Appendix A: Proofs

We suppress the dependence of various terms on α for readability and only explicitly note it when needed for clarity. For all derivatives, the variable of differentiation is α unless otherwise specified.

Proof of Proposition 1: To show that $V(\alpha)$ is concave in α, we argue that $\mathbb{E}[N_E(\alpha)]$ and $-\mathbb{E}[N_I(\alpha)]$, are concave in α, and thus the sum is concave. Direct computation shows that $\mathbb{E}[N_E(\alpha)]$ is concave increasing in $\lambda_{AE}(\alpha)$ and that $\lambda_{AE}(\alpha)$ is concave in α. Thus $\mathbb{E}[N_E(\alpha)]$ is concave. $\mathbb{E}[N_I(\alpha)]$ is linear in α and thus $V(\alpha)$ is concave. The optimal approval policy Eq. (8) is directly obtained from the FOC $V'(\alpha) = 0$. ■

Proof of Corollary 1: By the Implicit Function Theorem, we have that

$$\frac{\partial \alpha^*}{\partial x} = -\frac{\frac{\partial V'(\alpha^*)}{\partial x}}{\frac{\partial V'(\alpha^*)}{\partial \alpha}}$$

where x is the parameter of interest. The fact that $V(\alpha)$ is concave in α means the denominator is negative and thus the sign of $\frac{\partial \alpha^*}{\partial x}$ is given by the sign of $\frac{\partial V'(\alpha^*)}{\partial x}$. The FOC of the FDA's problem Eq. (6) is given by

$$V'(\alpha) = Q_E \frac{\partial \mathbb{E}[N_E(\alpha)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha)}{\partial \alpha} - \frac{Q_I}{\mu_I} \frac{\partial \lambda_{AI}(\alpha)}{\partial \alpha} \tag{A1}$$

where $\frac{\partial \mathbb{E}[N_E(\alpha)]}{\partial \lambda_{AE}} = \frac{K^2 \mu_E}{(K\mu_E + \lambda_{AE})^2}$, $\frac{\partial \lambda_{AE}(\alpha)}{\partial \alpha} = \lambda_{NDA}\ p\ \frac{\Phi'(\Phi^{-1}(1-\alpha) - \delta\sqrt{T_n})}{\Phi'(\Phi^{-1}(1-\alpha))}$, and $\frac{\partial \lambda_{AI}(\alpha)}{\partial \alpha} = \lambda_{NDA}\ (1-p)$ (directly from Eqs. (1)-(4), (5), and (7)).

We find the sign of the effect of each parameter on α^* as follows:

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_E}\right) = \operatorname{sgn}\left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) \geq 0$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_I}\right) = \operatorname{sgn}\left(-\frac{1}{\mu_I} \frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha}\right) \leq 0$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_I}\right) = \operatorname{sgn}\left(\frac{Q_I}{\mu_I^2} \frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha}\right) \geq 0$$

$$\begin{aligned}
\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \lambda_{NDA}}\right) &= \operatorname{sgn}\left(Q_E \left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}} \frac{\partial^2 \lambda_{AE}(\alpha^*)}{\partial \alpha \partial \lambda_{NDA}} + \frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}^2} \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \lambda_{NDA}} \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) - \frac{Q_I}{\mu_I} \frac{\partial^2 \lambda_{AI}(\alpha^*)}{\partial \alpha \partial \lambda_{NDA}}\right) \\
&= \operatorname{sgn}\left(\frac{Q_E}{\lambda_{NDA}} \left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha} + \frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}^2} \lambda_{AE}(\alpha^*) \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) - \frac{1}{\lambda_{NDA}} \frac{Q_I}{\mu_I} \frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha}\right) \\
&= \operatorname{sgn}\left(\frac{Q_E}{\lambda_{NDA}} \frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \lambda_{AE}^2} \lambda_{AE}(\alpha^*) \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) \leq 0
\end{aligned}$$

The second equality is due to the linearity of λ_{AE} and λ_{AI} on λ_{NDA}. The third equality is obtained by cancelling the first and third term in the sum, which corresponds to $V'(\alpha^*) = 0$. The sign of the last expression is negative due to the concavity of $\mathbb{E}[N_E]$ with respect to λ_{AE} and the fact that λ_{AE} is increasing in α.

We claim that $\frac{\partial \alpha^*}{\partial \mu_E}$ and $\frac{\partial \alpha^*}{\partial p}$ are non-monotonic and that $\lambda_{AE}(\alpha^*)/K\mu_E < 1$ is a sufficient condition to ensure that $\frac{\partial \alpha^*}{\partial \mu_E} \leq 0$ and $\frac{\partial \alpha^*}{\partial p} \geq 0$. The proof of this is given by straightforward differentiation:

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_E}\right) = \operatorname{sgn}\left(-K^2 \frac{(K\mu_E - \lambda_{AE}(\alpha^*))}{(K\mu_E + \lambda_{AE}(\alpha^*))^3}\right) \leq 0$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial p}\right) = \operatorname{sgn}\left(Q_E \frac{1}{p} \frac{K^2 \mu_E}{(K\mu_E + \lambda_{AE}(\alpha^*))^3} \frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha} (K\mu_E - \lambda_{AE}(\alpha^*)) + \frac{Q_I}{\mu_I} \lambda_{NDA}\right) \geq 0.$$

