

The Economics of Follow-on Drug Research and Development

Trends in Entry Rates and the Timing of Development

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Abstract

Objectives: The development of so-called 'me-too', or 'follow-on', drugs by the pharmaceutical industry has been viewed by some as duplicative and wasteful, while others have argued that these drugs often provide needed therapeutic options and inject some price competition into the marketplace. This study examines data on the trends in the speed with which competitive entry has occurred in the pharmaceutical marketplace and the competitive nature of the industry's development of these drugs.

Data and methods: We examined data on the entry rates of drugs in a large number of therapeutic classes over time, as well as detailed survey information on the relative timing of the development of drugs in the classes. Classes were defined according to chemical structure or pharmacologic mode of action and similarity of clinical use. We determined average times to initial and subsequent entry in drug classes by period and examined the timing of development milestones achieved by what have turned out to be follow-on drugs in relation to the development and approval of the first drug in a class to be approved.

Results: We found that the period of marketing exclusivity that the breakthrough drug in a new class enjoys has fallen dramatically over time (a median of 10.2 years in the 1970s to 1.2 years for the late 1990s). Approximately one-third of follow-on new drugs received a priority rating from the US FDA. The vast majority of the follow-on drugs for drug classes that were created in the last decade were in clinical development prior to the approval of the class breakthrough drug.

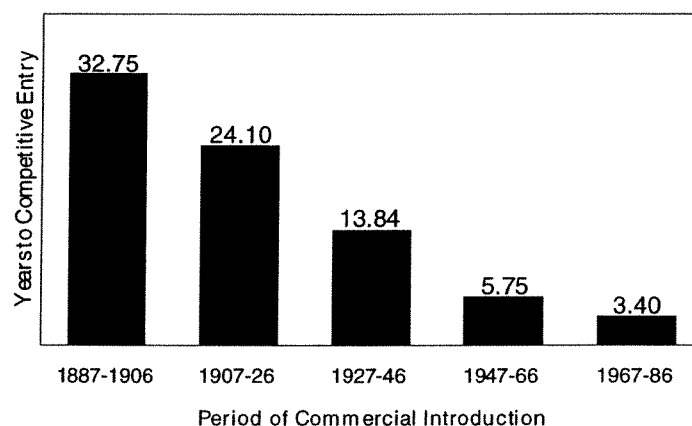
Conclusions: The data suggest that entry barriers have fallen over time for new drug introductions. The increased competitiveness of the pharmaceutical marketplace was likely fueled by changes over time on both the supply and demand sides. The development histories of entrants to new drug classes suggest that development races better characterise new drug development than does a model of *post hoc* imitation. Thus, the usual distinctions drawn between breakthrough and 'me-too' drugs may not be very meaningful.

Critics of the pharmaceutical industry have faulted it for developing and marketing many 'me-too' drugs. The term 'me-too' drug has been dated at least as far back as the 1960s⁽¹¹⁾ following increasing concerns over 'molecular modification' of approved drugs that were expressed in US Senate hearings on pricing and monopoly power in the pharmaceutical industry in the late 1950s and early 1960s (the so-called 'Kefauver hearings'). Although the term 'me-too' has come to be used in different ways, historically it has most often referred to a new drug entity with a similar chemical structure or the same mechanism of action as that of a drug already on the market. That is, a me-too drug is a new entrant to a therapeutic class that had already been defined by a separate drug entity that was the first in the class (sometimes referred to as the breakthrough drug) to obtain regulatory approval for marketing. Me-too drugs have also been characterised in a more value-neutral way as follow-on drugs,⁽¹²⁾ and that is how we term the concept here.

Industry critics maintain that research and development (R&D) expenditures on follow-on drugs are largely duplicative and wasteful. They argue that the resources used to develop them should instead be directed at developing more innovative treatments. Others, however, argue that

companies do not set out to develop drugs of no added value, and that, in any event, follow-on drugs provide better therapeutic options at the individual patient or patient subgroup level, and that they inject some price competition into the marketplace. The clinical and economic benefits of follow-on drugs have been discussed in some detail elsewhere.⁽¹³⁻⁷⁾ We offer some new indirect evidence of the clinical benefit of follow-on drugs in this paper, but we mainly focus on data that can illuminate how the competitiveness of pharmaceutical R&D has changed over time.

The period of marketing exclusivity that first movers enjoy after introduction of an innovation is an indicator of the degree to which entry barriers in an industry exist and their consequent impact on competitiveness. Agarwal and Gort⁽⁸⁾ examined this issue for innovation generally in the United States over a very lengthy period. They found that the speed of entry following launch of a sample of 46 innovations across a wide array of industries increased dramatically over time. The mean time to entry fell from approximately 33 years for a period at the turn of the 20th century to a little less than 3.5 years for the period 1967-86 (figure 1). As for potential explanations, the authors begin by citing Bain's⁽⁹⁾ seminal clas-



Source: Agarwal and Gort, *J Law Econ* 2001 44(April):161-77

Fig. 1. Mean time to initial competitive entry for a sample of 46 innovations.

sification of entry barriers: economies of scale and high sunk costs, absolute cost advantages and product differentiation advantages, as well as extensions that other scholars have noted such as advertising, control of scarce resources, the speed at which information disseminates, and technology lock-ins. They conclude that, overall, the increases in the speed of entry were due primarily to increased mobility of skilled labor, more rapid diffusion of scientific and technical information, more potential entrants (foreign firms) and expanding markets. The extent to which there have been changes in barriers to entry for individual industries and what explains those changes, however, can vary in nature and degree by industry. Thus, it is worth examining these issues in detail for the pharmaceutical industry.

The literature on speed to entry in pharmaceutical markets is not extensive. Kettler^[10] notes data on the time to a first follow-on drug compiled by a consulting firm. The speed to entry falls from 10 years in the 1960s to 0.25 years in the 1990s. However, only ten first-in-class drugs are examined covering a nearly 30-year period with no indication that steps were taken to be comprehensive, or even random. Towse and Leighton^[5] examined the time to entry for 19 drug classes from 1961 to 1997 for the UK. The mean time to first entry fell from 6.5 years in the 1960s to 2.5 years for the 1970s (although there were only two classes from the 1970s). The mean time to entry was lowest for the 1990s (2.0 years). It is worth examining whether these downward trends hold with a larger sample and for the US market. The US has historically been the largest national market for pharmaceutical sales, with its share of global sales increasing in the 1990s.^[11] The US has also been an even more important source of industry profits.

