

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

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

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:

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

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:

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

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 $\alpha_1^* \leq \alpha_2^* \leq \dots \leq \alpha_K^*$. To do this, we show that $V'_K(\alpha_{K+1}^*) \leq 0$ for any $K \geq 1$. 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:

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

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

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

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

Now we focus on the optimal expected benefits. We begin by showing that $V_K(\alpha_K^*) \leq V_{K+1}(\alpha_{K+1}^*)$, which first involves showing $V_K(\alpha) \leq V_{K+1}(\alpha)$ 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 $V_K(\alpha_K^*) \leq V_{K+1}(\alpha_K^*) \leq V_{K+1}(\alpha_{K+1}^*)$ completes the proof.

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

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

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

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

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

Proof of Proposition 2: We first show that the optimal endogenous approval policy is more stringent, i.e., $\tilde{\alpha}^* \leq \alpha^*$. 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, $V'(\tilde{\alpha}^*) \geq V'(\alpha^*) = 0$ and by concavity of $V(\alpha)$ (Proposition 1), we have that $\tilde{\alpha}^* \leq \alpha^*$.

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

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

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 $\mathbb{P}(\text{Path Success})$ 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.

| Disease | λ | Num. Trials per Path | $\mathbb{P}(\text{Phase Success})$ | | | $\mathbb{P}(\text{Path Success})$ | λ_{NDA} |
|---------------|-----------|-------------------------|------------------------------------|--------------|---------------|-----------------------------------|-----------------|
| | | | Phase I→II | Phase II→III | Phase III→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.

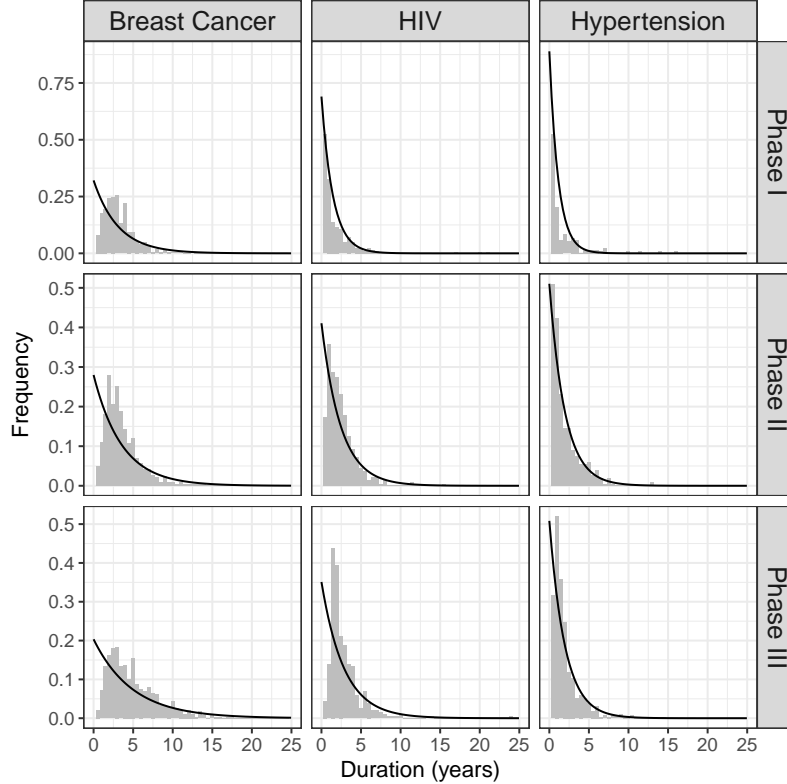
We examine whether clinical trial durations are approximately exponentially distributed for use in the $M/M/\infty$ queueing model (Figure B1). Although Phase I trials are not perfectly exponentially distributed, the latter phases more closely satisfy this assumption, and they comprise the majority of 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 $\mathbb{P}(\text{Path Success})$ 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 $\delta\sqrt{T_n}$ 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 $\delta\sqrt{T_n}$ to satisfy $0.90 = 1 - \Phi[\Phi^{-1}(1 - 0.025) - \delta\sqrt{T_n}]$.