Thus, $\lambda_{AE}(\alpha^*)/K\mu_E < 1$ is sufficient to guarantee α^* is decreasing in μ_E and increasing in p. ■

Proof of Corollary 2: We begin by showing that $\alpha_1^* \le \alpha_2^* \le \cdots \le \alpha_K^*$. To do this, we show that $V_K'(\alpha_{K+1}^*) \le 0$ for any $K \ge 1$. The concavity of $V_K(\alpha)$ will imply the desired inequality. Consider the following expression, where the notation $\mathbb{E}[N_E^K(\alpha)]$ is used to denote the expected number of effective drugs when there are K drug classes:

$$\begin{aligned} V_K'(\alpha_{K+1}^*) - V_{K+1}'(\alpha_{K+1}^*) &= Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_{K+1}^*)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha_{K+1}^*)}{\partial \alpha} - \frac{\partial \mathbb{E}[N_E^{K+1}(\alpha_{K+1}^*)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha_{K+1}^*)}{\partial \alpha} \right) \\ &= -Q_E \frac{\partial \lambda_{AE}(\alpha_{K+1}^*)}{\partial \alpha} \frac{(2K+1)\lambda_{AE}^2(\alpha_{K+1}^*)\mu_E + 2K(K+1)\lambda_{AE}(\alpha_{K+1}^*)\mu_E^2}{(K\mu_E + \lambda_{AE}(\alpha_{K+1}^*))^2 \ ((K+1)\mu_E + \lambda_{AE}(\alpha_{K+1}^*))^2} \le 0. \end{aligned}$$

From the optimality of α_{K+1}^*, we know that $V_{K+1}'(\alpha_{K+1}^*) = 0$, and thus noting that $V_K'(\alpha_{K+1}^*) \le 0$. As this holds for any K, we obtain the desired result. Next, consider a system in which $K = \infty$. We demonstrate that $\alpha_K^* \le \alpha_\infty^*$. Let's denote $\mathbb{E}[N_E^\infty(\alpha)] := \lim_{K\to\infty} \mathbb{E}[N_E^K(\alpha)] = \frac{\lambda_{AE}(\alpha)}{\mu_E}$, and thus $V_\infty(\alpha) := \lim_{K\to\infty} V_K(\alpha) = Q_E \mathbb{E}[N_E^\infty(\alpha)] - Q_I \mathbb{E}[N_I(\alpha)]$. Once again, we use the concavity of $V_K(\alpha)$ to establish the result. Consider the following expression:

$$\begin{aligned} V_K'(\alpha_\infty^*) - V_\infty'(\alpha_\infty^*) &= Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_\infty^*)]}{\partial \lambda_{AE}} \frac{\partial \lambda_{AE}(\alpha_\infty^*)}{\partial \alpha} - \frac{1}{\mu_E} \frac{\partial \lambda_{AE}(\alpha_\infty^*)}{\partial \alpha} \right) \\ &= -\frac{Q_E}{\mu_E} \ \frac{\lambda_{AE}(\alpha_\infty^*)}{\partial \alpha} \ \frac{\lambda_{AE}^2(\alpha_\infty^*) + 2K\lambda_{AE}(\alpha_\infty^*)\mu_E}{(K\mu_E + \lambda_{AE}(\alpha_\infty^*))^2} \end{aligned}$$

By the optimality of α_∞^*, we have that $V_\infty'(\alpha_\infty^*) = 0$, and thus $V_K'(\alpha_\infty^*) \le 0$. As a result, we have

$$\alpha_K^* \le \alpha_\infty^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p} \ \frac{Q_I/\mu_I}{Q_E/\mu_E} \right) + \frac{\delta\sqrt{I_n}}{2} \right)$$

where α_∞^* can be found by solving $V_\infty'(\alpha) = 0$.

Now we focus on the optimal expected benefits. We begin by showing that $V_K(\alpha_K^*) \le V_{K+1}(\alpha_{K+1}^*)$, which first involves showing $V_K(\alpha) \le V_{K+1}(\alpha)$ for all α. The following calculation shows that this is the case:

$$V_K(\alpha) - V_{K+1}(\alpha) = Q_E \left(\frac{K\lambda_{AE}(\alpha)}{K\mu_E + \lambda_{AE}(\alpha)} - \frac{(K+1)\lambda_{AE}(\alpha)}{(K+1)\mu_E + \lambda_{AE}(\alpha)} \right) = \frac{-Q_E\lambda_{AE}^2(\alpha)}{(K\mu_E + \lambda_{AE}(\alpha))((K+1)\mu_E + \lambda_{AE}(\alpha))}$$

The series of inequalities $V_K(\alpha_K^*) \le V_{K+1}(\alpha_K^*) \le V_{K+1}(\alpha_{K+1}^*)$ completes the proof.