In this study, we develop as comprehensive a list of new drug classes as we can to examine trends since the 1960s in the speed of competitive entry for new therapeutic drug introductions in the US pharmaceutical marketplace. We also explore the ratings

of therapeutic significance that the US FDA gave to new follow-on drugs at the time of marketing approval. Finally, we investigate the development histories of follow-on drugs in a new drug class and compare them to the approval and development histories of their corresponding first-in-class drugs.

Data and Methods

The Tufts Center for the Study of Drug Development (CSDD) maintains databases of new drugs and biopharmaceuticals approved in the US. We utilised these databases to provide a list of new chemical entities and new biopharmaceuticals approved in the US from 1960 onward.¹ We refer to both types of compounds as new drugs. To allow for a reasonable amount of time for competitive entry to occur, we restricted the search for first-in-class compounds to new drugs approved through 1998. The follow-on new drug approvals in each class that we examined were approved through 2003.

Approval dates for first-in-class and follow-on new drugs were taken from the CSDD databases. A therapeutic class was defined to consist of new drugs that had a similar chemical structure or the same pharmacological mode of action and that were used primarily for the same indications. We established classes and investigated development histories by examining information from a wide variety of sources, including CSDD databases, *Physicians Desk References* (PDRs), various issues of *The Medical Letter*, *The Merck Index*, the US FDA and various clinical pharmacology Web sites, pharmacopeias (*USP DI* and *American Hospital Formulary Service*), and commercial investigational drug databases (*iDdb3*, *The NDA Pipeline*, *PharmaProjects* and *R&D Focus*).² From an economic perspective, our definition of a drug class is conservative since drugs in one class will often compete to some extent in the marketplace with drugs from other classes that are used to treat the same conditions. Our focus, though, is on the rate

1 Excluded from analysis here are new diagnostic drugs and new salts, esters or formulations of existing drugs.

2 We excluded a small number of classes where the same sponsor marketed all entrants. There was no trend in the data in the number of such classes.

of entry and development of what have classically been thought of as me-too drugs. To further differentiate these new drugs, we grouped them according to the US FDA's therapeutic ratings of new drug approvals. The US FDA established a three-tiered rating system for prioritizing review of new drug applications in late 1975. New drugs thought at the time to represent a significant gain over existing therapy, a modest gain over existing therapy, and little or no gain over existing therapy were given an A, B and C rating, respectively. The US FDA altered its rating system to a two-tiered one in 1992; since then, the US FDA rates new drugs as either priority (P) or standard (S).

For purposes of analysis across a lengthy historical period, we grouped those approved new drugs that had received an A or B rating with those that had received a P rating to form a 'priority-rated' category. Similarly, we grouped new drugs that had been assigned a C rating by the US FDA with those that had been assigned an S rating to form a 'standard-rated' category. The US FDA retroactively rated new drugs approved during 1963–75 in conformance with the old rating scheme. We placed these new drugs in our priority and standard categories according to the above mapping of A-, B- and C-rated drugs.

Results

We identified 72 drug classes where the first-in-class compound was approved from 1960 to 1998. We then found 235 follow-on drugs for these 72 therapeutic classes that have been approved in the US through 2003. Thus, the mean number of compounds per class is 4.3 (including the first-in-class compounds). The number of drugs per class ranged from two to 16, with a median of three. More than two-thirds (69%) of the classes had four or fewer compounds in them.

Our data indicate that additional entry is uncommon for orphan drugs. This may be expected since

the markets for orphan drugs are typically quite small and will tend, therefore, to not support multiple approvals of the same type of drug. Only seven of the 72 classes with multiple entry have first-in-class approvals that had received an orphan drug designation.³ In addition, an overwhelming majority (80%) of the first-in-class drugs had received a priority rating for regulatory review by the US FDA. Thus, the typical new drug with follow-on entry in our dataset is a priority-rated non-orphan.

To uncover trends in the data on the speed of competitive entry, we partitioned the data into periods based on when the first-in-class drug was approved for marketing in the US. The data suggest that dividing the 1980s and 1990s into two periods would be instructive. Since our observations are necessarily restricted in time, there is the potential for a right-censoring problem for recent approvals. The most recent period that we consider is 1995 to 1998 for first-in-class approvals. However, for a number of reasons we argue that the censoring issue is not likely to be of significant, if any, concern when considering trends in the speed at which initial competitive entry occurs.

We consider additional approvals in a class through 2003. Thus, drugs that define a new class and were approved in our most recent period have had 5–9 years for follow-on entry to occur. Drugs approved in the next most recent period (1990–4) have had 9–14 years for initial competitive entry. Given that effective patent lifetimes for new drugs have averaged about 11–12 years,¹²⁾ that generic competition, once it occurs, is intense,¹²⁾ that new drug development is expensive,¹³⁾ and that new, often improved, classes frequently arise to treat the same conditions, censoring is potentially serious only for the most recent period. However, even for the most recent period the incentives for firms to pursue and obtain new drug approvals in the future for drugs that have not had chemically or pharmacologically similar follow-ons already approved are relatively low.

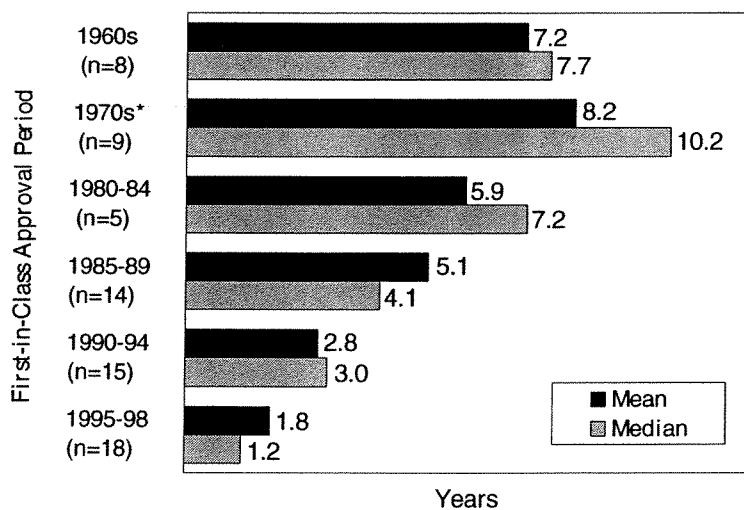
³ Forty-eight of the first-in-class compounds were approved after the US orphan drug legislation was enacted (4 January 1983). Prior to this legislation, very few drugs were developed for rare diseases and conditions. We include Protropin® as one of the seven drugs. Protropin® did not technically have orphan drug status at the time of regulatory approval. However, the manufacturer had applied for orphan drug designation prior to approval, which it received shortly after approval.

