WORKING PAPERS

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WORKING PAPER NO. 274

October 2004

BUREAU OF ECONOMICS
FEDERAL TRADE COMMISSION
WASHINGTON, DC 20580

Pharmaceutical Development Phases: a Duration Analysis

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October 2004

This paper estimates a duration model of late stage drug development in the pharmaceutical industry using publicly available data. The paper presents descriptive results on the estimated relationship between a particular drug's characteristics such as therapy category, route of administration and originator's size, and that drug's pathway through the three stages of human clinical trials and regulatory review. The results suggest that drugs with longer durations are less likely to succeed, drugs from larger firms are more likely to succeed and faster in the later phases of development, and that durations fell between 1995 and 2002.

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We would like to thank our colleagues at the FTC, CBO and NERA Economic Consulting for helpful comments and suggestions, in particular, Charles Capone, Anna Cook, Cary Elliot, Arlene Holen, Daniel Hosken, Elizabeth Schneirov, Steven Tenn and Philip Webre. We would also like to thank participants at the International Industrial Organization Conference and at the Econometric Society Meetings for helpful comments, and in particular, Margaret Kyle. We also thank two anonymous reviewers of the FTC working paper series for their comments. Finally, we thank Van V. Brantner for excellent research assistance. The views expressed are those of the authors and do not necessarily reflect the views either of the FTC Commission or any individual Commissioner or those of the Congressional Budget Office. All errors are ours. Suggestions are welcome.

1. Introduction

Understanding success rates and durations of drug development is important for understanding many of issues concerning pharmaceutical industry. For example, a recent study found the expected cost of developing the average drug is $802m, with much of that cost due to the low success rates and the long durations of new drug development (DiMasi et al, 2003). Despite the importance of accurately estimating success rates and durations, previous work has relied on relatively simple duration models or crude estimates. The estimation technique used in the paper is a substantial improvement over the estimation techniques that have been used to date. Using a multiple state mixed proportional hazard model the paper presents descriptive results of the relationship between a drug's observable characteristics such as therapy group, route of administration and originator's size, and the drug's pathway through each of the three stages of the human clinical trials as well as regulatory review. The paper's main findings are that success probabilities decrease with duration, drugs from larger firms have higher success rates and lower successful durations in the later phases of development and, simply as a function of calendar time drugs in development during the years 1995 to 2002 had shorter durations than drugs in development in the years 1989 to 1994.[1]

The multiple state mixed proportional hazard model is adjusted for discrete time and allows for a flexible functional form for the baseline hazard. The model is separately estimated for each of three stages of the human clinical trials.[2] The model also allows us to separately measure the relationship between observable drug characteristics and the length of time between beginning each phase and either successfully completing the phase or unsuccessfully completing the phase. The three estimated models may be linked to form a single model of approval through completion. For each phase, conditional on a drug's characteristics, we can make statements on the probability of success and expected duration. In fact, we calculate expected duration conditional on success, conditional on failure, or unconditionally on the exiting state. In addition to elapsed duration time, we separately specify the dependence of the hazard on the absolute calendar time and estimate this dependence as a step function with different levels for each calendar year. This specification

[1] It is important to note that the measured success rates and durations are to some extent the result of strategic behavior of the pharmaceutical firms, and thus we need to be careful in interpreting the econometric results. For example the measured relationship between firm size and success rates may lead one to conclude that large size causes success when exactly the reverse may be true. One suggested reason for many mergers in this industry is to improve the quality of the firms drug development pipeline (Danzon et al, 2003).

[2] Note that Phase 3 includes both the Phase 3 clinical trials and the regulatory review process.

allows us to test whether durations and success probabilities have changed over time. The data includes dates for entry into each phase of the human clinical trials and the market. The data also includes characteristic information for each drug including therapeutic category, chemical composition, route of administration, and the originating firm.

A number of papers, some of which are discussed below, have presented information on success rates and durations for drug development, however Dranove and Meltzer (1994) is the only one to our knowledge to use a duration model.[3] The authors use information on a drug's patent application date, the drug's NDA date and the drug's approval date to estimate successful durations for drugs with certain characteristics. The authors find that it takes 13.5 years for a drug to go from discovery to approval, but their results are conditional on success. Our interest is developing a broader understanding of the drug development process by estimating unconditional probabilities and durations, so we estimate a duration model with both successful and failed drugs. While our data set does not include information on the timing of pre-clinical development we have significantly more detailed information on late stage development through human clinical trials and regulatory review. One of the important questions for Dranove and Meltzer (1994) is whether "important" drugs have shorter successful durations through development and approval. In their analysis, Dranove and Meltzer (1994) use multiple measures of importance including citations in medical textbooks and drug sales. The authors find that important drugs do have shorter successful durations. This result that is consistent with the FDA's own analysis that "priority" drugs have shorter successful approval durations (FDA, 2001).[4] As information on whether a drug is important or a priority drug is only known for successful drugs we don't use this information in our analysis.

Below we estimate the relationship between a large number of drug characteristics including therapeutic category and both successful and unsuccessful durations. So for example the analysis shows whether anti-HIV/AIDS drugs had quicker successful durations or whether anti-cancer drugs had slower unsuccessful durations. We leave it to the reader to determine the "importance" of drugs with different characteristics. In terms of average success rates and successful durations in the data we find that anti-cancer drugs have higher success rates but similar successful durations to other drugs, while anti-HIV/AIDS drugs

[3] DiMasi et al (2003, 1995a, 1995b, 1991) and DiMasi (2001) use a duration model to calculated the overall 'predicted' success rates for drugs in Phase I, but the model is not used to estimate the actual durations or the transition probabilities.
[4] The FDA and the pharmaceutical firms categorize drugs into "priority" drugs and "standard" drugs at the time of the New Drug Application (NDA).

have much higher success rates and lower successful durations in both Phase II and Phase III.[5] However, once we condition on other characteristics of these drugs in the full duration model the only effect we find is that anti-cancer drugs have lower expected durations for Phase I and Phase II. In regards to anti-HIV/AIDS drugs we are unable to use this particular model to identify the impact of this therapeutic category in Phase III because there were no failed durations.

The FDA has stated that "the process of bringing a drug to a patient's bedside takes an average of 8.5 years" (February 2002). Other recent papers which present success rates and durations for pharmaceuticals include DiMasi et al (2003, 1995a, 1995b, 1991), DiMasi (2001) and Adams and Brantner (2003). In DiMasi et al (2003, 1995a, 1995b, 1991) the authors combine information on success rates and successful durations to calculate the expected cost of developing an approved drug. In their 2003 study the authors found that the expected capitalized cost per approved drug was $802m in 2000 dollars. The authors use a duration model to estimate the success rate for Phase I drugs at 21.5%. Average successful durations were estimated to be 7.5 years from the start of Phase I to marketing approval. The other three papers analyze success rates, durations and development costs for drugs in development during the 1970s and early 1980s. DiMasi (2001) analyzes the success rates of drugs that first filed an IND with the FDA between 1981 and 1992. He finds that US approval rates for drugs that were acquired, self-originated, and self-originated and first tested in humans in the US, were 33%, 17% and 9% respectively. By therapeutic class he finds substantial variation with anti-infectives having a success rate of 28% and respiratory drugs having a success rate of 12%. Adams and Brantner (2003) analyze a data set that is very similar to the one used here. Adams and Brantner (2003) present estimates of current success rates and simple successful durations for drugs with different characteristics. The authors find that the probability of a drug successfully moving from Phase I to market is 12% with a successful duration of 7.8 years.[6] The authors present these basic statistics for drugs from a large number of different categories including indication, route of administration, chemical composition and originating firm.