Next, we show that $V_K(\alpha_K^*) \le V_\infty(\alpha_\infty^*)$. To do this, we first show that $V_K(\alpha) \le V_\infty(\alpha)$ for all α as follows:

$$V_K(\alpha) - V_\infty(\alpha) = Q_E \left(\frac{K\lambda_{AE}(\alpha)}{K\mu_E + \lambda_{AE}(\alpha)} - \frac{\lambda_{AE}(\alpha)}{\mu_E} \right) = -\frac{Q_E}{\mu_E} \ \frac{\lambda_{AE}^2(\alpha)}{K\mu_E + \lambda_{AE}(\alpha)} \le 0.$$

The remainder of the proof follows from the series of inequalities $V_K(\alpha_K^*) \le V_\infty(\alpha_K^*) \le V_\infty(\alpha_\infty^*)$.

Next, we show $V_{K+1}(\alpha) - V_K(\alpha) > V_{K+2}(\alpha) - V_{K+1}(\alpha)$ by direct computation:

$$\begin{aligned} &V_{K+1}(\alpha) - V_K(\alpha) - (V_{K+2}(\alpha) - V_{K+1}(\alpha)) \\ &= Q_E \left[\left(\frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}} - \frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} \right) - \left(\frac{(K+2)\lambda_{AE}}{(K+2)\mu_E + \lambda_{AE}} - \frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}} \right) \right] \\ &= Q_E \ \frac{2\mu_E}{(K\mu_E + \lambda_{AE}) \ ((K+1)\mu_E + \lambda_{AE}) \ ((K+2)\mu_E + \lambda_{AE})} \ge 0. \end{aligned}$$

■

Proof of Proposition 2: We first show that the optimal endogenous approval policy is more stringent, i.e., $\tilde{\alpha}^* \le \alpha^*$. The endogenous $\tilde{\alpha}^*$ satisfy the FOC of Eq. (9) namely,

$$\tilde{V}'(\tilde{\alpha}^*) = V'(\tilde{\alpha}^*) - \frac{Q_I}{\mu_I} \frac{\lambda_{NDA}}{1+\alpha_o} = 0.$$

Thus, $V'(\tilde{\alpha}^*) \ge V'(\alpha^*) = 0$ and by concavity of $V(\alpha)$ (Proposition 1), we have that $\tilde{\alpha}^* \le \alpha^*$.

Part a). Let's assume $\tilde{\alpha}^* \le \alpha^* \le \alpha_o$. We have that $\tilde{V}(\tilde{\alpha}^*) \ge \tilde{V}(\alpha^*) \ge V(\alpha^*)$ where the first inequality is obtained from the optimality of $\tilde{\alpha}^*$, and the second inequality is obtained from Eq. (9) and noting $\alpha_o - \alpha^* \ge 0$.

Part b). Let's assume $\alpha_o \le \tilde{\alpha}^* \le \alpha^*$. We have that $\tilde{V}(\tilde{\alpha}^*) \le V(\tilde{\alpha}^*) \le V(\alpha^*)$, where the first inequality follows from Eq. (9) noting that $\alpha_o - \tilde{\alpha}^* \le 0$, and the last inequality follows from the optimality of α^*. ■

Appendix B: Parameter Estimation

B.1. Drug Development Parameters

Pre-FDA review parameters are estimated using publicly available data from clinicaltrials.gov and historical drug approval data from Drugs@FDA. For each disease considered (breast cancer, HIV, and hypertension), we perform an Advanced Search on clinicaltrials.gov with the following field settings: Search Terms: <insert disease>; Study Type: Interventional; Conditions: <insert disease>; Interventions: Drug. All other field settings were left blank. After downloading the data that resulted from this search, we exclude trials with the following criteria: (a) Non-drug intervention (Behavioral, Biological, Device, Dietary Supplement, Other, Procedure, Genetic, Radiation), (b) Conditions other than the disease of interest, (c) Enrollment = 0 or NULL, (d) Study Completion Date or Study Start Date NULL, (e) Duration of study = 0 or NULL, (f) Study Start Date before January 2000 or after December 2019, (g) Title or Condition fields do not indicate relevance of the trial to the disease of interest. After imposing criteria (a)-(g), we obtain a dataset consisting of 3,311 (breast cancer), 1,855 (HIV), and 2,105 (hypertension) trials.

Clinical Trial Initiation Rate. We compute the clinical trial initiation rate λ by averaging the number of Phase I trials that begin each year between 2000 and 2019, by disease (Table B1).

Table B1 Number of Phase I trials initiated per year.

Disease	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean
Breast Cancer	3	6	6	14	12	19	23	29	34	30	37	32	35	40	41	40	46	65	43	57	30.6
HIV	3	4	5	4	9	12	20	13	27	19	27	23	13	20	34	32	26	19	23	22	17.8
Hypertension	3	2	0	3	4	5	7	14	16	17	22	20	18	24	19	26	19	14	17	12	13.1

Source: National Institutes of Health (2020)

NDA Submission Rate. We adjust the Phase I initiation rate λ to obtain the NDA submission rate:

$$\lambda_{NDA} = \frac{\lambda}{\text{Trials per Path}} \mathbb{P}(\text{Path Success})$$

where "Path Success" refers to a drug completing clinical trial testing and the sponsoring firm filing an NDA and values for $\mathbb{P}$(Path Success) are given in Thomas et al. (2016). For each phase in the pathway, drugs typically undergo multiple trials; we adjust λ using values estimated by Wong et al. (2019) (Table B2).