We examined the potential for the emergence of new classes not considered here by closely examining the new drug approvals from the 1995 to 1998 period that have not had chemical or pharmacological follow-on new drug approvals. We used commercial investigational drug databases to determine whether there were any drugs currently in the clinical pipeline that are chemically or pharmacologically similar to any of the new drug approvals from 1995 to 1998 that are not included among our 72 classes. Of these compounds, we found only one priority-rated non-orphan drug, one standard-rated non-orphan drug and three orphan drugs for which there were other similar drugs in clinical development. Given the high failure rates for scientific reasons and research terminations for economic reasons associated with pharmaceutical drug development,^[14] there is no guarantee that even these potential competitors will ever reach the US marketplace. Thus, it is unlikely that our results

on time to entry will be materially affected by future approvals. Any such second approvals would also be atypical, in any event, in terms of the length of time from first-in-class approval.

Speed of Entry

The 72 drug classes, the first-in-class drug, the first follow-on drug in the class to be approved, and the period of class marketing exclusivity for the original drug are shown in table I. We grouped the data on the basis of the period during which the first-in-class drug was approved and calculated means and medians for those periods. The data show a sharp decline in the period of marketing exclusivity for first entrants since the 1970s (figure 2). The mean length of the marketing exclusivity period fell 78% from the 1970s to 1995–8 (8.2 to 1.8 years).⁴ Analysis of variance results indicate that the differences in means across periods are highly



* Two extreme outlier classes were excluded (SERMs and rifamycin antibiotics)

Fig. 2. Average period of marketing exclusivity for first entrants to a therapeutic class (time from first-in-class approval to first follow-on drug approval) by period of first-in-class US marketing approval.

⁴ The 1970s values increase to 10.5 years for the mean and the median if two outlier classes (selective estrogen receptor modulators [SERMs] and rifamycin antibiotics) are included in the analysis. The time to a first follow-on entrant for these classes were 19.4 and 21.6 years, respectively.

Table I. First-in-class^a new drugs, second entrants^b and time to competitive entry^c