Other related papers include Scott Morton (1999, 2001) and Reiffen and Ward (2002), who analyze approval rates and entry in the generic drug industry. Unfortunately,

[5] According to the CDER all HIV drugs that have undergone FDA approval have received accelerated approvals (Meadows, 2002). Note that drugs in our sample are in development in many countries, although the modal drug is being developed for the US market.

[6] Note that this success rate cannot be compared to the success rate presented in DiMasi et al (2003) as it is a crude measure calculated as the number of successful drugs over the number of non-censored drugs.

our data doesn't allow us to say anything in regards to this important area of pharmaceutical development.

The paper is organized as follows. In the next section, we give some background on drug development and describe the data used in this study. Section 3 presents the duration model that we estimate and Section 4 contains the results. Section 5 concludes and presents directions for future research.

2. Background and Data

The process of drug discovery to market in the United States can be decomposed into six distinct periods. The first period is commonly known as Preclinical. In general, after preclinical analysis, a company wishing to launch a drug on the US market files an Investigatory New Drug (IND) application with the FDA. If accepted, the drug goes into human clinical trials, which has three basic phases, called Phase I, Phase II and Phase III (the second, third and fourth periods, respectively). Generally, the phases are completed sequentially and after the Phase III trials have been completed, a company wishing to launch a drug on the US market will file a New Drug Application (NDA) with FDA and move into the fifth period. A drug that passes FDA review successfully is registered in the "Orange Book". Once registered, the drug moves into the sixth period and the company can launch the drug on to the US market. A similar process occurs in other developed countries.

In preclinical trials the pharmaceutical company uses genetic analysis, pharmacological tools and "animal models" to test for the safety and the effectiveness of the drug for particular disease indications. Unfortunately, because the data set analyzed below is based on information that is voluntarily given to the public by the drug's sponsor, the information on preclinical trials is not very accurate. Note that according to the FDA, only 1 in 1,000 drugs pass the preclinical stage and are proposed for testing in humans (FDA, 2002), however almost half the R&D expenditures occur in the preclinical stage of development (DiMasi et al, 2003, Levy, 1999)

The first phase of the human trials is called Phase I. Phase I trials are generally carried out on a healthy volunteer population of between 20 and 80. According to the FDA, "These studies are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness" (FDA, 2003). Phase II trials involve several hundred patients with the disease condition, and are designed to give an early indication of the drugs

effectiveness. Phase III trials are larger with patient numbers between several hundred and a few thousand, and are designed to give information on the balance between safety and effectiveness (Levy, 1999).

Pharmaprojects, the data set used in this study, was purchased from PJB Publication Ltd., an independent publisher of international business news and information services for the pharmaceutical, biotechnology, device and diagnostic, crop protection and animal health industries. The data set is based on public information, and as a result, tends to include drugs that are already in late stage development. Pharmaprojects contains information on 27,987 new branded drug entities that have reached the late stage development from 1980 to the present. For the purpose of this study, we limit attention to all drugs which began the FDA process for the first time between 1989 and 2002, and for which we have an entry date. We have thus excluded all drugs we know existed but for which we have no entrance date, since we cannot make a statement on the duration spent in development. We assume that the fact that the data are missing is independent of any of the modeled processes, such that dropping these observations introduces no bias or inconsistency in the resulting estimates. In the end, we keep 1,116 observations for Phase I, 1,259 for Phase II, and 761 for Phase III.

For each drug, there are three possible "exit states". First, the drug may *succeed* in completing the phase under study. Second, a drug may clearly *fail* to complete the phase. Such failure may be a combination of rejection by the FDA and withdrawal by the firm; we cannot separately identify these. Finally, a drug may be *censored*, which means that we know that a drug was still under consideration at some point in time, but we have no further information. Since the data set concludes in June of 2002, all drugs still in a development phase on that date are necessarily censored.

We had to make some decisions as to which categories to include in the model. For example, *primary indication* and *therapy* are very collinear, but the latter is more inclusive than the former. There may be several drugs with different (but related) primary indications, all of which are coded for anti-cancer therapy. Ultimately we include *therapy*, *route of administration*, *original material*, *originating company*, *originator's country*, and indications of existing patents. Table A describes these features of the data and provides some examples.[7]

[7] For complete descriptions, please refer to the Pharmaprojects User's Handbook.

Table A
Variable Definitions and Examples

Variable	Definition	Example
Original Materials	The source of materials from which drugs are originally derived.	Biologicals, chemicals, natural products,…
Originator	The company, academic institution or other non-industrial organization responsible for discovering the drug.	GlaxoSmithKline, Aventis, Pfizer,…
Patent	A government grant to an originator for a stated period of time, conferring upon the drug company a monopoly of the exclusive right to make, use and vend a particular drug.	Pharmacia company owns patents to Celebrex (an arthritis drug) and Detrol (a drug that treats bladder problems)
Originator Country	The country of origin of the originator or licensee.	The US, UK, Japan,…
Route of Administration	The specific route by which the drug is delivered to the patient	Parenteral (Injection), Transdermal (Patches), Respiratory (Inhalation),…
Therapy	A drug's therapy denotes the disease area for which it is being developed. If a drug is being developed in more than one disease areas, the description for each therapeutic activity identified will be listed. In such cases, the first code listed denotes the drug's Primary Therapeutic Activity.	Diseases of the circulatory system, diseases affecting blood cells, dermatological conditions…

We were not able to control for most quality related variables for each drug, since these are only available for drugs that reach the market. Finally, in order to allow for higher flexibility in our baseline hazard parameterization in this first stage of the estimation, we had to restrict the number of characteristics we could control for. In our future work, once the shape of the baseline function has been understood, we will then be able to estimate it using significantly fewer parameters and therefore freeing degrees of freedom to control for firm related variables, as well as market and policy related variables.

Having decided on what categories to include, we selected which characteristics within those categories to separately identify. These decisions were driven by economic and policy interest, and degrees-of-freedom considerations. Generally, only characteristics shared by at least 10% of the data were separately identified. This standard was reduced to 1% for those characteristics of particular economic or policy significance. In any case, no characteristic could be identified if it did not have some examples of both *success* and *failure*. Unfortunately, by this standard we were not able to separately identify anti-HIV therapies

for Phase III, since the data do not include a single example of a failed drug with that therapy.

Tables B.1, B.2.A and B.2.B below, present descriptive statistics of the complete sample. From Table B.1 we can see that, in each of the phases, there are always more drugs successfully completing a given phase than failing it, but the proportion of successes in relation to failures decreases as drugs move along the approval process. Also, we find that in both Phases I and II (but not for Phase III), failure durations are significantly longer than successful durations, meaning that as time goes by, a drug is more likely to fail than to succeed. The opposite occurs in Phase III, although statistically we cannot reject the hypothesis that failure and success durations are equal in Phase III. This is one of the features of the data that our model will be able to capture. More descriptive statistics of our sample related to probabilities and durations for success and failure for different groupings of drugs are presented in Tables B.2.A and B.2.B.