Table B2 Clinical trial success rates.

		Num. Trials	$\mathbb{P}$(Phase Success)				
Disease	λ	per Path	Phase I→II	Phase II→III	Phase III→NDA	$\mathbb{P}$(Path Success)	λ_{NDA}
Breast Cancer	30.6	1.6	0.641	0.230	0.342	0.05	0.96
HIV	17.8	2.0	0.695	0.427	0.727	0.21	1.87
Hypertension	13.1	2.0	0.589	0.241	0.555	0.08	0.55

Sources: National Institutes of Health (2020), Wong et al. (2019), Thomas et al. (2016)

Trial Duration. The mean time to complete all clinical trial testing $1/\mu_{CT}$ is the sum of the mean durations of Phase I, Phase II, and Phase III (Table B3). Since we cannot link a drug's specific clinical trial pathway from Phase I to FDA review, we instead use average durations.

We examine whether clinical trial durations are approximately exponentially distributed for use in the $M/M/\infty$ queueing model (Figure B1). Although Phase I trials are not perfectly exponentially distributed, the latter phases more closely satisfy this assumption, and they comprise the majority of total drug development time. In Section 5.4, we relax the exponential assumption by sampling from the empirical distributions.

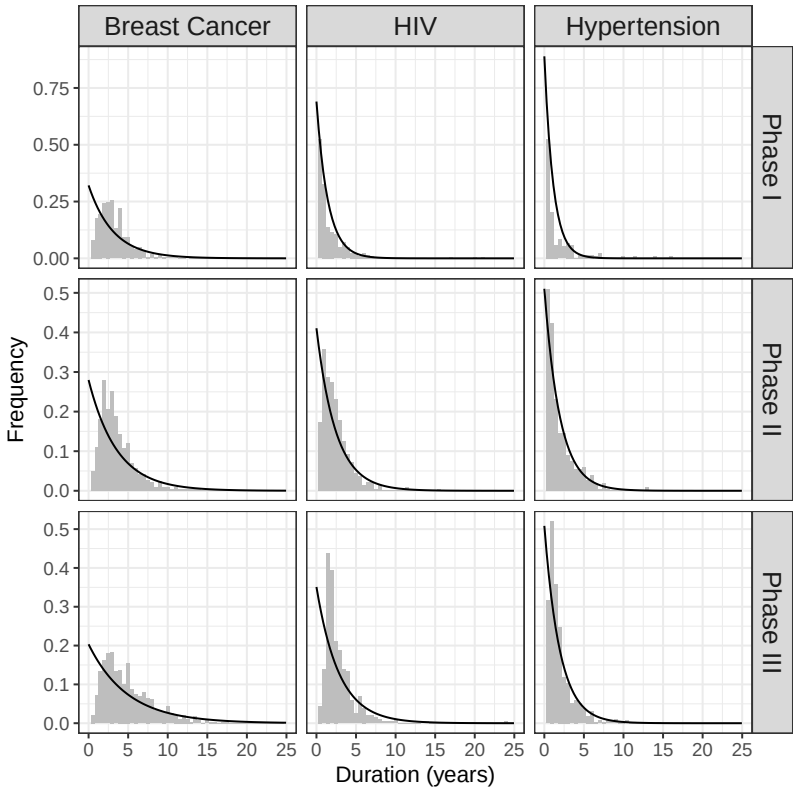
Trial Abandonment Rate. For each disease, we compute the trial abandonment rate μ_{AB} using $\mathbb{P}$(Path Success) from Thomas et al. (2016), our previously estimated μ_{CT}, and the following relationship from our queueing model: $\mathbb{P}(\text{Path Success}) = \frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$.

Table B3 Mean clinical trial duration by phase.

Disease	Phase I	Phase II	Phase III	Total
Breast Cancer	3.1 years	3.6 years	4.9 years	11.6 years
HIV	1.4 years	2.4 years	2.8 years	6.7 years
Hypertension	1.1 years	1.9 years	2.0 years	5.0 years

Source: National Institutes of Health (2020)

Figure B1 Histograms of the duration of Phase I, Phase II, and Phase III clinical trials.



Clinical Trial Information. In our model, we assume all trials are of the same size n. Clinical trial information $\delta\sqrt{I_n}$ is calculated by assuming the statistical power of the trial—the probability the FDA approves a drug conditional on it being effective—is 90%, and a traditional statistical significance level of $\alpha = 2.5\%$. We therefore compute $\delta\sqrt{I_n}$ to satisfy $0.90 = 1 - \Phi\left[\Phi^{-1}(1-0.025) - \delta\sqrt{I_n}\right]$.

B.2. Post-Approval Parameters

Effectiveness Probability. We assume that, conditional on undergoing FDA review, the probability that a drug is effective is 90% but we vary this from 85% to 95% in sensitivity analysis (Section 5.2). Across all diseases, the probability of approval once a drug reaches FDA review is 85% (Thomas et al. (2016)), so this is a reasonable lower bound for the effectiveness probability at this stage. Of course, it is not possible to directly observe this value, as we cannot determine whether non-FDA-approved drugs are actually effective.

Number of Drug Classes. We estimate the number of unique drug classes K based on historical approvals and current standards of care for breast cancer (Table B7), HIV (Table B9), and hypertension (Table B8).