Class	First in class	US approval date	Second entrant	US approval date	Time to entry (y)
K+ sparing diuretic	Aldactone [®] (spironolactone)	01/02/1960	Dyrenium [®] (triamterene)	08/10/1964	4.6
benzodiazepine	Valium [®] (diazepam)	11/15/1963	Serax [®] (oxazepam)	06/04/1965	1.6
first generation quinolone	NegGram [®] (nalidixic acid)	03/06/1964	UtiBID [®] (oxolinic acid)	07/01/1975	11.3
bile acid sequestrant	Cuemid [®] (cholestyramine resin)	10/15/1964	Colestid [®] (colestipol)	04/04/1977	12.5
loop diuretic	Lasix [®] (furosemide)	07/01/1966	Edecrin [®] (ethacrynic acid)	01/10/1967	0.5
fibrate	Atromid-S [®] (clofibrate)	02/08/1967	Lopid [®] (gemfibrozil)	12/21/1981	14.9
benzimidazole (anthelmintic)	Mintezol [®] (thiabendazole)	04/07/1967	Vermox [®] (mebendazole)	06/28/1974	7.2
beta-antagonist	Inderal [®] (propranolol HCl)	11/13/1967	Lopressor [®] (metoprolol tartrate)	08/07/1978	10.7
pyrimidine nucleoside analogue	Cytosar [®] (cytarabine)	06/17/1969	FUDR [®] (floxuridine)	12/18/1970	1.5
first generation cephalosporin	Keflex [®] (cephalexin)	01/04/1971	Velosef [®] (cephradine)	08/05/1974	3.6
rifamycin antibiotic	Rifadin [®] (rifampin)	05/21/1971	Mycobutin [®] (rifabutin)	12/23/1992	21.6
retinoid (dermatologic)	Retin-A [®] (tretinoin)	10/20/1971	Accutane [®] (isotretinoin)	05/07/1982	10.6
beta-agonist	Alupent Syrup [®] (metaproterenol sulfate)	07/31/1973	Bricanyl [®] (terbutaline sulfate)	03/25/1974	0.7
anthracycline	Adriamycin [®] (doxorubicin)	08/07/1974	Cerubidine [®] (daunorubicin HCl)	12/19/1979	5.4
alpha-blocker	Minipress [®] (prazosin HCl)	06/23/1976	Hytrin [®] (terazosin HCl)	08/07/1987	11.1
H2-antagonist	Tagamet [®] (cimetidine)	08/16/1977	Zantac [®] (ranitidine)	06/09/1983	5.8
biphosphonate	Didrone [®] (etidronate disodium)	09/01/1977	Aredia IV [®] (pamidronate disodium)	10/31/1991	14.2
selective estrogen receptor modulator	Nolvadex [®] (tamoxifen)	12/30/1977	Fareston [®] (toremifene citrate)	05/29/1997	19.4
platinum anticancer	Platinol [®] (cisplatin)	12/19/1978	Paraplatin [®] (carboplatin)	03/03/1989	10.2
second generation cephalosporin	Ceclor [®] (cefaclor)	04/04/1979	Cefzil [®] (cefprozil monohydrate)	12/23/1991	12.7
ACE-inhibitor	Capoten [®] (captopril)	04/06/1981	Vasotec [®] (enalapril maleate)	12/24/1985	4.7
calcium channel blocker	Isoptin [®] (verapamil)	08/12/1981	Procardia [®] (nifedipine)	12/31/1981	0.4
guanine derivative	Zovirax [®] (acyclovir)	03/29/1982	Cytovene [®] (ganciclovir)	06/23/1989	7.2
insulin (rDNA)	Humulin [®] (insulin)	10/28/1982	Novolin R [®] (insulin)	06/25/1991	8.7
chromatin function inhibitor	VePesid [®] (etoposide)	11/10/1983	Vumon [®] (teniposide)	07/14/1992	8.7
LHRH-agonist	Lupron [®] (leuprolide acetate)	04/09/1985	Zoladex [®] (goserelin acetate)	12/29/1989	4.7
non-sedating antihistamine	Seldane [®] (terfenadine)	05/08/1985	Hismanal [®] (astemizole)	12/29/1988	3.6
cannabinoids for nausea	Marinol [®] (dronabinol)	05/31/1985	Cesamet [®] (nabilone)	12/26/1985	0.6
human growth hormone (rDNA)	Protropin [®] (somatrem)	10/17/1985	Humatrope [®] (somatropin)	03/08/1987	1.4
thienamycin	Primaxin [®] (imipenem/cilastatin) sodium	11/26/1985	Merrem I.V. [®] (meropenem)	06/21/1996	10.6
second generation quinolone	Noroxin [®] (norfloxacin)	10/31/1986	Cipro [®] (ciprofloxacin HCl)	10/22/1987	1.0
nucleoside reverse transcriptase inhibitor	Retrovir [®] (zidovudine)	03/19/1987	Videx [®] (didanosine)	10/09/1991	4.6
statin (HMG-CoA inhibitor)	Mevacor [®] (lovastatin)	08/31/1987	Pravachol [®] (pravastatin sodium)	10/31/1991	4.2
tissue plasminogen activator (rDNA)	Activase [®] (alteplase [TPA])	11/13/1987	Retavase [®] (reteplase)	10/30/1996	9.0
alpha-1 proteinase inhibitor	Prolastin [®] (alpha-1-proteinase inhibitor)	12/02/1987	Aralast [®] (alpha-1-proteinase inhibitor)	12/23/2002	15.1
selective serotonin reuptake inhibitor	Prozac [®] (fluoxetine HCl)	12/29/1987	Zoloft [®] (sertraline HCl)	12/30/1991	4.0
nonsteroidal anti-androgen	Eulexin [®] (flutamide)	01/27/1989	Proscar [®] (finasteride)	06/19/1992	3.4
third generation cephalosporin	Suprax [®] (cefixime)	04/28/1989	Vantin [®] (cefepodoxime proxetil)	08/07/1992	3.3
proton pump inhibitor	Prilosec [®] (omeprazole)	09/14/1989	Prevacid [®] (lansoprazole)	05/10/1995	5.7
synthetic triazole	Diflucan [®] (fluconazole)	01/29/1990	Sporanox [®] (itraconazole)	09/11/1992	2.6
surfactant	Exosurf Neonatal [®] (colfosceril palmitate)	08/02/1990	Survanta [®] (beractant)	07/01/1991	0.9
5HT3-antagonist	Zofran IV [®] (ondansetron HCl)	01/04/1991	Kytril [®] (granisetron HCl)	12/29/1993	3.0
ADP-induced platelet aggregation inhibitor	Ticlid [®] (ticlopidine)	10/31/1991	Plavix [®] (clopidogrel bisulfate)	11/17/1997	6.1
extended spectrum macrolide	Biaxin [®] (clarithromycin)	10/31/1991	Zithromax [®] (azithromycin)	11/01/1991	0.0
Factor VIII (rDNA)	Recombinate [®] (rurioctocog alfa)	01/01/1992	Kogenate [®] (Factor VIII)	02/02/1993	1.1
triptan	Imitrex [®] (sumatriptan succinate)	12/28/1992	Zomig [®] (zolmitriptan)	11/25/1997	4.9
taxane	Taxol [®] (paclitaxel)	12/29/1992	Taxotere [®] (docetaxel)	05/14/1996	3.4
low-molecular-weight heparin	Lovenox [®] (enoxaparin)	03/29/1993	Fragmin [®] (dalteparin sodium)	12/22/1994	1.7
interferon	Betaseron [®] (interferon beta-1b)	07/23/1993	Avonex [®] (interferon beta-1a)	05/17/1996	2.8
cholinesterase inhibitor	Cognex [®] (tacrine)	09/09/1993	Aricept [®] (donepezil)	11/25/1996	3.2
H1-antagonists (ophthalmic)	Livostin [®] (levocabastine)	11/10/1993	Patanol [®] (olopatadine HCl)	12/18/1996	3.1
serotonin and norepinephrine reuptake inhibitor	Effexor [®] (venlafaxine HCl)	12/28/1993	Serzone [®] (nefazodone HCl)	12/22/1994	1.0
macrolide immunosuppressive	Progra [®] (tacrolimus)	04/08/1994	Rapamune [®] (sirolimus)	09/15/1999	5.4
carbonic anhydrase inhibitor	Trusopt [®] (dorzolamide HCl)	12/09/1994	Azopt [®] (brinzolamide)	04/01/1998	3.3
nonpeptide angiotensin-receptor blocker	Cozaar [®] (losartan potassium)	04/14/1995	Diovan [®] (valsartan)	12/23/1996	1.7

Table I. First-in-class^a new drugs, second entrants^b and time to competitive entry (Continued)^f