An important characteristic of the data is that most of the event dates are registered on the fifteenth of each month.[8] This does not necessarily mean that the events themselves actually happened on that date. There is therefore some ambiguity as to the actual event dates; we can only be sure of the timing to within one month. For example, if an event occurs between January 16th and February 15th, it will be recorded as "February 15th", and an event that occurs between February 16th and March 15th will be recorded as "March 15th". We therefore redefine month 1 of year *y* as the period from the December 16th of year *y*-1 through the January 15th of year *y*, month 2 of year *y* as January 16th through February 15th of year *y*, and so on.

Table B.1
Summary Descriptive Statistics

	Phase I		**Phase II**		**Phase III**	
	Cases	Mean Duration (months)	Cases	Mean Duration (months)	Cases	Mean Duration (months)
Complete Durations	999	22.1	881	34.0	448	44.9
Successful	806	19.7	508	29.9	254	47.0
Failed	193	31.9	373	39.5	194	42.1
Probability of Success	80.7%		57.7%		56.7%	
Expected Successful Duration	**96.6**					
Probability of Success	**26.4%**					

[8] Other large groupings occur on the first or second of the month, but the modal date range is the fifteenth through the seventeenth.

Table B.2.A
Descriptive Statistics - Crude Probability of Success (and Duration[*1]) for each Phase

	Phase 1	Phase 2	Phase 3
All Drugs	0.81	0.57	0.57
	(19.68)	(29.87)	(47)
Big Pharma	0.73	0.50	0.69
	(19.62)	(25.11)	(41.43)
Non Big Pharma	0.82	0.59	0.54
	(18.76)	(29.92)	(49.07)
Biologicals	0.90	0.67	0.70
	(17.87)	(31.87)	(45.63)
Chemicals	0.84	0.66	0.66
	(19.63)	(29.41)	(47.74)
Natural Products	0.90	0.77	0.61
	(21.5)	(19.44)	(46.14)
Alimentary	0.89	0.77	0.71
	(20.13)	(28.04)	(44.82)
Oral	0.88	0.77	0.71
	(20.49)	(28.31)	(44.88)
Parenteral	0.93	0.74	0.69
	(19.26)	(31.5)	(48.29)
Intravenous	0.92	0.80	0.67
	(18.05)	(30.91)	(47.29)
Subcutaneous	0.97	0.81	0.88
	(19.5)	(34.16)	(49.86)
Intramuscular	0.91	0.79	0.85
	(21.4)	(31.73)	(53.18)
Respiratory	0.71	0.43	0.83
	(19.7)	(21.89)	(40.8)
Topical	0.89	0.79	0.71
	(15.32)	(23.22)	(56.16)
Transdermal	0.70	0.73	0.75
	(22.43)	(24.63)	(32.67)
Anti-Alzheimer's Desease	0.83	0.60	0.33
	(19.37)	(46.11)	(39.5)
Anti-Arthritis	0.94	0.66	0.69
	(18.21)	(32.53)	(44.91)
Anti-Asthma	0.85	0.51	0.78
	(16.48)	(35.44)	(41)
Anti-Cancer	0.88	0.73	0.66
	(21.79)	(30.23)	(48)
Anti-Diabetes	0.86	0.65	0.89
	(18.58)	(23.15)	(47.75)
Anti-Hypertension	0.81	0.75	0.81
	(10.73)	(39.17)	(44.12)
Anti-HIV/AIDS	0.86	0.62	0.94
	(21.63)	(21.57)	(24.31)
Anti-Parkinson's Desease	0.82	0.70	0.63
	(18.5)	(44.14)	(63.4)
Anti-Thrombosis	0.79	0.64	0.44
	(21.32)	(35)	(59.75)

[*1] Duration is measured in months.

Table B.2.B
Descriptive Statistics - Crude Probability of Failure (and Duration[*1]) for each Phase

		Phase 1	Phase 2	Phase 3
All Drugs		0.19	0.43	0.43
		(31.9)	(39.47)	(42.1)
Big Pharma		0.27	0.50	0.31
		(32.83)	(31.95)	(32.25)
Non Big Pharma		0.18	0.41	0.46
		(30.98)	(40.64)	(44.39)
Biologicals		0.10	0.33	0.30
		(36.09)	(43.52)	(30.65)
Chemicals		0.16	0.34	0.34
		(27.35)	(39.78)	(47.55)
Natural Products		0.10	0.23	0.39
		(27.67)	(41.5)	(52.56)
Alimentary		0.11	0.23	0.29
		(29.15)	(38.53)	(51.6)
	Oral	0.12	0.23	0.29
		(29.15)	(39.58)	(51.35)
Parenteral		0.07	0.26	0.31
		(31.09)	(48.21)	(41.59)
	Intravenous	0.08	0.20	0.33
		(30.71)	(49.27)	(40.71)
	Subcutaneous	0.03	0.19	0.13
		(29)	(29.17)	(38)
	Intramuscular	0.09	0.21	0.15
		(36)	(44.33)	(13.5)
Respiratory		0.29	0.57	0.17
		(36.88)	(38.75)	(46)
Topical		0.11	0.21	0.29
		(17.75)	(47.17)	(39.7)
Transdermal		0.30	0.27	0.25
		(25)	(43.67)	(49.5)
Anti-Alzheimer's Desease		0.17	0.40	0.67
		(39.5)	(50.83)	(51.88)
Anti-Arthritis		0.06	0.34	0.31
		(14.5)	(46.2)	(45)
Anti-Asthma		0.15	0.49	0.22
		(22.33)	(44.76)	(47.5)
Anti-Cancer		0.12	0.27	0.34
		(32.67)	(38.15)	(44.21)
Anti-Diabetes		0.14	0.35	0.11
		(12.75)	(37.29)	(22)
Anti-Hypertension		0.19	0.25	0.19
		(37.4)	(56.75)	(46)
Anti-HIV/AIDS		0.14	0.38	0.06
		(37.5)	(38.38)	(57)
Anti-Parkinson's Desease		0.18	0.30	0.38
		(49.33)	(38.33)	(47.3)
Anti-Thrombosis		0.21	0.36	0.56
		(34.2)	(35.56)	(53.2)

[*1] Duration is measured in months.

3. The Model

This section presents a brief description of the duration model used in this paper.[9] Imagine a process characterized by *K* distinct, mutually exclusive exiting states. For the present study, these would be *success* and *failure* in completing a development phase.[10] The point of departure is the specification of the transition intensity of going to state *k* at time *t*. Let us denote this as $\theta_k(t)$, and it is defined by:

$$\theta_k(t) = \lim_{dt \to 0} \frac{\Pr(t \le T < t + dt, K = k \mid T \ge t)}{dt}. \tag{3.1}$$

These transition intensities may depend on observed covariates *x* and unobserved heterogeneity *v*. We assume standard specifications for the transition intensity. In particular, we assumed:

$$\theta_k(t \mid x, v) = \psi_k(t)\theta_k^0(x)v_k, \tag{3.2}$$

where the baseline transition intensity is given by ψ_k, θ_k^0 is a strictly positive function of the covariates *x*, and v_k is state-specific unobserved heterogeneity such as effort by the firm. For details on regularity conditions and other restrictions, please see Lancaster (1997).