Health Benefits. We define Q_E as the gain in population health benefits per year per approved effective drug class on the market $\mathbb{E}[N_E(\alpha)]$. Using historical trends in mortality rates by disease (CDC 2016), and past drug approvals (National Cancer Institute (NCI) 2020, AIDSinfo 2020, FDA 2020), we calculate life-

years gained per approved drug class. We multiply this value by the total market size (CDC (2019, 2020), Siddiqi et al. (2016), Breast Cancer Society 2020) to obtain Q_E (Table B4).

Table B4 Health Benefits per Newly Approved Effective Drug.

Disease	Period Considered	Num. Drug Classes Approved over Period	Life Expectancy Gain per Drug Class	Total U.S. Market Size	Health Benefits Q_E
Breast Cancer	1968-2015	10	0.015 years	253,000	3,790 life-years
HIV	1981-2014	6	0.091 years	1,200,000	108,000 life-years
Hypertension	1968-2015	4	0.037 years	106,000,000	3,922,000 life-years

Sources: CDC (2016, 2019, 2020), Siddiqi et al. (2016), Breast Cancer Society (2020), National Cancer Institute (NCI) (2020), AIDSinfo (2020), FDA (2020)

Health Harms. We define Q_I as total life-years lost per year following a one-unit increase in the expected number of approved ineffective drugs on the market $\mathbb{E}[N_I(\alpha)]$. Given the rarity of ineffective drugs gaining FDA approval, we cannot directly observe their impact on population-wide life expectancy. Instead, we assume that the total health costs of approving an ineffective drug Q_I/μ_I are proportional to the total health benefits of approving an effective drug Q_E/μ_E, with a constant ratio:

$$\text{ratio} = \frac{Q_I/\mu_I}{Q_E/\mu_E}$$

To compute a baseline ratio, we utilize the abnormal stock returns following announcement of FDA approval $AR_{approval}$, or market withdrawal $AR_{withdrawal}$ of a drug. Using historical data for 49 publicly traded pharmaceutical firms between 1990 and 2001, Sarkar and de Jong (2006) estimate an abnormal return for new drug approval of 3.77%, consisting of abnormal returns associated with initial review by FDA, the approval announcement, the final approval announcement, and the day following the final approval. In a different study of 108 firms withdrawing drugs between 1966 and 1998, Ahmed et al. (2002) estimate an abnormal return of -7.85% following drug withdrawal. We note that out of the 108 drug withdrawals included in the study, 59 are due to drugs being ineffective for the approved indication. Thus, we compute the ratio as:

$$\text{ratio} = \frac{AR_{withdrawal}}{AR_{approval}} = \frac{0.0785}{0.0377} \approx 2$$

We vary the ratio in sensitivity analysis (Section 5.2) to examine its impact on the optimal policy α^*.

Market Duration. FDA-approved effective drugs spend a period $1/\mu_E$ on the market, consisting of time on patent $1/\mu_{PAT}$ and as a generic $1/\mu_{GEN}$ (Table B5). Standard U.S. patent protection is 20 years, with patents typically filed at the pre-clinical phase, on average 4.5 years before Phase I trials commence (PhRMA 2015). To obtain $1/\mu_{GEN}$, we examine FDA records of drugs that were discontinued for reasons unrelated to safety or efficacy; this assumes the drugs eventually became obsolete and exited the market (FDA 2019).

Table B5 Post-approval market duration.

Disease	Post-Approval Time on Patent $1/\mu_{PAT}$	Post-Approval Time as Generic $1/\mu_{GEN}$	Total Time on Market $1/\mu_E$	Post-Approval Time until Withdrawal $1/\mu_I$
Breast Cancer	5.0 years	20.2 years	25.2 years	7.8 years
HIV	10.5 years	17.1 years	27.6 years	14.5 years
Hypertension	13.2 years	13.0 years	26.2 years	2.8 years

Sources: PhRMA (2015), Drugs@FDA

FDA-approved ineffective drugs spend a period $1/\mu_I$ on the market, calculated as the average time until withdrawal, for each disease considered (Table B6). Note, this may underestimate the full duration as withdrawn drugs can cause patient harm, accelerating their removal.

Table B6 List of FDA-approved drugs that were withdrawn from the market.

Disease	Drug	Approval	Withdrawal	Time on Market	Source
Breast cancer	Avastin*	Feb 2004	Nov 2011	7.8 years	Drugsite Trust (2018)
HIV	Hivid	Jun 1992	Dec 2006	14.5 years	AIDS InfoNet (2017)
Hypertension	Ticrynafen	May 1979	Jun 1982	2.7 years	Manier et al. (1982)
Hypertension	Posicor	Jun 1997	Jun 1998	1.0 years	Bradbury (1998)
Hypertension	Valturna	Sep 2009	Jul 2012	2.8 years	FDA (2016)

* Avastin's indication for breast cancer was removed but the drug itself remained on the market.

Table B7 FDA-approved breast cancer drugs.