Class	First in class	US approval date	Second entrant	US approval date	Time to entry (y)
prostacyclin	Flolan [®] (epoprostenol sodium)	09/20/1995	Remodulin [®] (treprostinil)	05/21/2002	6.7
protease inhibitor	Invirase [®] (saquinavir)	12/06/1995	Norvir [®] (ritonavir)	03/01/1996	0.2
aromatase inhibitor	Arimidex [®] (anastrozole)	12/27/1995	Femara [®] (letrozole)	07/25/1997	1.6
topoisomerase-1 inhibitor	Hycamtin [®] (topotecan HCl)	05/28/1996	Camptosar [®] (irinotecan HCl)	06/14/1996	0.1
prostaglandin analogue (ophthalmic)	Xalatan [®] (latanoprost)	06/05/1996	Rescula [®] (unoprostone isopropyl)	08/03/2000	4.2
non-nucleoside reverse transcriptase inhibitor	Viramune [®] (nevirapine)	06/21/1996	Rescriptor [®] (delavirdine mesylate)	04/04/1997	0.8
leukotriene	Accolate [®] (zafirlukast)	09/26/1996	Zyflo [®] (zileuton)	12/09/1996	0.2
third generation quinolone	Zagam [®] (sparfloxacin)	12/19/1996	Raxar [®] (grepafloxacin)	11/06/1997	0.9
thiazolidinedione	Rezulin/Prelay [®] (troglitazone)	01/29/1997	Avandia [®] (rosiglitazone)	05/25/1999	2.3
folitropin (rDNA)	Gonal-F [®] (folitropin alpha)	09/29/1997	Follistim [®] (folitropin beta)	09/29/1997	0.0
meglitinide	Prandin [®] (repaglinide)	12/22/1997	Starlix [®] (nateglinide)	12/22/2000	3.0
COMT inhibitor	Tasmar [®] (tolcapone)	01/29/1998	Comtan [®] (entacapone)	10/19/1999	1.7
hirudin-based thrombin inhibitor	Refludan [®] (lepirudin)	03/06/1998	Angiomax [®] (bivalirudin)	12/15/2000	2.8
cGMP-specific PDE5 inhibitor	Viagra [®] (sildenafil citrate)	03/27/1998	Levitra [®] (vardenafil)	08/19/2003	5.4
glycoprotein IIb/IIIa antagonist	Aggrastat [®] (tirofiban HCl)	05/14/1998	Integrilin [®] (eptifibatide)	05/18/1998	0.0
glucagon (rDNA)	GlucaGen [®] (glucagon)	06/22/1998	Glucagon [®] (glucagon)	09/11/1998	0.2
COX-2 inhibitor	Celebrex [®] (celecoxib)	12/31/1998	Voxx [®] (rofecoxib)	05/20/1999	0.4

a First-in-class drugs taken from US approvals during 1960 to 1998.

b Follow-on US approvals for identified classes taken through 2003.

statistically significant ($F_{3,64} = 6.41$, $p < 0.0001$). Similarly, without making the normality assumptions necessary for an analysis of variance test, the nonparametric Kruskal-Wallis test indicates that the medians are different by statistically significant amounts ($\chi^2(5) = 22.04$, $p = 0.0005$).

We also examined trends in the speed of entry in new drug classes in a regression context (table II). The time from first-in-class approval to first follow-on approval in a class was regressed on the

year in which the first-in-class drug was approved.^{5b} The period of analysis was allowed to vary by including or excluding the most recent period in figure 2 and by including or excluding the 1960s (since the data in figure 2 did not suggest an increase in the speed of entry from the 1960s to the 1970s). All of the coefficients are statistically significant and the regressions suggest the speed at which entry to drug classes occurred increased at the rate of approximately 2–4 years per decade.

Table II. Regression results for trends in the time to market entry following a first in class approval

Period of first-in-class approval	Intercept ^a	p-Value	YEARONE ^{a,c}	p-Value	R ²	Estimated decline in time to entry per decade (y)
1960-94	394.7674 (109.7793)	0.0036	-0.1962 (0.0654)	0.0041	0.15	2.0
1960-98 ^b	450.2641 (94.2863)	<0.0001	-0.2243 (0.0475)	<0.0001	0.25	2.2
1970-94	752.4869 (184.8176)	0.0002	-0.3762 (0.0931)	0.0002	0.28	3.8
1970-98	713.3425 (122.0798)	<0.0001	-0.3564 (0.0614)	<0.0001	0.36	3.6

a The coefficient estimate is given with its standard error in parentheses.

b The regression for the 1960-98 period was corrected for estimated first order autocorrelation. Ordinary least squares regressions were used for all other periods.

c The YEARONE variable represents the year in which a first-in-class drug was approved for marketing in the US.

5 Tradenames are used for identification purposes only and do not imply product endorsement.

5b We also examined double logarithmic, semi-logarithmic and polynomial specifications. The linear regression performed as well as some of these forms, and much better than others.

Table III. Average time (y) to market entry for second and third follow-on drugs

Period of US marketing approval for first entrant in class	Time from first to second follow-on drug			Time from second to third follow-on drug		
	mean	median	n	mean	median	n
1960s	13.4	16.1	9	8.0	5.1	5
1970s	5.6	4.2	10	4.9	3.7	5
1980s	3.5	3.4	17	2.2	2.0	13
1990s ^a	2.5	1.7	22	1.4	0.9	9

a First entrant approvals taken through 1998.

We also looked beyond the first follow-on entrant to consider average times to second and third follow-on entrants in a class. The means and medians are shown in table III, and they also indicate that competition increased over time because later entrants tended to enter the market sooner. Analysis of variance results for testing whether there are differences in means across periods for the time to a second follow-on entrant ($F_{3,54} = 15.37$, $p < 0.0001$) and for the time to a third follow-on entrant ($F_{3,28} = 4.30$, $p = 0.0130$) showed highly statistically significant differences. Similarly, the Kruskal-Wallis test results are highly significant for both the time to a second follow-on entrant ($\chi^2(3) = 14.33$, $p = 0.0025$) and the time to a third follow-on entrant ($\chi^2(3) = 9.28$, $p = 0.0258$).

Is First-in-Class the Best-in-Class?

The original approval in a drug class is often referred to as a breakthrough drug. It is thought by some that drugs in the class that follow the breakthrough drug typically do not contribute anything that is clinically noteworthy. We do not attempt here our own analysis of the clinical properties of the compounds in our dataset or a review of the clinical literature on these drugs. However, we can shed some light on the extent to which the first-in-class drug is the best-in-class by examining the therapeutic ratings that the US FDA has assigned to follow-on drugs.⁶

Given that the first-in-class drug is already on the market treating a given condition with an acceptable risk/benefit ratio, it is probably fair to say the US FDA is not generally much disposed to giving a priority rating for a new drug in the same class for what might be fairly modest improvements in convenience, safety profiles or efficacy. Nonetheless, we found that approximately one-third of all follow-on drugs have received a priority rating from the US FDA (figure 3). In addition, 57% of all classes have at least one follow-on drug that received a priority rating. These values likely underestimate the extent to which the best-in-class drug is not the first-in-class, because, as noted above, it is unlikely that relatively minor improvements in an existing chemical or pharmacologic class will result in a priority rating from the US FDA.