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 | Drug (Brand Name) | Approval |
|-------------------------------------|------------|---|----------|
| Alkylating Agents | | Biphosphonate Therapy | |
| Thiotepa (Tepadina) | March 1959 | Zoledronate (Zometa) | Aug 2001 |
| Cyclophosphamide (Cytoxan) | Nov 1959 | Pamidronate (Aredia) | May 2002 |
| Other Chemotherapy | | Alendronate (Fosamex) | Feb 2008 |
| Methotrexate (Trexall) | Aug 1959 | Denosumab (Xgeva) | Jun 2010 |
| Vinblastine (Velban) | Aug 1987 | Ibandronate (Boniva) | Apr 2012 |
| Vincristine (Oncovin) | Apr 1988 | Risedronate (Actonel) | Jun 2014 |
| Fluorouracil 5-FU (Adrucil) | Aug 1991 | Anthracyclines | |
| Gemcitabine (Gemzar) | May 1996 | Doxorubicin (Adriamycin) | Dec 1987 |
| Irinotecan (Camptosar) | Jun 1996 | Mitoxantrone (Novantrone) | Apr 2006 |
| Capecitabine (Xeloda) | Apr 1998 | Epirubicin (Ellence) | Sep 2008 |
| Temozolomide (Temodar) | Aug 1999 | Liposomal Doxorubicin (Doxil) | Feb 2013 |
| Ixabepilone (Ixempra) | Oct 2007 | Aromatase Inhibitors | |
| Eribulin (Halaven) | Nov 2010 | Anastrozole (Arimidex) | Jun 2010 |
| Topotecan (Hycamtin) | Dec 2010 | Exemestane (Aromasin) | Apr 2011 |
| Platinum Drugs | | Letrozole (Femara) | Jun 2011 |
| Cisplatin (Platinol) | Dec 1978 | Combination Chemotherapy | |
| Carboplatin (Paraplatin) | Mar 1989 | Docetaxel & Cyclophosphamide | N/A |
| Ovarian Suppression | | Docetaxel, Doxorubicin & Cyclophosphamide | N/A |
| Goserelin (Zoladex) | Dec 1989 | Docetaxel & Carboplatin | N/A |
| Leuprolide (Lupron) | Apr 1993 | Paclitaxel & Capecitabine | N/A |
| Abarelix (Plenaxis) | Nov 2003 | Docetaxel & Capecitabine | N/A |
| Buserelin (Suprefact) | N/A | Docetaxel & Carboplatin | N/A |
| Taxanes | | Paclitaxel & Carboplatin | N/A |
| Paclitaxel (Taxol) | Dec 1992 | Paclitaxel & Capecitabine | N/A |
| Docetaxel (Taxotere) | May 1996 | Paclitaxel & Carboplatin | N/A |
| Paclitaxel (Abraxane) | Jan 2005 | Irinotecan & Temozolomide | N/A |
| Vinca Agents | | Gemcitabine & Carboplatin | N/A |
| Vinorelbine (Navelbine) | Dec 1994 | Ixabepilone & Capecitabine | N/A |
| Hormone Therapy | | Doxorubicin & Cyclophosphamide | N/A |
| Megestrol Acetate (Megace) | Aug 1971 | Doxorubicin, Cyclophosphamide & Paclitaxel | N/A |
| Toremifene (Fareston) | May 1997 | Doxorubicin, Cyclophosphamide & Docetaxel | N/A |
| Tamoxifen (Nolvadex) | Feb 2003 | Epirubicin & Cyclophosphamide | N/A |
| Raloxifene (Evista) | Dec 1997 | Cyclophosphamide, Doxorubicin, & Fluorouracil | N/A |
| Fulvestrant (Faslodex) | Apr 2002 | Cyclophosphamide, Methotrexate & 5-Fluorouracil | N/A |
| Targeted Biologics | | 5-Fluorouracil, Doxorubicin & Cyclophosphamide | N/A |
| Trastuzumab (Herceptin) | Sep 1998 | 5-Fluorouracil, Epirubicin & Cyclophosphamide | N/A |
| Bevacizumab (Avastin) | Feb 2004 | Source: National Cancer Institute (NCI) (2020) | |
| 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 | | |

Table B8 FDA-approved hypertension drugs.