From here we define the associated hazard function $\theta(t \mid x, v)$, or the probability of exiting at *t* conditional on survival up to *t*, as:

$$\theta(t \mid x, v) = \sum_{k=1}^{K} \theta_k(t \mid x, v), \tag{3.3}$$

$$\theta(t \mid x, v) = \lim_{dt \to 0} \frac{\Pr(t \le T < t + dt \mid T \ge t, x, v)}{dt}. \tag{3.4}$$

This, in turn, defines the survival function $\overline{F}(t \mid x, v)$, or the probability of exiting after *t*:

$$\overline{F}(t \mid x, v) = \exp\left\{-\int_0^t \theta(s \mid x, v)ds\right\} = \exp\left\{-\sum_{k=1}^{K}\int_0^t \theta_k(s \mid x, v)ds\right\}. \tag{3.5}$$

The empiricist is interested in the joint probability of exiting at *t* and going to state *k*. In continuous time, and still conditioning on both *x* and *v*, this is given immediately by:

$$f(t, k \mid x, v) = \theta_k(t \mid x, v)\overline{F}(t \mid x, v). \tag{3.6}$$

Written somewhat loosely, and omitting the dependence on *x* and *v*, this is simply:

$$\Pr(T = t, K = k) = \Pr(T = t, K = k \mid T \ge t)\Pr(T \ge t). \tag{3.7.a}$$

An alternative decomposition is:

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[9] For more information on this type of analysis please see Abbring and van den Berg (2003), Bonnal et al (1997), Meyer (1990), van den Berg (2000) and Metz (2003).

[10] Censoring is not an independently modeled exiting state.

$$\Pr(T = t, K = k) = \Pr(T = t \mid K = k)\Pr(K = k). \tag{3.7.b}$$

Denoting by π_k the probability of exiting to state k (unconditional on time), this is obtained by integrating (3.6) over time:

$$\pi_k = \int_0^\infty \theta_k(s)\overline{F}(s)ds, \tag{3.8}$$

which in turn can be used to define the probability of exiting at time t conditional on exiting to state k as:

$$f_k(t) = \frac{\theta_k(t)\overline{F}(t)}{\pi_k} = \frac{\theta_k(t)\sum_{i=1}^{K}\pi_i\overline{F}_i(t)}{\pi_k}. \tag{3.9}$$

This is true in continuous time. But our data are discrete, and by that we mean that we do not observe the exact moment at which exit occurs. Instead, since the data are sampled at discrete intervals of time, we only know that an exit took place within a window of time.

More formally, to construct the discrete time multiple state model we have to define the statement $\Pr(t_u < T \le t_{u+1}, K = k)$, for a window of time indexed by u. This is the joint probability of exiting to state k during the window of time *u*. From (3.8), we know that $f_k(t)$ defines the density governing the "probability of exiting at time t conditional on exiting to state k", hence the probability of exiting in the window, conditional on going to state k, is given by:

$$\Pr(t_u < T \le t_{u+1} \mid K = k) = F_k(t_{u+1}) - F_k(t_u) = \int_{t_u}^{t_{u+1}} f_k(s)ds. \tag{3.10}$$

Therefore, the probability of exiting in the window of time *u* and going to state *k* is:

$$\Pr(t_u < T < t_{u+1}, K = k) = \pi_k\left(F_k(t_{u+1}) - F_k(t_u)\right) = \int_{t_u}^{t_{u+1}} \pi_k f_k(s)ds, \tag{3.11}$$

which can be restated in terms of the transition intensities, using (3.8), as:

$$\Pr(t_u < T \le t_{u+1}, K = k) = \int_{t_u}^{t_{u+1}} \theta_k(s)\overline{F}(s)ds. \tag{3.12}$$

This is the probability of interest, conditional on observed covariates *x* and unobserved heterogeneity *v*. Let *G*(*v*) denote the distribution of *v*. Then, the empirical probability statement becomes:

$$\Pr(t_u < T \le t_{u+1}, K = k \mid x) = \int \left(\int_{t_u}^{t_{u+1}} \theta_k(s \mid x, v) \bar{F}(s \mid x, v) ds \right) dG(v), \tag{3.13}$$

which is equivalent to:

$$\Pr(t_u < T \le t_{u+1}, K = k \mid x) = \int_{t_u}^{t_{u+1}} \theta_k(s \mid x) \bar{F}(s \mid x) ds, \tag{3.14}$$

when the following are defined:

$$\theta_k(t \mid x) = \frac{\int \theta_k(t \mid x, v) \bar{F}(t \mid x, v) dG(v)}{\bar{F}(t \mid x)}, \text{ and} \tag{3.15}$$

$$\bar{F}(t \mid x) = \int \bar{F}(t \mid x, v) dG(v). \tag{3.16}$$

We can see that a full specification of the transition intensities is sufficient to characterize the entire distribution of events in our model.

In this paper we estimate three duration models, one for each of the three phases of drug approval process. These can be easily linked to form a single model of approval through completion. Specifically, the probability that a drug will pass through Phase I and II is given by:

$$\Pr(PhaseI, PhaseII) = \Pr(PhaseII \mid PhaseI) \Pr(PhaseI). \tag{3.17}$$

The first duration model will give us the probability of completing Phase I, and the second model will give us the probability of completing Phase II conditioned on the fact that the drug completed Phase I. The third model estimates the probability of completing Phase III conditioned on completion of Phase II and (superfluously) Phase I. This is true by construction.

The advantages of separately modeling the phases are that certain factors may be more important in some phases than others, that some covariates change at the beginning of each phase, and that the sample of data generally improves through the different stages. That is, while there is some concern that Phase I data may be somewhat self-selected, the Phase III data essentially cover the complete population.

4. Results

In this section we present the estimation, hypothesis test results and simulation results for Phases I, II, and III. In all cases, inferences are based on the "robust" variance estimator, which allows the outer-product gradient to differ from the inverse negative Hessian. We

first discuss the main results obtained for all the three phases of development, and then we describe in more detail the findings for each of these phases individually.

The results of our estimation allow us to test for the influence of each of the controlled drug characteristics on both expected duration and probability of success and failure. Among the several characteristics tested is the "size" of the company sponsoring the drug. This is proxied by the number of drugs that company has in any stage of the development process. An interesting question is whether larger companies are better able to have successful outcomes at shorter durations. Another subject of interest is whether the time spent in review increased or decreased over time. This will be tested by the yearly dummy variables. We can evaluate whether they are all equal, and if not, we can assess whether they are (weakly) monotonic.

Before analyzing the effects of the characteristics we controlled for, we are interested in determining how success and failure behave as time goes by. Recalling from section 3, the baseline transition intensities measure the probability of *success* or *failure* as elapsed time passes: increasing (decreasing) intensities mean that the probability of exit increases (decreases) as time goes by. As we can see from Figures A, B and C presented next, these baseline intensities capture a main feature of the data as described in Table B.1 (section 2) containing some of the summary statistics of the data: that for both Phases I and II, as time goes by the likelihood of failure is relatively higher than of success, while the opposite happens in Phase III, although less significantly.

With respect to the covariates, there are two questions that may be answered: (*i*) How do given characteristics affect the probability that a drug will successfully complete a given review phase?; and (*ii*) How do given characteristics affect the expected duration in a given review phase?

For any regressor, there is an estimated coefficient for the *success* and one for the *failure* transitions. The sum of these coefficients suggests the effect of the correspondent regressors on the expected duration (a positive sum implies a higher likelihood of exiting, either by succeeding or by failing, which in turn induces a shorter duration). The difference between the *success* and the *failure* coefficients provide information on the probability of success (a positive difference suggests a shift of probability mass towards *success* in relation to *failure*, and therefore, it will translate into a relatively higher probability of *success* than *failure*).