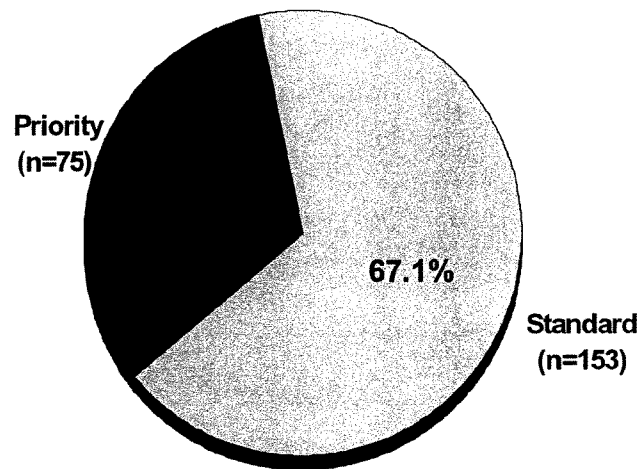
We also found that a substantial number of late entering follow-on drugs had priority ratings. Approximately one in five of the follow-on drugs with priority ratings (16 of 75) were the fourth or later follow-on drug to be approved. Only about one-third of the classes had four or more follow-on drugs. In this smaller set of classes, 48% of the follow-on drugs that had received a priority rating (15 of 31) were the fourth or later follow-on.

Relative Development Histories

Drug development is a very lengthy process. It has been estimated to last 10–15 years, on average, from discovery to marketing approval.¹⁵¹ The length of the development process for many drugs and our data on the speed of entry suggest that much development on what turn out to be follow-on drugs occurs prior to approval of the breakthrough drug. CSDD data on milestones in the development process allows us to quantify the extent to which that is true for various phases of development.

As table IV indicates, for all classes since the early 1980s at least one follow-on drug was synthesized, and at least one had initial pharmacolog-

⁶ The rating system is a management tool for the US FDA that is intended to help it better allocate its resources. It is thus not based on a set of standards that necessarily remains fixed over time. If, suddenly, the submissions from industry were all rated priority or all rated standard, then the rating system would cease to be a useful management tool. It is likely then that to some degree, the rating system is endogenous. It is also the case that some drugs prove to be more useful than originally thought after they have been in widespread use for some time.



Note: Ratings were not available for seven compounds

Fig. 3. Distribution of US FDA ratings of therapeutic significance for follow-on drugs approved in the US from 1960 to 2003 (for therapeutic classes where the first-in-class drug was approved in the US from 1960 to 1998).

ical testing, prior to approval of the first-in-class drug. Similarly, initial clinical testing for at least one follow-on drug in a class occurred prior to approval of the first-in-class drug for all of the classes from the 1990s. A majority of all classes had at least one follow-on drug with a US investigational new drug application (IND) filing prior to approval of the first-in-class drug since the 1980s, with this being the case for 85% or more of the classes since the late 1980s. Finally, nearly all classes from the 1995-8 period had at least one fol-

low-on drug with phase III testing initiated before the first drug in the class was approved.

It is even more instructive to see the shares of follow-on drugs that had reached various development milestones before the first drug in their class was approved.⁷ Table V shows such shares since the 1960s. Nearly all of the follow-on drugs for classes where the first-in-class drug was approved in the 1990s were synthesised, had initial pharmacological testing, and were in clinical testing somewhere in the world before the first-in-class drug was approved. A

Table IV. Share of therapeutic classes with at least one follow-on drug with development phase initiated prior to first-in-class approval by period of first-in-class US approval

Development phase	Percentage (%) initiated prior to first-in-class approval					
	1960s	1970s	1980-4	1985-9	1990-4	1995-8
Synthesis	67 (n = 9)	55 (n = 11)	100 (n = 3)	100 (n = 7)	100 (n = 10)	100 (n = 8)
First pharmacological test	44 (n = 9)	50 (n = 10)	100 (n = 3)	100 (n = 9)	100 (n = 11)	100 (n = 10)
First in humans anywhere	44 (n = 9)	36 (n = 11)	75 (n = 4)	80 (n = 10)	100 (n = 14)	100 (n = 11)
IND filing	44 (n = 9)	27 (n = 11)	60 (n = 5)	85 (n = 13)	87 (n = 15)	100 (n = 16)
Phase II	11 (n = 9)	18 (n = 11)	60 (n = 5)	75 (n = 12)	82 (n = 11)	100 (n = 8)
Phase III	11 (n = 9)	18 (n = 11)	25 (n = 4)	58 (n = 12)	54 (n = 13)	90 (n = 10)

⁷ Censoring could potentially be an issue here for the more recent periods. However, there is likely even less reason to suspect that it would be a material issue here than it is for time to first entry. Not only has a significant amount of time already elapsed, but also in these cases not just one but multiple competitors are already on the market, thereby further reducing the incentive to develop and market additional entrants to the class.

Table V. Share of follow-on drugs with development phase initiated prior to first-in-class approval by period of first-in-class US approval

Development phase	Percentage (%) initiated prior to first-in-class approval					
	1960s	1970s	1980-4	1985-9	1990-4	1995-8
Synthesis	32 (n = 31)	45 (n = 22)	85 (n = 13)	100 (n = 15)	100 (n = 14)	100 (n = 12)
First pharmacological test	26 (n = 31)	43 (n = 21)	83 (n = 12)	75 (n = 20)	100 (n = 17)	93 (n = 15)
First in humans anywhere	17 (n = 42)	27 (n = 26)	50 (n = 16)	67 (n = 30)	92 (n = 24)	96 (n = 23)
IND filing	16 (n = 44)	16 (n = 31)	30 (n = 27)	55 (n = 47)	59 (n = 34)	85 (n = 34)
Phase II	3 (n = 34)	10 (n = 21)	31 (n = 16)	48 (n = 31)	75 (n = 16)	83 (n = 18)
Phase III	3 (n = 35)	13 (n = 24)	11 (n = 19)	39 (n = 31)	45 (n = 22)	67 (n = 21)

majority of the follow-on drugs for the late 1980s and early 1990s classes had INDs filed before the first-in-class approval, and a very sizable majority of the follow-on drugs for the late 1990s classes had an IND filing before the first drug in the class was approved. Later stage clinical testing had also begun for a substantial number of follow-on drugs prior to the first-in-class approval. This occurred for phase II with more than three-quarters of the follow-on drugs for the 1990s classes and for phase III with two-thirds of the follow-on drugs for the late 1990s classes.