| Drug (Brand Name) | Approval | Drug (Brand Name) | Approval |
|---|----------|--|----------|
| Antiadrenergic | | Metoprolol-Hydrochlorothiazide (Lopressor HCT) | Aug 2004 |
| Reserpine (Raudixin) | Mar 1955 | Moexipril-Hydrochlorothiazide (Uniretic) | Mar 2007 |
| Guanadrel (Hylorel) | Dec 1982 | Nadolol-Bendroflumethiazide (Corzide) | Mar 2007 |
| Methyldopa (Aldomet) | Feb 1986 | Amlodipine-Benazepril (Lotrel) | May 2007 |
| Clonidine (Catapres) | Jul 1987 | Quinapril-Hydrochlorothiazide (Accuretic) | Aug 2007 |
| Prazosin (Minipress) | Sep 1988 | Aliskiren-Valsartan (Valturna) | Sep 2009 |
| Guanabenz | Apr 1995 | Losartan-Hydrochlorothiazide (Hyzaar) | Oct 2010 |
| Phentolamine (Regitine) | Mar 1998 | Aliskiren-Hydrochlorothiazide (Amturnide) | Dec 2010 |
| Terazosin (Hytrin) | Mar 1998 | Telmisartan-Hydrochlorothiazide (Micardis) | Sep 2011 |
| Doxazosin (Cardura) | Oct 2000 | Irbesartan-Hydrochlorothiazide (Avalide) | Sep 2012 |
| Guanfacine (Tenex) | Oct 2012 | Valsartan-Hydrochlorothiazide (Diovan) | Sep 2012 |
| Phenoxybenzamine (Dibenzyline) | Jan 2017 | Candesartan-Hydrochlorothiazide (Atacand) | Dec 2012 |
| Guanethidine (Ismelin) | N/A | Amlodipine-Valsartan (Exforge) | Mar 2013 |
| Angiotensin Converting Enzyme (ACE) Inhibitor | | Amlodipine-Atorvastatin (Caduet) | Nov 2013 |
| Deserpidine (Harmony) | Apr 1957 | Amlodipine-Olmesartan (Twynsta) | Jan 2014 |
| Captopril (Capoten) | Feb 1996 | Amlodipine-Valsartan-Hydrochlorothiazide (Exforge HCT) | Jun 2015 |
| Enalapril (Vasotec) | Jan 2001 | Olmesartan-Hydrochlorothiazide (Benicar HCT) | Oct 2016 |
| Lisinopril (Prinivil) | Jul 2002 | Amlodipine-Olmesartan (Azor) | Nov 2016 |
| Moexipril (Univasc) | May 2003 | Deserpidine-Hydrochlorothiazide | N/A |
| Benazepril (Lotensin) | Feb 2004 | Guanethidine-Hydrochlorothiazide (Esimil) | N/A |
| Fosinopril (Monopril) | May 2005 | Methyldopa-Chlorothiazide (Aldoclor) | N/A |
| Quinapril (Accupril) | Jun 2006 | Vasodilators | |
| Trandolapril (Mavik) | Jun 2007 | Hydralazine (Apresoline) | Oct 1978 |
| Ramipril (Altace) | Jun 2008 | Minoxidil | Jul 1999 |
| Perindopril (Coversyl) | Nov 2009 | Mecamylamine (Inversine) | Mar 2013 |
| Amlodipine & Perindopril (Prexalia) | Jan 2015 | Beta Blockers | |
| Diuretics | | Propranolol (Inderal) | Nov 1985 |
| Chlorothiazide (Diuril) | Sep 1958 | Penbutolol (Levatol) | Dec 1987 |
| Polythiazide (Renese) | Sep 1961 | Atenolol (Tenormin) | Jan 1992 |
| Hydrochlorothiazide (Microzide) | Jan 1973 | Nadolol (Corgard) | Oct 1993 |
| Furosemide (Lasix) | Oct 1981 | Metoprolol (Lopressor) | Dec 1993 |
| Methyclothiazide | Jun 1982 | Pindolol (Visken) | Jan 1994 |
| Hydroflumethiazide (Saluron) | May 1985 | Acebutolol (Sectral) | Apr 1995 |
| Amiloride (Midamor) | Jan 1986 | Timolol (Betimol) | Mar 1997 |
| Spironolactone (Aldactone) | Jul 1986 | Labetalol (Trandate) | Aug 1998 |
| Triamterene-Hydrochlorothiazide (Dyazide) | Dec 1987 | Betaxolol (Kerlone) | Oct 1999 |