Figure A

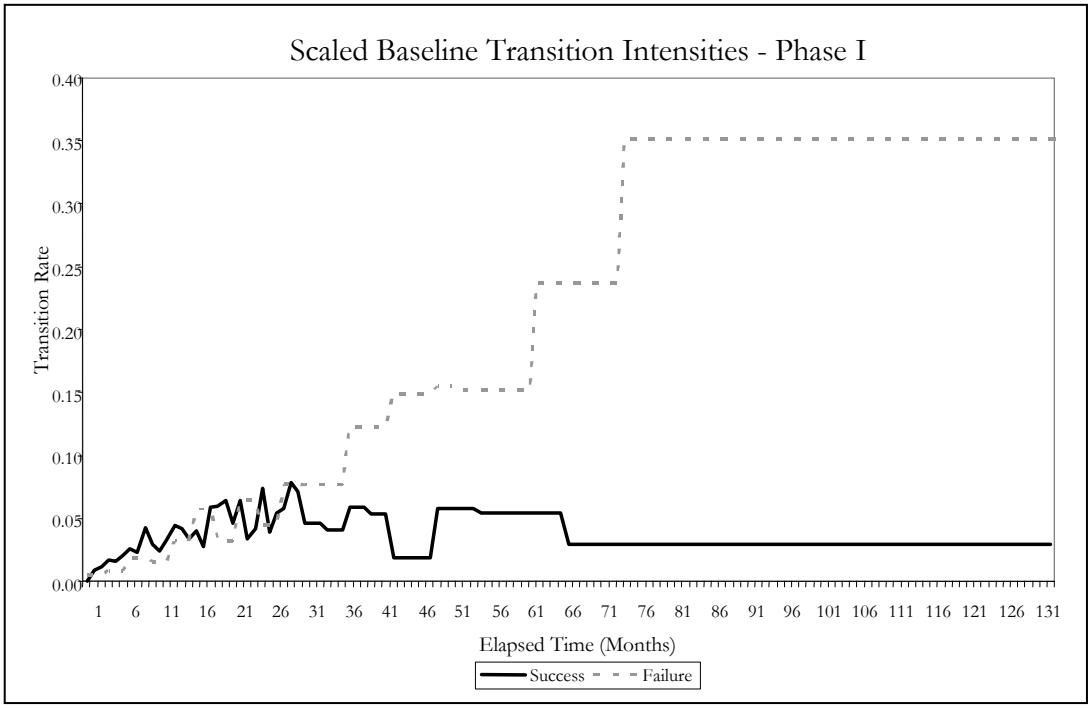


Figure B

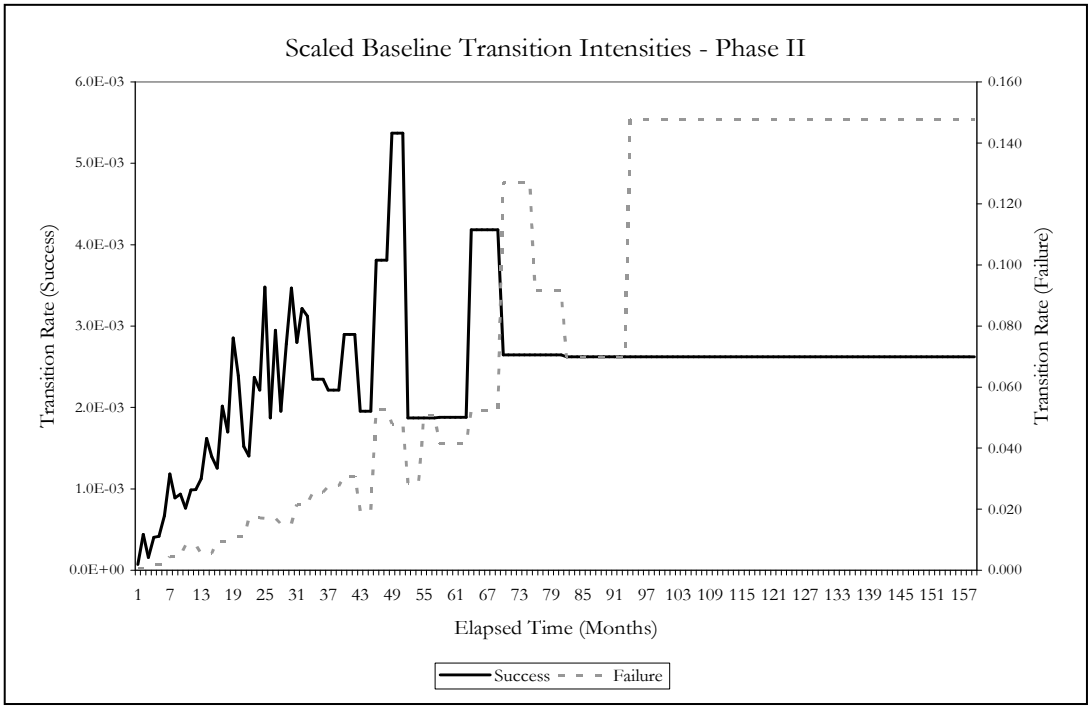


Figure C

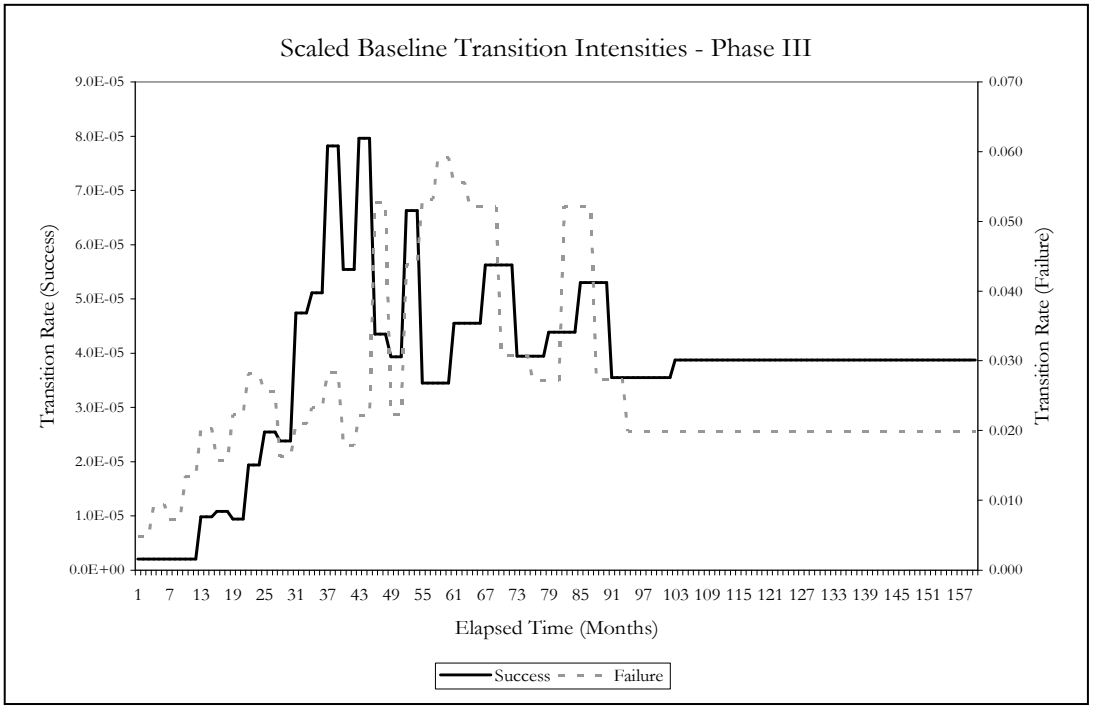

Scaled Baseline Transition Intensities - Phase III
Transition Rate (Success)
9.0E-05
8.0E-05
7.0E-05
6.0E-05
5.0E-05
4.0E-05
3.0E-05
2.0E-05
1.0E-05
0.0E+00
Transition Rate (Failure)
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
1 7 13 19 25 31 37 43 49 55 61 67 73 79 85 91 97 103 109 115 121 127 133 139 145 151 157
Elapsed Time (Months)
Success
Failure