Drug (Brand Name)	Approval
Alkylating Agents	
Thiotepa (Tepadina)	March 1959
Cyclophosphamide (Cytoxan)	Nov 1959
Other Chemotherapy	
Methotrexate (Trexall)	Aug 1959
Vinblastine (Velban)	Aug 1987
Vincristine (Oncovin)	Apr 1988
Fluorouracil 5-FU (Adrucil)	Aug 1991
Gemcitabine (Gemzar)	May 1996
Irinotecan (Camptosar)	Jun 1996
Capecitabine (Xeloda)	Apr 1998
Temozolomide (Temodar)	Aug 1999
Ixabepilone (Ixempra)	Oct 2007
Eribulin (Halaven)	Nov 2010
Topotecan (Hycamtin)	Dec 2010
Platinum Drugs	
Cisplatin (Platinol)	Dec 1978
Carboplatin (Paraplatin)	Mar 1989
Ovarian Suppression	
Goserelin (Zoladex)	Dec 1989
Leuprolide (Lupron)	Apr 1993
Abarelix (Plenaxis)	Nov 2003
Buserelin (Suprefact)	N/A
Taxanes	
Paclitaxel (Taxol)	Dec 1992
Docetaxel (Taxotere)	May 1996
Paclitaxel (Abraxane)	Jan 2005
Vinca Agents	
Vinorelbine (Navelbine)	Dec 1994
Hormone Therapy	
Megestrol Acetate (Megace)	Aug 1971
Toremifine (Fareston)	May 1997
Tamoxifen (Nolvadex)	Feb 2003
Raloxifene (Evista)	Dec 1997
Fulvestrant (Faslodex)	Apr 2002
Targeted Biologics	
Trastuzumab (Herceptin)	Sep 1998
Bevacizumab (Avastin)	Feb 2004
Everolimus (Afinitor)	Mar 2009
Pertuzumab (Perjeta)	Jun 2012
Ado-trastuzumab emtansine (Kadcyla)	Feb 2013
Palbociclib (Ibrance)	Feb 2015
Lapatinib (Tykerb)	Sep 2015
Ribociclib (Kisqali)	Mar 2017
Neratinib maleate (Nerlynx)	July 2017
Abemaciclib (Verzenio)	Sep 2017
Olaparib (Lynparza)	Jan 2018
Biphosphonate Therapy	
Zoledronate (Zometa)	Aug 2001
Pamidronate (Aredia)	May 2002
Alendronate (Fosamex)	Feb 2008
Denosumab (Xgeva)	Jun 2010
Ibandronate (Boniva)	Apr 2012
Risedronate (Actonel)	Jun 2014
Anthracyclines	
Doxorubicin (Adriamycin)	Dec 1987
Mitoxantrone (Novantrone)	Apr 2006
Epirubicin (Ellence)	Sep 2008
Liposomal Doxorubicin (Doxil)	Feb 2013
Aromatase Inhibitors	
Anastrozole (Arimidex)	Jun 2010
Exemestane (Aromasin)	Apr 2011
Letrozole (Femara)	Jun 2011
Combination Chemotherapy	
Docetaxel & Cyclophosphamide	N/A
Docetaxel, Doxorubicin & Cyclophosphamide	N/A
Docetaxel & Carboplatin	N/A
Paclitaxel & Capecitabine	N/A
Docetaxel & Capecitabine	N/A
Docetaxel & Carboplatin	N/A
Paclitaxel & Carboplatin	N/A
Paclitaxel & Capecitabine	N/A
Paclitaxel & Carboplatin	N/A
Irinotecan & Temozolomide	N/A
Gemcitabine & Carboplatin	N/A
Ixabepilone & Capecitabine	N/A
Doxorubicin & Cyclophosphamide	N/A
Doxorubicin, Cyclophosphamide & Paclitaxel	N/A
Doxorubicin, Cyclophosphamide & Docetaxel	N/A
Epirubicin & Cyclophosphamide	N/A
Cyclophosphamide, Doxorubicin, & Fluorouracil	N/A
Cyclophosphamide, Methotrexate & 5-Flourouracil	N/A
5-Flourouracil, Doxorubicin & Cyclophosphamide	N/A
5-Flourouracil, Epirubicin & Cyclophosphamide	N/A

Source: National Cancer Institute (NCI) (2020)

Table B8 FDA-approved hypertension drugs.

