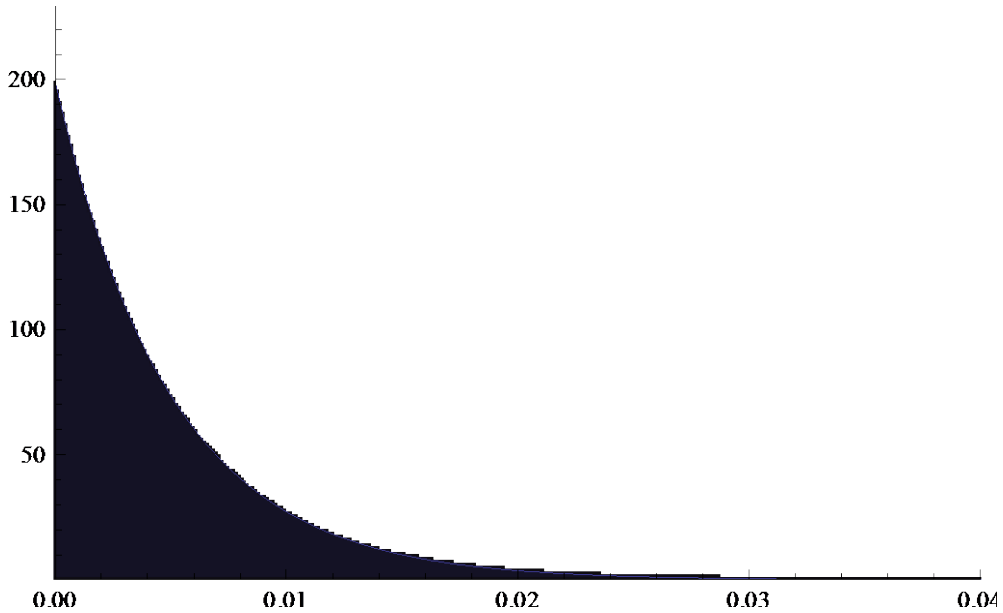
In this section, we will work out a simple example to demonstrate some of principles we derived above. Assume we want to release all drugs which we believe have an average probability of side effects of less than 3%; we set $p_{thresh} = 3$. First, assume we have a prior belief of $Beta(4,196)$,



which has a mean of 2%. If we run a clinical trial of size 100, our threshold for the number of side effects in the trial will be 5; at most 5% of the clinical trial can experience side effects for the drug to be released. This demonstrates that an optimistic prior belief (one with a mean less than our threshold) results in a side effect cutoff in our clinical trial that is higher than our threshold.

If we run a clinical trial of size 200, our threshold for the number of side effects will instead be 8; at most 4% of the clinical can experience side effects for the drug to be released. This demonstrates that the larger the size of the clinical trial, the closer the cutoff percentage for side effects in the trial will be to the threshold.

Finally, if we instead had a prior belief of $Beta(1,199)$,



which has a mean of 0.5% and is significantly more skewed to the right our thresholds for a clinical trial of size 100 and 200 would be 8% and 5.5%, respectively. This demonstrates that the more skewed our prior belief is to the right the higher our cutoffs for clinical trials.

6. CONCLUSION

Given this analysis, we come to the following conclusions about how clinical trial data should be interpreted. If you believe that drugs are generally safe, and are very confident in that fact (P_{prior} is skewed to the left of p_{thresh}), then you should set your standards for clinical trial data to be higher than your actual desired side effect probability. On the other hand, if you believe that drugs are generally dangerous, and are very confident in that fact (P_{prior} is skewed to the right of p_{thresh}), then you should set your standards for clinical trial data to be lower than your actual desired side effect probability. Finally, the larger your clinical trial (the greater C is), the closer you should set your standards for clinical trial data to your actual desired side effect probability.

Figure 1
FDA Risk Balancing