| Atenolol-Chlorthalidone (Tenoretic) | Jul 1992 | Carteolol (Ocupress) | Jan 2000 |
| Indapamide (Lozol) | Jul 1995 | Bisoprolol (Zebeta) | Jun 2001 |
| Bumetanide (Bumex) | Nov 1996 | Esmolol (Brevibloc) | May 2005 |
| Metolazone (Zaroxolyn) | Dec 2003 | Carvedilol (Coreg) | Sep 2007 |
| Torsemide (Demadex) | May 2005 | Nebivolol (Bystolic) | Jul 2015 |
| Ethacrynic Acid (Edecrin) | Jul 2015 | Penbuterol | N/A |
| Combination Therapy | | Calcium Channel Blockers | |
| Deserpidine-Methyclothiazide (Enduronyl) | Aug 1961 | Verapamil (Calan) | Jul 1992 |
| Reserpine-Polythiazide (Renese-R) | Oct 1963 | Nicardipine (Cardene) | Dec 1996 |
| Reserpine-Chlorthalidone (Regroton) | May 1964 | Diltiazem (Cardizem) | Dec 1999 |
| Reserpine-Methyclothiazide (Diutensen-R) | Sep 1975 | Isradipine (DynaCirc) | Apr 2006 |
| Reserpine-Hydrochlorothiazide (Hydroserpine) | Jan 1977 | Amlodipine (Norvasc) | Jun 2007 |
| Hydralazine-Reserpine-Hydrochlorothiazide (Hydrap-ES) | Sep 1977 | Felodipine (Plendil) | Apr 2008 |
| Hydralazine-Hydrochlorothiazide (Apresazide) | Sep 1977 | Nifedipine (Procardia) | Jun 2010 |
| Timolol-Hydrochlorothiazide (Timolide) | Dec 1981 | Nisoldipine (Sular) | Jan 2011 |
| Reserpine-Chlorothiazide (Diupres) | May 1982 | Other Renin-Angiotensin System Antagonists | |
| Reserpine-Hydroflumethiazide | Mar 1983 | Aliskiren (Tekturna) | Mar 2007 |
| Reserpine-Trichlormethiazide | Apr 1983 | Eplerenone (Inspra) | Aug 2008 |
| Methyldopa-Hydrochlorothiazide (Aldoril) | Feb 1987 | Angiotensin II Receptor Blockers | |
| Propranolol-Hydrochlorothiazide (Inderide) | Apr 1987 | Losartan (Cozaar) | Oct 2010 |
| Spironolactone-Hydrochlorothiazide (Aldactazide) | Jul 1987 | Eprosartan (Teveten) | Nov 2011 |
| Triamterene-Hydrochlorothiazide (Dyazide) | Dec 1987 | Azilsartan and Chlorthalidone (Edarbyclor) | Dec 2011 |
| Clonidine-Chlorthalidone (Combipres) | Dec 1987 | Irbesartan (Avapro) | Oct 2012 |
| Amiloride Hydrochlorothiazide (Moduretic) | May 1988 | Candesartan (Atacand) | Jan 2014 |
| Atenolol-Chlorthalidone (Tenoretic) | Jul 1992 | Telmisartan (Micardis) | Jul 2014 |
| Enalapril-Diltiazem (Teczem) | Oct 1996 | Valsartan (Diovan) | Jun 2015 |
| Enalapril Felodipine (Lexxel) | Dec 1996 | Nevivolol and Valsartan (Byvalson) | Jun 2016 |
| Captopril-Hydrochlorothiazide (Capozide) | Dec 1997 | Amlodipine and Olmesartan (Olmesartan) | Oct 2016 |
| Bisoprolol-Hydrochlorothiazide (Ziac) | Sep 2000 | Source: FDA (2020) | |
| Enalapril-Hydrochlorothiazide (Vaseretic) | Sep 2001 | | |
| Eprosartan-Hydrochlorothiazide (Teveten HCT) | Nov 2001 | | |
| Lisinopril-Hydrochlorothiazide (Zestoretic) | Jul 2002 | | |
| Benazepril-Hydrochlorothiazide (Lotensin HCT) | Feb 2004 | | |

Table B9 FDA-approved HIV drugs.

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

Source: AIDSinfo (2020)

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