Drug (Brand Name)	Approval
Antiadrenergic	
Reserpine (Raudixin)	Mar 1955
Guanadrel (Hylorel)	Dec 1982
Methyldopa (Aldomet)	Feb 1986
Clonidine (Catapres)	Jul 1987
Prazosin (Minipress)	Sep 1988
Guanabenz	Apr 1995
Phentolamine (Regitine)	Mar 1998
Terazosin (Hytrin)	Mar 1998
Doxazosin (Cardura)	Oct 2000
Guanfacine (Tenex)	Oct 2012
Phenoxybenzamine (Dibenzyline)	Jan 2017
Guanethidine (Ismelin)	N/A
Angiotensin Converting Enzyme (ACE) Inhibitor	
Deserpidine (Harmonyl)	Apr 1957
Captopril (Capoten)	Feb 1996
Enalapril (Vasotec)	Jan 2001
Lisinopril (Prinivil)	Jul 2002
Moexipril (Univasc)	May 2003
Benazepril (Lotensin)	Feb 2004
Fosinopril (Monopril)	May 2005
Quinapril (Accupril)	Jun 2006
Trandolapril (Mavik)	Jun 2007
Ramipril (Altace)	Jun 2008
Perindopril (Coversyl)	Nov 2009
Amlodipine & Perindopril (Prestalia)	Jan 2015
Diuretics	
Chlorothiazide (Diuril)	Sep 1958
Polythiazide (Renese)	Sep 1961
Hydrochlorothiazide (Microzide)	Jan 1973
Furosemide (Lasix)	Oct 1981
Methyclothiazide	Jun 1982
Hydroflumethiazide (Saluron)	May 1985
Amiloride (Midamor)	Jan 1986
Spironolactone (Aldactone)	Jul 1986
Triamterene-Hydrochlorothiazide (Dyazide)	Dec 1987
Atenolol-Chlorthalidone (Tenoretic)	Jul 1992
Indapamide (Lozol)	Jul 1995
Bumetanide (Bumex)	Nov 1996
Metolazone (Zaroxolyn)	Dec 2003
Torsemide (Demadex)	May 2005
Ethacrynic Acid (Edecrin)	Jul 2015
Combination Therapy	
Deserpidine-Methyclothiazide (Enduronyl)	Aug 1961
Reserpine-Polythiazide (Renese-R)	Oct 1963
Reserpine-Chlorthalidone (Regroton)	May 1964
Reserpine-Methyclothiazide (Diutensen-R)	Sep 1975
Reserpine-Hydrochlorothiazide (Hydroserpine)	Jan 1977
Hydralazine-Reserpine-Hydrochlorothiazide (Hydrap-ES)	Sep 1977
Hydralazine-Hydrochlorothiazide (Apresazide)	Sep 1977
Timolol-Hydrochlorothiazide (Timolide)	Dec 1981
Reserpine-Chlorothiazide (Diupres)	May 1982
Reserpine-Hydroflumethiazide	Mar 1983
Reserpine-Trichlormethiazide	Apr 1983
Methyldopa-Hydrochlorothiazide (Aldoril)	Feb 1987
Propranolol-Hydrochlorothiazide (Inderide)	Apr 1987
Spironolactone-Hydrochlorothiazide (Aldactazide)	Jul 1987
Triamterene-Hydrochlorothiazide (Dyazide)	Dec 1987
Clonidine-Chlorthalidone (Combipres)	Dec 1987
Amiloride Hydrochlorothiazide (Moduretic)	May 1988
Atenolol-Chlorthalidone (Tenoretic)	Jul 1992
Enalapril-Diltiazem (Teczem)	Oct 1996
Enalapril Felodipine (Lexxel)	Dec 1996
Captopril-Hydrochlorothiazide (Capozide)	Dec 1997
Bisoprolol-Hydrochlorothiazide (Ziac)	Sep 2000
Enalapril-Hydrochlorothiazide (Vaseretic)	Sep 2001
Eprosartan-Hydrochlorothiazide (Teveten HCT)	Nov 2001
Lisinopril-Hydrochlorothiazide (Zestoretic)	Jul 2002
Benazepril-Hydrochlorothiazide (Lotensin HCT)	Feb 2004
Metoprolol-Hydrochlorothiazide (Lopressor HCT)	Aug 2004
Moexipril-Hydrochlorothiazide (Uniretic)	Mar 2007
Nadolol-Bendroflumethiazide (Corzide)	Mar 2007
Amlodipine-Benazepril (Lotrel)	May 2007
Quinapril-Hydrochlorothiazide (Accuretic)	Aug 2007
Aliskiren-Valsartan (Valturna)	Sep 2009
Losartan-Hydrochlorothiazide (Hyzaar)	Oct 2010
Aliskiren-Hydrochlorothiazide (Amturnide)	Dec 2010
Telmisartan-Hydrochlorothiazide (Micardis)	Sep 2011
Irbesartan-Hydrochlorothiazide (Avalide)	Sep 2012
Valsartan-Hydrochlorothiazide (Diovan)	Sep 2012
Candesartan-Hydrochlorothiazide (Atacand)	Dec 2012
Amlodipine-Valsartan (Exforge)	Mar 2013
Amlodipine-Atorvastatin (Caduet)	Nov 2013
Amlodipine-Telmisartan (Twynsta)	Jan 2014
Amlodipine-Valsartan-Hydrochlorothiazide (Exforge HCT)	Jun 2015
Olmesartan-Hydrochlorothiazide (Benicar HCT)	Oct 2016
Amlodipine-Olmesartan (Azor)	Nov 2016
Deserpidine-Hydrochlorothiazide	N/A
Guanethidine-Hydrochlorothiazide (Esimil)	N/A
Methyldopa-Chlorothiazide (Aldoclor)	N/A
Vasodilators	
Hydralazine (Apresoline)	Oct 1978
Minoxidil	Jul 1999
Mecamylamine (Inversine)	Mar 2013
Beta Blockers	
Propranolol (Inderal)	Nov 1985
Penbutolol (Levatol)	Dec 1987
Atenolol (Tenormin)	Jan 1992
Nadolol (Corgard)	Oct 1993
Metoprolol (Lopressor)	Dec 1993
Pindolol (Visken)	Jan 1994
Acebutolol (Sectral)	Apr 1995
Timolol (Betimol)	Mar 1997
Labetalol (Trandate)	Aug 1998
Betaxolol (Kerlone)	Oct 1999
Carteolol (Ocupress)	Jan 2000
Bisoprolol (Zebeta)	Jun 2001
Esmolol (Brevibloc)	May 2005
Carvedilol (Coreg)	Sep 2007
Nebivolol (Bystolic)	Jul 2015
Penbuterol	N/A
Calcium Channel Blockers	
Verapamil (Calan)	Jul 1992
Nicardipine (Cardene)	Dec 1996
Diltiazem (Cardizem)	Dec 1999
Isradipine (DynaCirc)	Apr 2006
Amlodipine (Norvasc)	Jun 2007
Felodipine (Plendil)	Apr 2008
Nifedipine (Procardia)	Jun 2010
Nisoldipine (Sular)	Jan 2011
Other Renin-Angiotensin System Antagonists	
Aliskiren (Tekturna)	Mar 2007
Eplerenone (Inspra)	Aug 2008
Angiotensin II Receptor Blockers	
Losartan (Cozaar)	Oct 2010
Eprosartan (Teveten)	Nov 2011
Azilsartan and Chlorthalidone (Edarbyclor)	Dec 2011
Irbesartan (Avapro)	Oct 2012
Candesartan (Atacand)	Jan 2014
Telmisartan (Micardis)	Jul 2014
Valsartan (Diovan)	Jun 2015
Nevivolol and Valsartan (Byvalson)	Jun 2016
Amlodipine and Olmesartan (Olmesartan)	Oct 2016

