New Drug Development:
Estimating entry from human clinical trials

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I. Introduction

The dynamics of drug development is one of the defining characteristics of the pharmaceutical industry. Despite its importance to the industry, there is little information on how long it takes for particular drugs to go through human clinical trials and the probabilities of successful completion. Recently, a number of authors have started making use of historical data on the development of drugs through human clinical trials in the US and elsewhere in the world (for example, Abrantes-Metz, 2003, Kyle, 2002, Danzon et al, 2003). These authors are using this data examine determine the relationship between drug characteristics and successful durations, market entry, and the use of licensing arrangements, respectively. The type of this historical data has the potential to provide industry analysts with a much better picture of late stage pharmaceutical development and new drug entry. The current paper presents some summary statistics on duration and frequencies of successful completion of the human clinical trials. While this analysis is not sophisticated or detailed enough to provide answers to many of the questions research practitioners are interested in, it does provided readers with some stylized facts to guide future work.

The paper analyzes a sample of drugs that have entered human clinical trials anywhere in the world between 1989 and 2002. The data provides information on entry and exit dates from the three different stages of the human clinical trials for the first indication that the drug was being developed (post-1989). The data also provides information on drug characteristics such as primary indication, chemical composition, route of administration and originating company. The analysis provides frequencies with which drugs with different characteristics successfully complete the different stages of the human clinical trials. For example, drugs that have been originally developed by one of the 10 largest drug companies have a higher than average probability of getting to market. The analysis also provides mean durations for drugs that successfully complete the different stages of the human clinical trials. For example, AIDS drugs are in human clinical trials for an average of 5 years, which is 3 years shorter than the average drug in the sample. In general, the results presented should not be interpreted as causal effects of drug characteristics on success rates or successful durations. Rather these results should be interpreted as descriptive or simply as statistical observations of the drug development process.

Analysis of drug development and new drug entry must address two major questions. First, do "important" new drugs get through the regulatory process quicker than other drugs? In the US, the FDA offers a number of programs aimed to encourage development of important or life-saving drugs, including prioritizing drugs at registration and offering fast tracks through human clinical trials and registration for specified drugs (particularly AIDS drugs). According to the FDA, priority drugs that successfully complete the review process have significantly shorter durations than standard drugs (FDA, 2003). Dranove and Metzler (1994) analyze the FDA's role in drug development durations by analyzing successful duration from discovery to market for US drugs. The authors find that economic indicators seem to be more important in determining durations than "scientific" indicators. This paper and Abrantes-Metz (2003) use more detailed data on the durations and failure rates for drugs in human clinical trials. This paper analyses successful durations through human clinical trials and the governmental review process by primary indication and finds significant differences across different indications. In particular, AIDS drugs and cancer drugs tend to have shorter successful durations. Note that these results should be interpreted with care, as drugs analyzed are going through different regulatory environments throughout the world.[1] Note also that we have not controlled for the actions of the drug companies and their ability to determine success rates and durations.

Second, are there economies of scale or scope in drug development? Graves and Langowitz (1993) find a positive relationship between R&D expenditures and the number of new chemical entities produced. In their analysis often large pharmaceutical firms, Henderson and Cockburn (1996) find a similar relationship between the number of new drug patents and development output. Danzon et al. (2003) find that success rates are increasing with the overall number of drugs that a firm develops and the number of drugs in the relevant therapeutic area.[2] As stated above, the results presented below suggest that drugs discovered by larger companies have a higher probability of getting to market. However, the results also show substantial heterogeneity in the success rates for some of the largest firms. This heterogeneity suggests that firms may have different strategies for investing in drug development.[3] While there may be

[1] See Kyle (2002) for a discussion of the differences across countries.

[2] Danzon et al (2003) discuss the influence that alliances and licenses have on drug development success rates.

[3] It is interesting to consider the similarities between expenditure on new drugs and the expenditure on

development in prior to 1995. A recent change in the industry has been the introduction of biotechnology drugs into human clinical trials. The results show that biotech drugs tend to have higher probabilities of getting to market although their average durations are similar to the average durations over all drugs. The results also suggest significant differences between drugs with different routes of administration (ROA). Oral drugs seem to be quicker to market but with a lower probability of successful completion of human clinical trials. This result is consistent with an equilibrium story that oral drugs have higher expected returns, however these results are not based on a structural estimation so should be interpreted with care. For example, it may simply be the case that it is easier to conduct trials on oral drugs.