These results suggest a development race for drugs in a new therapeutic class, rather than a scenario where firms engage in low risk imitation of a proven breakthrough. This conclusion is further buttressed when we look at the development history of the breakthrough drug and compare it to the development histories of the follow-on drugs in its class. Figure 4 shows that in a substantial number of cases in recent periods, the first drug in a class to reach the US marketplace was not the first to enter clinical testing either in the US or anywhere in the world.⁸

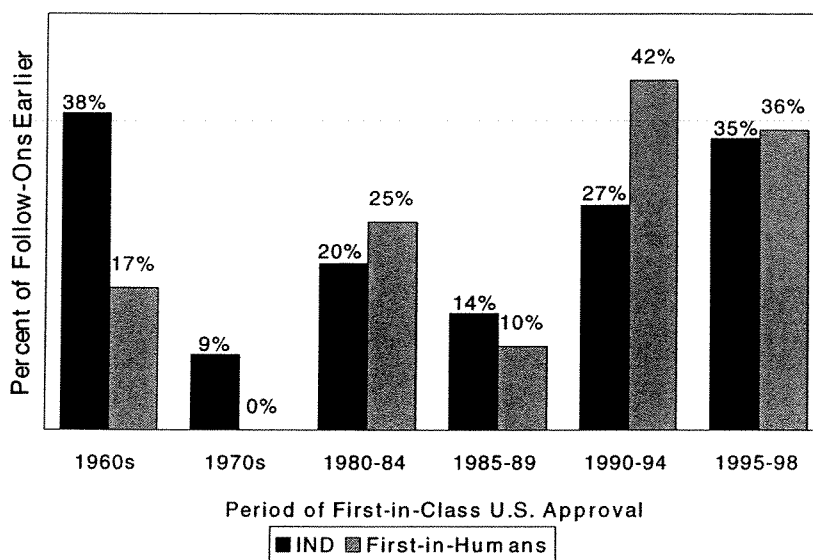


Fig. 4. Percentage of follow-on drugs approved in the US from 1960 to 2003 that were first tested in humans anywhere in the world or had an IND filed prior to that for their first-in-class compound (for therapeutic classes where the first-in-class drug was approved in the US from 1960 to 1998).

⁸ The IND results for the 1960s may be somewhat skewed since the US IND process was not initiated until 1963 after the 1962 Amendments to the *US Federal Food, Drug, and Cosmetic Act of 1938* were enacted. INDs were filed in 1963 for drugs that had already been in clinical testing in the US in prior years. Otherwise, though, the results are conservative since we do not have complete information on the development histories of the drugs.

Discussion

Our evidence on market entry shows that the periods during which first entrants are sheltered from the direct competition that arises when close substitutes in the same drug class are launched have tended to diminish substantially over time. Competition from these therapeutic substitutes can have a substantial impact on firm profits. Lichtenberg and Philipson^[16] argue that what they term 'between-patent' competition can be at least as important a determinant of firm profitability over the product lifecycle as 'within-patent' (i.e. generic) competition. Whether quicker entry has an overall negative impact on incentives to innovate and so on R&D spending depends on the mix of reasons for the increased competition. If the net effect of the factors driving the change is that returns per unit of time pre- and post-entry increase enough, then incentives to innovate can be preserved or even heightened. Thus, a full assessment of the impact of changes in the competitiveness of the pharmaceutical marketplace should depend on an evaluation of the reasons for change.

A number of supply and demand side hypotheses about the pharmaceutical marketplace can help explain the trends that we observed on speed to entry. Technological advances in basic biomedical science can open up opportunities for development for many firms by creating viable leads.^[17] The drug industry's shift away from random screening toward a more targeted rational drug design approach to drug discovery has increased the advantages obtained from connectedness to scientific networks, and so has increased the likelihood that a number of firms will be working on compounds in the same class at more or less the same time. The growth of the biotech sector in the 1980s and 1990s, as well as the increase in R&D spending by traditional pharmaceutical firms is likely related at least in part to the expansion of scientific opportunities. Even when restricting attention to small molecule development, an evaluation of the companies that obtained new drug approvals in the 1990s shows that, despite increased merger activity, output became less concentrated as more firms entered the industry as successful first-time developers of new drugs.^[18]

On the demand side, a number of developments were likely critical factors influencing the speed of competitive entry. US legislation allowing easier generic entry (*Drug Price Competition and Patent Term Restoration Act of 1984*) has increased pressures since the late 1980s to get new drugs in a class to market sooner. The emphasis that managed care placed on constraining health care costs in the 1990s also raised price sensitivities in a growing segment of the pharmaceutical marketplace. This likely had a dual effect on competitive entry. It reduced first-mover advantages for breakthrough drugs and increased the impact that the loss of patent protection on one member of a class has on the sales of other members of the class. In addition, incentives to develop and launch new entrants to a class more quickly depend on the growth of markets. Expenditures on pharmaceuticals in the US grew rapidly in the 1990s. Danzon and Pauly^[19] argue that the growth of prescription drug insurance coverage in the US in the 1990s expanded pharmaceutical markets and accounted for a substantial share of their growth. Grabowski et al.,^[2] for example, found that worldwide lifecycle sales for new drug introductions in the early 1990s were substantially higher in real terms than lifecycle sales for early 1980s introductions. Finally, whether due to supply-side influences such as the growth and rapid diffusion of scientific information or to demand side changes such as increased within-class competitive pressures or expanding markets, a more rapid development of new classes intended to replace older classes that treat the same conditions also likely increased pressures to get additional entrants to an existing class to market sooner.

Criticisms of follow-on drug development have been based primarily on the perception that these drugs offer very little or no additional value. A full assessment of the social rate of return to follow-on drug development must account for any clinical and economic benefits that it engenders. Drugs in the same class can differ in their side effect and efficacy profiles, adverse drug reactions, drug-drug interactions, dosing schedules, and delivery systems.^[3] It is also well known that clini-

cal responses to different drugs in a class can vary significantly by individual. Physicians traditionally have adopted a trial and error process for finding a drug in a class that works well for an individual patient. Advances in pharmacogenomics may one day allow physicians to routinely make *a priori* optimal drug choices at the individual level. Having a range of therapeutic options available is therefore clinically advantageous.