Table C

	Phase I				Phase II				Phase III			
Simulations	**Expected Duration**	**Failure Duration**	**Success Duration**	**Probability of Success**	**Expected Duration**	**Failure Duration**	**Success Duration**	**Probability of Success**	**Expected Duration**	**Failure Duration**	**Success Duration**	**Probability of Success**
Baseline	18	21	16	49.09%	38	38	33	10.28%	61	59	105	5.48%
Anti-Cancer	36	46	29	43.93%	42	43	36	8.70%	59	58	106	2.46%
Anti-HIV	27	37	22	67.19%	31	32	28	10.47%	NA	NA	NA	
Anti-Hypertensive	17	20	15	58.23%	38	39	33	11.28%	69	67	118	4.80%
Alimentary	25	39	21	75.93%	48	52	38	33.77%	93	85	106	35.51%
Parenteral	20	36	17	85.76%	52	56	42	25.27%	108	100	119	42.51%
Topical	20	30	17	79.69%	54	59	43	30.69%	85	78	103	27.46%
Biological	55	97	43	79.47%	48	49	40	13.23%	117	105	141	33.79%
Biological Protein	31	40	25	58.19%	59	63	47	27.61%	127	129	127	56.11%
Chemical	28	40	23	68.89%	49	53	40	29.90%	108	108	125	35.98%
Natural Product	33	57	26	79.82%	48	53	38	36.52%	99	90	126	25.19%
Large Company	20	24	17	54.34%	33	34	29	13.68%	55	52	94	5.56%
Small Company	25	31	21	53.76%	47	48	40	9.68%	68	67	122	1.98%
New Patent	26	38	21	71.66%	44	47	36	26.15%	73	67	100	18.17%
5 Year Old Patent	30	40	24	60.95%	45	46	37	19.50%	71	66	106	12.83%

Expected Duration is presented in months. The baseline case is: Therapy – "all others"; ROA – "all others"; OM – "others"; Company size – "mid-size (6-10 drugs)"; Originator country – "U.S."; Patent – "no"; Date – "1989:1. (Note: "all others" means "all other groups within each category not separately identified")

Table D in Appendix summarizes the inferences drawn from the sums and differences of coefficients for each of the three phases. Significant results (defined as those with t-statistics greater than 1.64 in absolute value (90% confidence)) are indicated with "++" or "- -" depending on whether they increase or decrease the measure in question. Suggestive results (defined as those with t-statistics greater than 1.15 in absolute value (75% confidence)) are indicated with "+" or "–". We caution the reader again that the critical value of zero is merely suggestive. Ultimately, simulation is necessary in order to identify the effect of each regressor on the probabilities and expected durations. Table C summarizes some of the findings of our simulation.

All results are relative to a baseline drug, which is not intended to be representative at this stage, but simply a benchmark against which we compare the effects of each individual characteristic, one at a time. For therapies, the benchmark is "all other therapies" not separately identified. For routes of administration, the results are relative to "all other routes of administration". The baseline original materials classification is "other" for Phases I and II, and "unknown or other" for Phase III. The originator company size baseline is "mid-size" (6-10 drugs), and the originator country baseline is "U.S. or not otherwise identified", which is a list that changes very slightly from phase to phase. This hypothetical drug has "no Patent" and initiated the process in January 1989. We are interested in studying when we change one of these drug characteristics at a time, what is the impact in the probabilities and expected durations of success and failure.

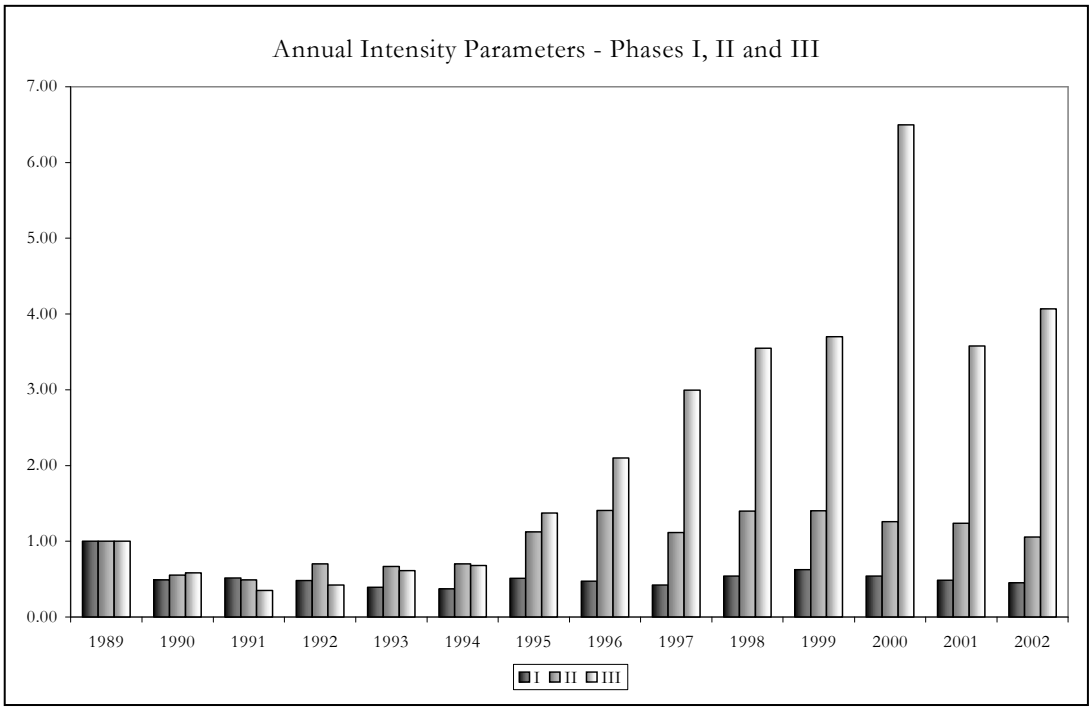
In any of the phases, therapies have a small effect on success or duration for the most part, with slightly higher probabilities of success and durations than the baseline. Among the simulated results in Table C, anti-cancer is almost always the therapy with the longest duration and the lowest probability of success, aside from Phase III where anti-hypertensive's duration is the longest.[11] Notice that this is consistent with the findings in Table B.2.A, although the two sets of results are not directly comparable since in our experiment we are changing one characteristic at a time, while in the sample when we compare one drug to another they will differ for more than just one characteristic. This is important to keep in mind every time the results from our simulation are compared to the descriptive statistics of the data presented in section 2.

[11] Notice that we were unable to separately identify the anti-HIV group in Phase III, since in this sample there were no failures for this category.