The paper proceeds as follows. Section II presents a brief description of the drug development process. Section III describes the data used in the analysis, and provides definitions of the variables used. Section IV presents and discusses the results. Section V concludes.

II. Human Clinical Trials

The process of drug discovery to market 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, for example, 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 1, Phase 2 and Phase 3 (the second, third and fourth periods, respectively). Any IND may be filled for one or more phases. Generally, the phases are completed sequentially and after the Phase 3 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 countries.[4]

In preclinical trials, the pharmaceutical company uses general 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 (Levy, 1999)

The first phase of the human trials is called Phase 1. Phase 1 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 2 trials involve several hundred patients with the disease condition, and are designed to give an indication of the drugs effectiveness. Phase 3 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).

III. Data

Pharmaprojects contains information on 27,987 new drug entities that have reached the late stage development from 1980 to 2002. For the purposes of this study, we limited the sample size to 3,328 drugs that have entered either Phase I, or Phase II, or Phase III of the human clinical trials [illegible] clinical st thavailac

substantial self-selection bias in the sample.[6] Although not reported, the good news is that most of the censo

company's world revenue for 2001 was one of the top ten in the pharmaceutical industry. One concern

Finally, the data provides a number of other measures of drug characteristics including the drug's route of administration and the drug's original material. The drug's route of administration is categorized by a number of degrees of specificity. For example, a pill is categorized as "alimentary", and "oral". We report results as specifically as possible while having enough drugs in the category for sensible statistics. The drug's original material is similarly categorized, so a particular biotech drug may be categorized as "biological", and then "recombinant protein". We report the statistics at the highest category level.

Table (2) represents the number of drugs in each phase of development according to their company size, material, route of administration and market size. Since 1989, first time entry drugs number 1,796 for Phase I, 1,879 for Phase II, and 1,025 for Phase III. Of the 398 drugs that have been launched worldwide, only 217 of them have been launched into the US market. 1,465 of the 3,328 drugs in the sample have been withdrawn or discontinued from development.

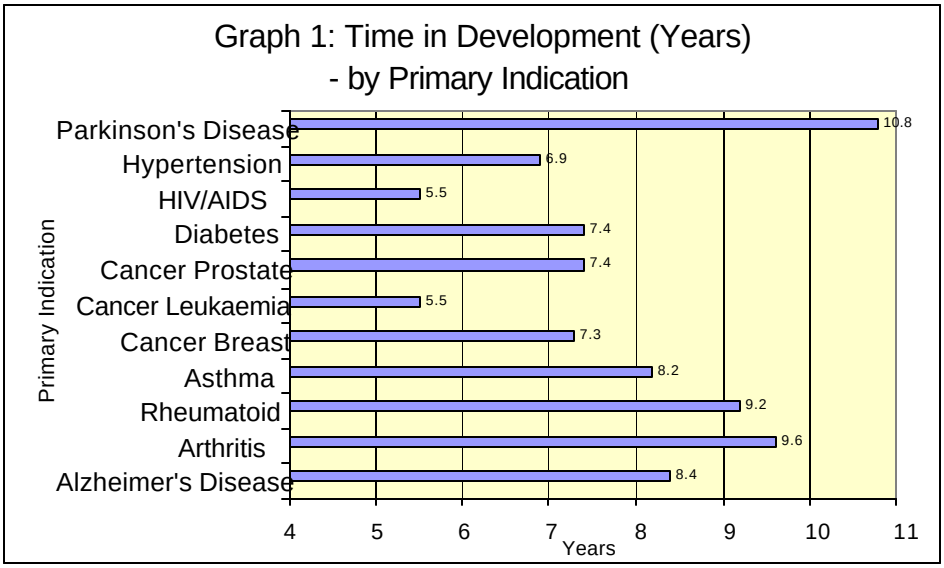
IV. Results

i) Do important drugs get to market faster?

In the US, the FDA has instituted policies that give pharmaceutical companies the opportunity to get "important" drugs to market. These policies include faster review of "priority" drugs and fast-tracking of human clinical trials for certain drugs. Priority drugs are defined by the FDA at the time of registration (generally after the completion of the Phase 3 clinical trials). The FDA also offers the opportunity for some drugs to shorten their time in human clinical trials and in this way, "fast-track" drugs to market. Time in development is calculated by adding together the average duration that drugs in the sample spend in each stage of development. On average, it takes just under 8 years for a drug to go from Phase I of human clinical trials to market launch in the US. The same figures for Phase II and Phase III drugs are 6.7 and 3.7 years respectively. More specifically, an average drug spends 1.7 in Phase I, 2.4 years in Phase II, and 3.7 years in Phase III before launch.