Multiple drugs in a class also generate some degree of price competition.¹⁴⁻⁷¹ For example, DiMasi¹⁵ found that for 20 new entrants to existing classes that were introduced in the US from 1995 to 1999, 80% were launched at a discount to the price leader and 65% were launched at a discount to the average price for the class (actual transaction prices for a very large pharmacy benefit manager were used). The average percentage change was a 26% discount relative to the price leader and a 14% discount relative to the class average. The presence of multiple drugs in a class also gives managed care leverage in extracting rebates for drugs in the class. These additional cost reductions were not included in the data obtained for the study.

Finally, we should also consider what might be called a 'system benefit' to follow-on drug development. Incremental innovations lead to a stream of improvements that over time can yield substantial benefits. This phenomenon is not unique to the pharmaceutical industry. The social value of the cumulative effects of incremental innovations can often greatly exceed those of the original breakthroughs.¹²⁰

It is difficult to quantify the impacts of all of these effects for drugs as a whole, but some recent research has been instructive. In a series of papers, Lichtenberg²¹⁻²³ has demonstrated that, in aggregate, newer drugs (in terms of time on the market)

appear to be associated with increased longevity and reductions in medical expenditures that substantially outweigh the drugs' added costs. These analyses do not distinguish between first-in-class and follow-on drugs, but given our data on the development histories of first-in-class and follow-on drugs, such distinctions may, for the most part, be meaningless. The prevailing drug development paradigm is one in which a number of firms will pursue investigational drugs with similar chemical structures or the same mechanism of action before any drug in the class obtains regulatory marketing approval. One of the drugs will win the race, and then be viewed as the breakthrough drug for the class. Thus, the typical drug development model is one in which firms are, in effect, engaged in development races, as opposed to one that is characterized by after-the-fact imitation.⁹

While the standard drug development paradigm appears to have yielded substantial net benefits, one can still consider whether improvements can be made through policy initiatives.

One policy proposal to deal with what its proponents perceive to be a problem of excessive me-too drug research has been increasingly propounded recently in a variety of fora, such as medical journal editorials, magazine commentaries, newspaper editorials and op-ed pieces.¹²⁴⁻²⁷¹ Under this proposal, manufacturers would be required to conduct head-to-head randomised controlled comparator clinical trials where the investigational drug is compared to what is thought to be the best-in-class prior-approved drug before regulatory authorities are allowed to grant the new drug marketing approval.¹⁰ Supply side policies such as these that seek to place hurdles on manufacturers so that they will not find it worthwhile to develop follow-on drugs are highly problematic for a number of reasons.

9 In light of growing cost containment pressures, industry managers have suggested to us that firms are increasingly pursuing a best-in-class strategy, in which winning the race is not as important as developing a drug with a particularly attractive clinical or economic profile.

10 For example, Relman and Angell²⁵ state: "FDA regulations should be changed to require that new drug applications include evidence not only of the safety and the efficacy of a new drug, but also of the drug's effectiveness in relation to existing products of the same type. Approval should depend in part on whether the new drug adds something useful in terms of greater effectiveness, greater safety, fewer side effects, or substantially greater convenience... That policy change alone would dramatically improve the medical value of new prescription drugs, since drug companies would have no incentive to turn out me-too drugs and would have to shift their R&D emphasis to finding more innovative ones."

Not all drugs that are chemically similar will necessarily have an acceptable benefit-risk ratio. Some might be quite toxic or not effective at all. Investigational drugs can fail even for classes where there are successes. It is even occasionally possible that a drug that meets existing regulatory hurdles will later turn out to have problems that result in it being withdrawn. The more firms working in the same area because science has led them there, the more likely that one or more will find drugs in a class with acceptable benefit-risk ratios. If we pursue policies that substantially reduce the number of organisations independently pursuing a new area, we may end up with nothing approved in that area.

The basis for much of what is wrong with a registration hurdle policy for follow-on drugs derives from the fact that, as our results indicate, much follow-on development occurs before there are any drugs approved in the class. If a manufacturer has to prove that its drug is superior in some attribute and noninferior in all others to every drug in the class that is already on the market before the registration authority is allowed to approve the drug, then the cost of getting drugs to market can be increased substantially.¹¹ What is probably most critical, though, is that, given the way that follow-on drug development often proceeds, this policy will greatly increase uncertainty. A firm can start a development program in one way, only to find partway through it that it has to change course and do comprehensive head-to-head comparisons with a drug that happened to reach the marketplace before its drug. This can even happen more than once in development. That is, the firm would be required to hit a moving target. Such a policy may well increase uncertainty about future costs and the likelihood of approval to the point that no firm is willing to risk development in some areas. This can have additional negative derivative effects. For example, a study by Henderson and Cockburn^[29] provides evidence that pharmaceutical research has valuable knowledge spillover effects within and across firms. Thus, a chain of beneficial events can be interrupted.

On the demand side, policies that some have considered for European markets have included not reimbursing follow-on drugs at all, or reimbursing them at significant discounts.^[10] The flip-side proposal is to reward the development of a drug that is determined to be innovative with a price premium. Proponents of such a policy might argue that this just mimics what the market does. But it likely would not mimic it perfectly, or perhaps even well. It seems that a more reasonable demand-side approach is to encourage or fund health economic analyses and disease management programs for drugs already in the marketplace, so that consumers, physicians, and payers can make more informed decisions on what represents true value for money. Manufacturers will automatically factor in the preferences of informed consumers and their agents (physicians) when making their decisions to initiate or continue development projects. To some extent this already occurs given the policies, programs and practices of some national reimbursement authorities and managed care. A focus on value for money in the US is also likely to increase over time, as the new Medicare law (*Medicare Prescription Drug, Improvement and Modernization Act of 2003*) is implemented.^[30]

New drug development is a complex, risky process and manufacturer decisions about which avenues to pursue and how to pursue them are subject to numerous scientific and economic factors. The data that we have analysed, however, do strongly indicate that distinctions commonly drawn between the development of breakthrough and me-too drugs in a therapeutic class are usually not very meaningful or useful. We hope that such analyses will better inform policy discussions that depend on assumptions about the nature of therapeutic class competition.

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11 The ALLHAT antihypertensive study was a comparative efficacy trial of certain drugs in a number of antihypertensive classes. This one study took 8 years to complete and cost approximately \$US125 million.^[28]

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