Alimentary is the most successful Route of Administration (ROA) in Phase II both in our simulation and in the data (summary statistics in Table B.2.A). With respect to the OM's, aside from Phase III, Biologicals have by far the longest successful durations when compared to all other OM groups (in particular, when compared to Chemicals). We found the same results in the data. In regards to sponsorship by a "large" drug company there is some evidence in Phase III that drugs from "larger" companies are both more likely to succeed and at shorter durations than those from "smaller" ones.

Table E in Appendix summarizes the hypothesis tests conducted for all the phases. Specifically, we identify for each phase those tests with a p-value > 0.05, such that we can reject the hypothesis in question at the 95% confidence level. We see that the phases generally support the same inferences.

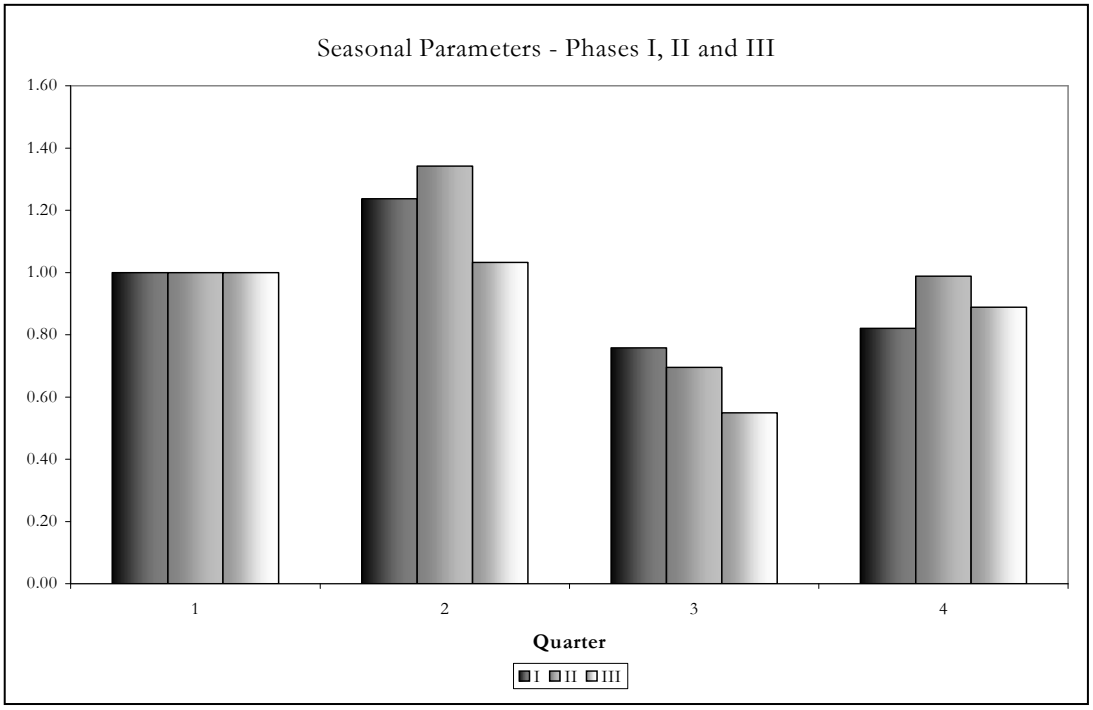
Figure D



The annual intensity parameters are presented in Figure D. It can be clearly seen that while the intensity of Phase I review has been essentially constant (and, at 95% confidence, statistically constant), there is some increase in Phase II and a significant increase in Phase III, maybe reflecting the effects of the Prescription Drug User Fee Act (PDUFA) of 1992, which intended to hasten the review process without affecting the quality of the same. The PDUFA authorized the FDA to collect fees from companies that produce certain human drug and biological products. Any time a company wants the FDA to approve a new drug or biological prior to marketing it must submit an application along with a user fee to support its review process. Even though the Act is from 1992, it takes time to acquire new technology and train personnel to provide faster service, and that may be the reason why the effects on Phases II and III only became more noticeable in 1995. It is important to note that a good proportion of the drugs in the data set are not directly affected by FDA policy because they are primarily being developed for a non-US market. It is also important to note that if the FDA has reduced its review times this will directly affect the duration of Phase III as the duration from the NDA to marketing approval is included in our measure of Phase III. Finally, any effect on Phase II durations would be indirect.

The seasonal parameters for each of the phases are represented in Figure E. The first group of bars represents the first quarter seasonal parameters for all three phases, which were normalized to 1. As we can see, within each quarter there is not much variability across phases. In fact, this figure suggests that the seasonal pattern is essentially the same in all phases, a very nice consistency of results across the models. Indeed, if we calculate the arithmetic average of the log seasonal coefficients and test whether the log coefficients of each phase are equal to those averages, we cannot reject the hypothesis. Also notice that the quarter with the highest activity in all the phases is the second, while the slowest quarter in terms of decisions taken is the third.

Figure E



Note that if a characteristic has a positive coefficient under *success*, this is not equivalent to a negative coefficient under *failure*. Both have the effect of increasing the probability of success, but a positive coefficient will tend to shorten the expected duration, while a negative coefficient will tend to lengthen it. Figure A in the previous subsection presents the baseline transition intensities for both *success* and *failure*, each scaled by its respective constant.

Few of the therapies have statistically distinct effects on successful durations. The most significant effect is also the most surprising: anti-cancer therapies are negatively associated with successful durations. This means not only that such drugs are less likely to succeed, but also that their expected durations are longer. If the two transition intensities to *success* and *failure* were equally scaled (which, in general, they are not), then the probability of success would increase if the difference between the *success* and *failure* coefficients were positive, and the expected duration would decrease if the sum of the coefficients were positive. The only unambiguously significant therapy for failure durations is analgesic. Such drugs are more likely to succeed, and have higher expected durations. The broad conclusion

is that, with the exception of anti-cancer and analgesic treatments, success or failure in Phase I is generally unrelated to a drug's intended therapy.[12]

On the other hand, different routes of administration can have significant effects on both successful and failed durations. In particular, alimentary, parenteral, and topical drugs are all much more likely to succeed than other routes of administrations. However, it is difficult to discern their impact on expected durations, since generally they have positive coefficients for *success* and negative coefficients for *failure*.

The different original materials can have significant impacts on success and duration in Phase I. Generally, any of the identified original materials will increase the probability of success as well as the expected duration relative to the baseline "other". Another way of saying this is that those materials other than the ones identified lead to quick failures. Biologicals have the highest probability of succeeding in Phase I, but also the longest duration by far, especially when compared to Chemicals.

We conduct a number of Wald tests on various hypotheses regarding these coefficients. The results are summarized in Table E. We can reject the hypothesis that the covariate coefficients under *success* are, as a set, equal to zero, and similarly for those under *failure*. We can also reject the hypothesis that the log baseline transition values equal zero, for both *success* and *failure*.

While we separately identify different subsets of parenteral routes of administration, we cannot reject the hypothesis that in fact all the coefficients are equal. That is true for both *success* and *failure*. We similarly cannot reject the hypothesis that the coefficients on *original material* are all equal.

For Phase I, we cannot reject the hypothesis that the effects from companies of different sizes are all equal. In other words, there is no advantage or disadvantage to being sponsored by a larger company. While the country of origin does not impact *success*, we can reject the hypothesis that all the coefficients are equal under *failure*.