Graph 1 presents a graph showing the estimated duration for the drugs in the data set by their primary indication. While it takes just 5.5 years on average for HIV/AIDS drugs to get from Phase I to the market, it takes drugs for Parkinson's disease almost twice that long to go through the same process. Drugs

for arthritis also spend more than 9 years, and asthma drugs spend more than 8 years in clinical trials on average. HIV/AIDS, anti-hypertension, and leukemia cancer drugs are some drugs that spend less than 7 years in clinical development. Again, this result is suggestive, but more sophisticated analysis is necessary to determine whether more important drugs get to market faster, and why.



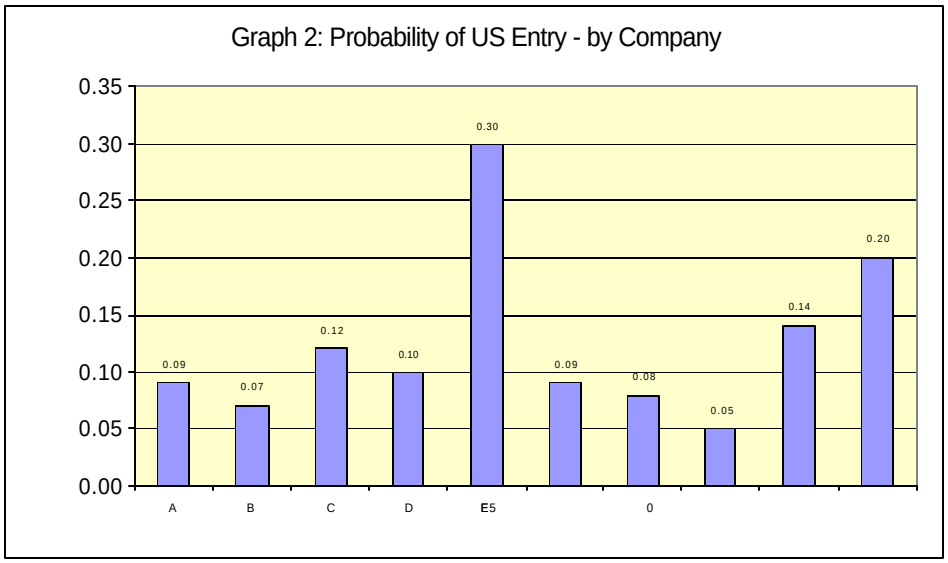
ii) Are there economies of scale or scope in drug development?

While the data and the analysis is not nearly detailed enough to get at this question, we can present some summary statistics on the relationship between firm size (as measured by revenue) and success probabilities and successful durations. The probabilities are calculated by multiplying together the estimated probabilities of a drug moving from one particular stage in development to the next stage. The method of calculation can be expressed by the following equation:

Pr (Launch=1|Phase I=1) = Pr (Launch=1|Phase III =1) x Pr (Phase III=1|Phase II=1) x Pr (Phase II=1|Phase I=1)

In words: probability of drugs being launched onto the market when they enter Phase I equals the product of the probability of drugs getting from Phase I to Phase II multiplied by the probability of the drugs in Phase II advancing to Phase III, multiplied by the probability of drugs in Phase III being launched onto the US market.

The reason behind this method is that information on all stages of clinical development is available for only a limited number of drugs. By studying this group of drugs exclusively, we would significantly reduce the sample size, and thereby, potentially exclude important information. Instead, we calculate the probabilities of the drugs in each phase of development getting to the next phase from the time they entered Phase I clinical trial until their launch to the market, and then multiplying the results together. The probabilities of drugs moving from a particular stage to the next are calculated using the number of drugs