Source: FDA (2020)

Table B9 FDA-approved HIV drugs.

Drug (Brand Name)	Approval
Nucleoside Reverse Transcriptase Inhibitors	
Zidovudine (Retrovir)	Mar 1987
Didanosine (Videx)	Oct 1991
Stavudine (Zerit)	Jun 1994
Lamivudine (Epivir)	Nov 1995
Abacavir (Ziagen)	Dec 1998
Didanosine (Videx EC)	Oct 2000
Tenofovir Disoproxil Fumarate (Viread)	Oct 2001
Emtricitabine (Emtriva)	Jul 2003
Protease Inhibitors	
Saquinavir (Invirase)	Dec 1995
Idinavir (Crixivan)	Mar 1996
Ritonavir (Norvir)	Mar 1996
Nelfinavir (Viracept)	Mar 1997
Atazanavir (Reyataz)	Jun 2003
Fosamprenavir (Lexiva)	Oct 2003
Tipranavir (Aptivus)	Jun 2005
Darunavir (Prezista)	Jun 2006
Non-Nucleoside Reverse Transcriptase Inhibitors	
Nevirapine (Viramune)	Jun 1996
Delavirdine (Rescriptor)	Apr 1997
Efavirenz (Sustiva)	Sep 1998
Etravirine (Intelence)	Jan 2008
Nevirapine (Viramune XR)	Mar 2011
Rilpivirine (Edurant)	May 2011
Fusion or Entry Inhibitors	
Enfuvirtide (Fuzeon)	Mar 2003
Maraviroc (Selzentry)	Aug 2007
Combination Medications	
Lamivudine & Zidovudine (Combivir)	Sep 1997
Lopinavir & Ritonavir (Kaletra)	Sep 2000
Abacavir, Lamivudine & Zidovudine (Trizivir)	Nov 2000
Abacavir & Lamivudine (Epzicom)	Aug 2004
Emtricitabine & Tenofovir (Truvada)	Aug 2004
Efavirenz, Emtricitabine & Tenofovir (Atripla)	Jul 2006
Emtricitabine, Rilpivirine & Tenofovir (Complera)	Aug 2011
Cobicistat, Elvitegravir, Emtricitabine & Tenofovir (Stribild)	Aug 2012
Abacavir, Dolutegravir & Lamivudine (Triumeq)	Aug 2014
Atazanavir & Cobicistat (Evotaz)	Jan 2015
Cobicistat & Darunavir (Prezcobix)	Jan 2015
Cobicistat, Elvitegravir, Emtricitabine & Tenofovir (Genvoya)	Nov 2015
Emtricitabine, Rilpivirine & Tenofovir (Odefsey)	Mar 2016
Emtricitabine and Tenofovir (Descovy)	Apr 2017
Dolutegravir & Rilpivirine (Juluca)	Nov 2017
Bictegravir, Emtricitabine, Tenofovir & Alafenamide (Biktarvy)	Feb 2018
Lamivudine & Tenofovir (Cimduo)	Feb 2018
Darunavir, Cobicistat, Emtricitabine & Tenofovir (Symtuza)	Jul 2018
Doravirine, Lamivudine & Tenofovir (Delstrigo)	Aug 2018
Dolutegravir & Lamivudine (Dovato)	Apr 2019
Integrase Inhibitors	
Raltegravir (Isentress)	Oct 2007
Dolutegravir (Tivicay)	Aug 2013
Elvitegravir (Vitekta)	Sep 2014
Pharmacokinetic Enhancers	
Cobicistat (Tybost)	Sep 2014
Post-Attachment Inhibitors	
Ibalizumab (Trogarzo)	Mar 2018

Source: AIDSinfo (2020)

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