Finally, we are not able to reject the hypothesis that the baseline hazard intensities are (weakly) monotonic. We conduct this test by finding the isotonic regression fit to each baseline, and then testing whether the transitions are significantly different from this regression fit. In other words, it appears that the baseline transitions to *success* and *failure* are non-decreasing as time passes.

[12] A Wald test that all therapy coefficients are zero is, however, rejected: test statistic of 88.54 against a critical value of 65.17 implies a p-value of 0.

As with Phase I, few therapies have distinct effects on successful duration in Phase II. Exceptions include analgesics, formulations, and monoclonal antibodies. Analgesics and monoclonal antibodies have effects similar to (though more significant than) those found for Phase I. Examining effects related to failure durations, only anti-arthritic therapies show significant impacts. Anti-cancer therapies continue to be associated with longer durations, and reduced probabilities of success, but less significantly so than in the previous phase. It may be the case that Phase I trials filter out many of the marginal anti-cancer drugs. Anti-HIV therapies still show no significant impact on either *success* or *failure* durations.

As in Phase I, alimentary, parenteral, and topical routes of administration are positively related to successful durations, and negatively related to failure durations. From the differences in coefficients we see clearly that they are therefore strongly associated with increased probabilities of success, but from the sum of coefficients, their impact on expected duration is less clear, and nominally suggests longer durations.

Recombinant protein biologicals, chemicals, and natural products are all positively associated with successful durations. The same directional effects were observed in Phase I, but there they were not significant. The significantly negative effects on failure durations observed in Phase I continue in Phase II. Looking at the sums and differences of coefficients, we draw essentially the same inferences in Phase II as in Phase I, namely that these original materials are associated with both longer durations and increased probabilities of success when compared to the effects of most other regressors.

There continues to be the suggestion that sponsorship from larger companies is positively related to successful durations, but also to failure durations. This is similar to what was found for Phase I, but is more pronounced. The implication is that expected durations are shorter for drugs sponsored by larger companies, but the ultimate probability of success may not be different from the baseline. These inferences are clear when examining the sums and differences of coefficients.

Generally the data from Phase II support many of the same inferences as Phase I. There are some exceptions. In Phase II, the different parenteral routes of administration are statistically distinct in their effects on *success*, though again not on *failure*. Also, we can reject the hypothesis that the effects of drug company size are all equal. However, we cannot reject the hypothesis that they are weakly monotonic for both *success* and *failure*. We are also able to reject the hypothesis that the intensity parameter – as measured by the yearly dummies – is constant, but not that it is monotonic.

Please note that because there were fewer observations in Phase III, we were not able to identify as many characteristics as we could in Phases I and II. Many patterns observed in Phases I and II are again observed in Phase III. The route of administration and original materials characteristics are again positively related to success and to increased expected durations. There is a clearer indication that larger companies are associated with both increased probabilities of success and shorter durations.

Inferences drawn from the Phase III data are quite similar to those from Phase II. There are some exceptions. As with Phase I, we cannot reject the hypothesis that all parenteral characteristics have equal effects on successful durations. Also, we are now able to reject the hypothesis that all originating companies have equal effects.

5. Conclusions

This paper estimates a full multiple state mixed proportional hazard model separately for each of the three stages of human clinical trials using a publicly available historical data set on drugs in development. The paper presents descriptive results showing the estimated relationship between a particular drug's observed characteristics and that drug's pathway through human clinical trials and regulatory approval. The results suggest that success rates fall with durations particularly for Phase I and Phase II, success rates are higher for larger firms, and durations have tended to fall since 1995.

Recently, estimated success rates and durations were used to determine that the average drug cost $802m to bring to market (DiMasi et al, 2003). Despite the importance of these estimates, much of the previous analysis reported crude success rates and durations (DiMasi, 2001, Adams and Brantner, 2003) or relatively simple duration models to calculate success rates (DiMasi et al, 2003) or successful durations (Dranove and Meltzer, 1994). This paper estimates a single more general duration model with both successful and failed exit states and detailed characteristic information.

In future work the authors hope to estimate a new version of the model that uses results presented above to restrict the functional form and increase the number of estimated covariates. We also hope to present simulation results for a richer set of scenarios.

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Table D
Sums and Differences of Coefficients - Phases I, II, and III

	Probability of Success				Expected Duration		
	I	II	III		I	II	III
Analgesics	++	--	NA		++	++	NA
Anti-anginal, etc.			--				++
Anti-arthritic		--	NA		-		NA
Anti-asthma			--				
Anti-cancer			-		++	++	
Anti-hypertensive					--		
Anti-Parkinsonian						++	+
Anti-HIV			NA			-	NA
Anti-thrombotic	--	NA	NA			NA	NA
Biotechnology	-	NA	NA			NA	NA
Female contraceptive, fertility	+				++		
Formulation		++	+				
Memory enhancer			NA			++	NA
Monoclonal antibody	+	+	-			--	
Neurologicals						++	++
Recombinant vaccine	++	NA	NA			NA	NA
Recombinants		+					
Alimentary	++	++	++		+		
Transdermal			++				
Parenteral	++	++	++			+	++
Parenteral, intravenous	++	++	++				
Parenteral, unknown	++	++	+		+	++	
Respiratory			++			+	++
Topical	++	++	++			+	
Biological	++		+		++		
Biological, nucleic acid		++	NA			++	NA
Biological, protein	+	++	++		++	+	+
Biological, protein, antibody			++		++	++	
Biological, protein, recombinant	++	++	+		++		
Biological, viral	++	++			++		
Chemical	++	++	+		++		
Natural Product	++	++	+		++		
2 drugs		-	++				
3 drugs						-	
4-5 drugs (I,II), 4 drugs (III)							--
6-10 drugs (I,II), 5-6 drugs (III)					--	--	
11-15 drugs (I,II), 7-9 drugs (III)			+				-
16-30 drugs (I,II), 10-14 drugs (III)		-	++		-	--	--
15-22 drugs (III)			++				--
31+ drugs (I,II), 23+ drugs (III)			+		-	--	-
Canada			NA		-	--	NA
France					+	++	
Germany	+		+		+	+	
Italy			NA				NA
Japan		-			+		+
Switzerland					+		
United Kingdom	-	--				-	-
USA			+				
Patent Exists	++	++	++				
Age of Patent	-	--	-			+	

Table E
Test Statistic Results - Phases I, II, and III

Variable Sets	Test Description	* p-value > 0.05 I	II	III
	All Covariates Equal 0: Success			
	All Covariates Equal 0: Failure			
	Log Baseline Hazard Equals 0: Success			
	Log Baseline Hazard Equals 0: Failure			
ROA	All Parenteral Coefficients Equal: Success	*		*
	All Parenteral Coefficients Equal: Failure	*	*	*
OM	All Biological Coefficients Equal: Success	*	*	*
	All Biological Coefficients Equal: Failure	*	*	*
Originator	All Coefficients Equal: Success	*		
	All Coefficients Equal: Failure	*	*	
	Monotonic Coefficients: Success	*	*	*
	Monotonic Coefficients: Failure	*	*	*
Country	All Coefficients Equal: Success	*	*	
	All Coefficients Equal: Failure			
Seasonality	All Coefficients Equal (no seasonality)			
Intensity	All Coefficients Equal (constant FDA intensity)	*		
	Monotonic Coefficients	*	*	*
Baseline Hazards	Is Baseline Monotonic: Success	*	*	*
	Is Baseline Monotonic: Failure	*	*	*