Graph 2: Probability of US Entry - by Company
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.09
0.07
0.12
0.10
0.30
0.09
0.08
0.05
0.14
0.20
A
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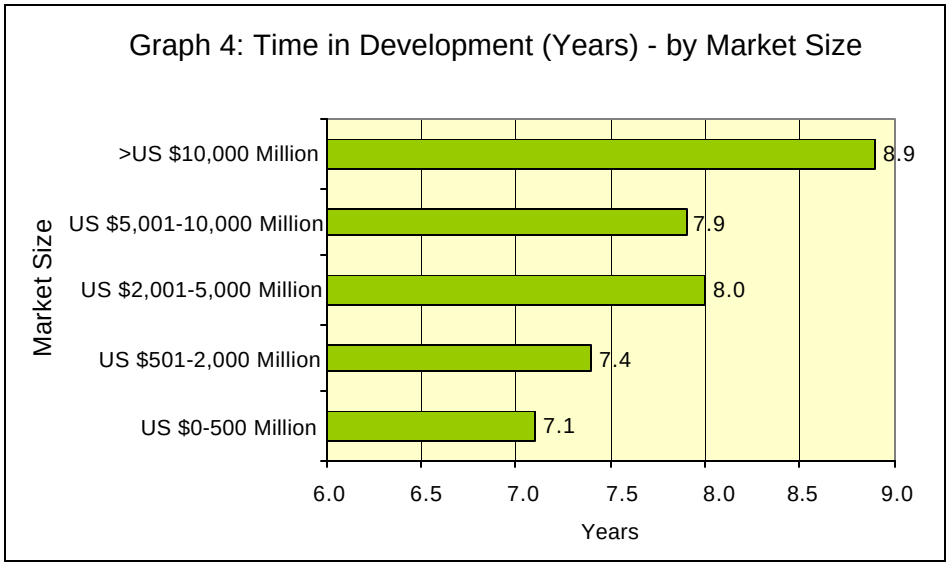
drugs with markets between $500 million and $2 billion have almost 1 in 2 probability of getting to market. However, the overall picture is far from clear. There are 100 drugs in Phase 1 that have a market size as being over $10 billion, of these drugs only 4 have reached the market in the US. Tables (5) and (6) present the success rates on two subsets of drugs, those indicated for arthritis and those indicated for hypertension. Arthritis drugs associated with a market size over $5 billion have a less than average probability of getting to market, while similar hypertension drugs have a greater than average probability of getting to market. Finally, it is not clear how to interpret such success rates as in equilibrium we would expect a negative relationship between expected returns and successful probabilities (Danzon et. al., 2003).



In regards to successful durations, Graph (4) shows that time in development is generally increasing in market size, with large market drugs taking almost 2 years longer to get to market than small market drugs. The results presented in Tables (8) and (9) shows that this pattern also seems to hold for the two subsets of drugs (arthritis and hypertension). It is again not clear how to interpret such statistics given that companies decide whether or not to end development and how much to spend on continued development, based on their expectation of market return.

iv) What effect do drug characteristics have on success rates and successful durations?

Table (4) presents the success rates in regards to entry from different phases of development for different categories of route of administration and different original materials. In regards to route of administration, oral drugs seem to have a relatively high probability of getting to market, but drugs delivered by subcutaneous injection have an even higher probability of getting to market. At more general category levels there is not much different between success rates for alimentary drugs and parenteral drugs (injections). In regards to original materials, biologicals seem to have higher success rates than other types of drugs. The most interesting result from Tables (5) and (6) is that almost all intravenous drugs get to market for arthritis, while no intravenous drugs get to market for hypertension. Similarly, a high percentage of biological drugs get to market for arthritis, while there is only one biological in the sample that has been developed for hypertension and that drug did not get passed Phase 1.

Table (7) presents the time in development for drugs with different characteristics. The table shows that drugs that would be relatively easy to administer, including orals, respiratory and transdermal (for example patches), are quicker to market than drugs delivered by injection. In particular, drugs delivered by intramuscular injection take over 9 years to get from Phase 1 to market, while transdermal drugs take less than 7 years to get from Phase 1 to market. It is not clear whether these results indicate that drugs with higher returns will get to market quicker or whether it is simply easier to conduct human clinical trials when drugs have particular routes of administration.

V. Conclusion

Drug development is one of the salient characteristics of the pharmaceutical industry. However, it is not an area of the industry for which we have a lot of information. Recently, a number of authors have started to

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APPENDIX

Table 1: Drugs That Appear in Each Phase of Development

	Number	Percent
Phase 1 only	931	28%
Phase 2 only	786	24%
Phase 3 only	466	14%
Phase 1 and Phase 2 only	586	18%
Phase 1 and Phase 3 only	52	2%
Phase 2 and Phase 3 only	280	8%
Phase 1, Phase 2 and Phase 3	227	7%
Total	3328	100%

Table 3: Primary Indication - Number of Drugs by Category

	Phase 1	Phase 2	Phase 3	US Launch	World Launch	Ceased	Phase

Table 4: Probability of US Entry of Clinically Developed Drugs from Phase of Development (Number of Drugs in the Sample)

		Phase 1	Phase 2	Phase 3
All Drugs		0.12	0.17	0.38
		(1366)	(1218)	(542)
Big Pharma		0.10	0.17	0.47
		(217)	(219)	(127)
Non Big Pharma		0.12	0.17	0.36
		(1149)	(999)	(415)
Biologicals		0.25	0.31	0.53
		(309)	(218)	(75)
Chemicals		0.19	0.25	0.45
		(725)	(664)	(343)
Natural Products		0.18	0.23	0.37
		(50)	(45)	(30)
Alimentary		0.28	0.34	0.51
		(301)	(308)	(200)
	Oral	0.29	0.35	0.51
		(290)	(296)	(197)
Parenteral		0.28	0.32	0.49
		(405)	(343)	(147)
	Intravenous	0.30	0.34	0.48
		(209)	(195)	(86)
	Subcutaneous	0.43	0.45	0.61
		(43)	(39)	(18)
	Intramuscular	0.39	0.45	0.69
		(36)	(23)	(13)
Respiratory		0.17	0.25	0.67
		(36)	(27)	(6)
Topical		0.27	0.37	0.50
		(49)	(38)	(42)
Transdermal		0.13	0.21	0.44
		(23)	(17)	(9)
US $0-500 Million		0.09	0.13	0.26
		(133)	(128)	(69)
US $501-2,000 Million		0.16	0.23	0.47
		(418)	(391)	(186)
US $2,001-5,000 Million		0.13	0.19	0.40
		(506)	(400)	(159)
US $5,001-10,000 Million		0.09	0.14	0.44
		(178)	(172)	(64)
> US $10,000 Million		0.04	0.06	0.13

	(100)	(110)	(55)

Table 5: Probability of US Entry from Phase of Development
(Number of Drugs in the Sample) - Arthritis*

	Phase 1	Phase 2	Phase 3
All Drugs	0.30	0.36	0.61
	(42)	(34)	(18)
Big Pharma	0.43	0.57	1.00
	(4)	(7)	(4)
Biologicals	0.60	0.67	1.00
	(20)	(12)	(3)
Chemicals	0.24	0.32	0.62
	(21)	(21)	(13)
Orals	0.32	0.35	0.56
	(11)	(16)	(9)
Intravenous**	0.83	0.83	0.83
	(9)	(4)	(6)
Large Market	0.19	0.29	0.50
	(12)	(12)	(10)

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Intravenous**	0.00	0.00	0.00
	(5)	(6)	(2)
Large Market	0.30	0.37	0.58
	(25)	(31)	(19)

*By any Indication
**No Drugs Have Made to the Market

Table 7: Time in Development (Years)

		Phase 1	Phase 2	Phase 3
All Drugs		7.8	6.1	3.7
Big Pharma		7.1	5.5	3.4
Non Big Pharma		8.0	6.4	3.9
Biologicals		8.0	6.4	3.7
Chemicals		7.7	6.1	3.7
Natural Products		7.3	5.5	3.9
Alimentary		7.5	5.8	3.5
	Oral	7.5	5.8	3.5
Parenteral		8.2	6.6	4.0
	Intravenous	7.9	6.3	3.7
	Subcutaneous	8.7	7.1	4.2
	Intramuscular	9.2	7.4	4.6
Respiratory		6.7	5.1	3.3
Topical		7.7	6.4	4.5
Transdermal		6.8	4.9	2.9
N		1796	1879	1025

Table 8: Time in Development (Years) - Arthritis**

	Phase 1	Phase 2	Phase 3
All Drugs	7.9	6.4	3.7
Big Pharma	8.3	6.9	3.8
Biologicals	5.8	4.5	2.1
Chemicals	9.2	7.1	4.4
Orals	8.4	6.5	3.5
Intravenous	NA*	NA*	4.3
Large Market	9.5	8.0	4.8
N	55	63	31

**By any Indication

* Number of observations is insufficient for calculation

Table 9: Time in Development (Years) - Hypertension**

	Phase 1	Phase 2	Phase 3
All Drugs	7.3	6.4	3.2
Big Pharma	7.5	6.4	3.2
Biologicals	NA*	NA*	NA*
Chemicals	7.3	6.5	3.2
Orals	6.4	5.6	3.2
Intravenous	NA*	NA*	NA*
Large Market	7.1	6.4	3.4

N	**35**	**50**	**47**

**By any Indication

* Number of observations is insufficient for calculation