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Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

20 YEARS IMPACT REPORT

ANALYSIS & INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

CNS drugs take 20% longer to develop and to approve vs. non-CNS drugs

CNS share of all U.S. approvals has remained steady at 10%-12% since the 1980s

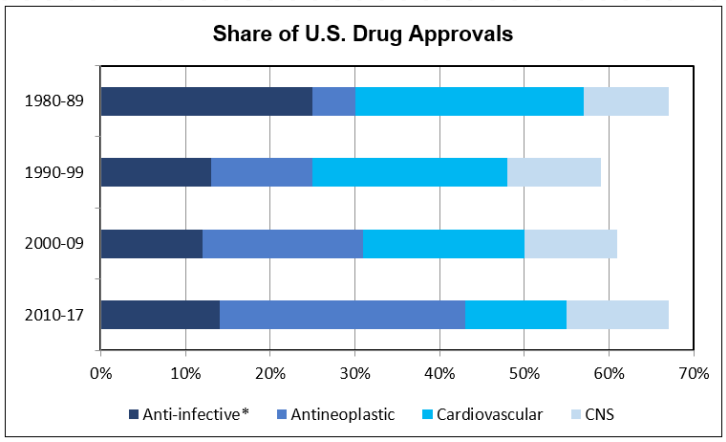
- Mean clinical development time was 36% longer for CNS compared to non-CNS approvals in 2000-05, 41% longer for 2006-11, but 6% shorter for 2012-17.
- During 2000-17, mean approval phase time for CNS drugs was 38% longer than for non-CNS drugs.
- Mean total phase time (sum of clinical and approval phase lengths) for CNS drugs ranged from 8.2 years for anti-psychotics to 12.6 years for multiple sclerosis treatments.
- The most prevalent disease areas among the 57 CNS drug approvals during 2000-17 were epilepsy and psychosis, each with 10 new drug approvals.
- During 2000-17, 28.1% of CNS drugs, vs. 51.4% of non-CNS drugs, received a priority rating from the U.S. Food and Drug Administration (FDA) and 22.8%, vs. 33.1% of non-CNS drugs, obtained an orphan drug designation.

Due to the complex nature of the conditions they are developed to treat, central nervous system—or CNS—drugs face greater development challenges compared to non-CNS drugs, due in large part to our poor understanding of the underlying pathophysiology of many of the disorders, as well as difficulty identifying and measuring appropriate clinical endpoints. As a result, CNS drugs typically spend more time in clinical development and regulatory review, and they experience lower approval rates, compared to non-CNS drugs. Despite these challenges, CNS drug approvals by the FDA as a share of all drug approvals not only has remained relatively steady over nearly four decades, but has increased slightly over that time.

The opportunity and challenge for drug developers is clear. Opportunity arises from the estimate that CNS disorders will constitute nearly 15% of the global disease burden by 2020. The challenges are to decrease development time and increase success rates without sacrificing safety, while simultaneously reigning in overall development costs. This report summarizes a recent Tufts CSDD analysis of 509 drugs and biologics that received FDA approval from 2000 to 2017.

Since the 1980s, CNS share of new drug approvals in the U.S. has remained stable at 10%-12%

New drug and biologics approvals for the four largest therapeutic classes



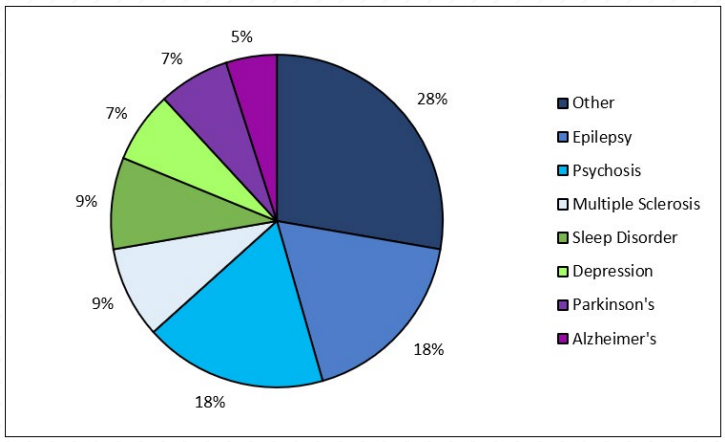
* Anti-infective excludes AIDS antivirals

Source: Tufts Center for the Study of Drug Development

- Despite lengthier than average clinical development and approval phase times, since the 1980s, the CNS share of new drug approvals in the U.S. by decade has ranged from 1-in-10 to 1-in-8.
- The relative share of new cardiovascular drug approvals has declined steadily, from 27% in the 1980s to 12% in 2010-17. The anti-infective share of approvals declined from 25% during the 1980s to 12% during 2000-09, but increased to 14% during 2010-17.
- Over the same period, approvals of oncology drugs grew substantially as a share of all approvals, from 5% in the 1980s to 29% in 2010-17.

The CNS therapeutic class encompasses therapies for a diverse set of diseases

Distribution of U.S. CNS approvals, 2000-2017 by indication (n=57)

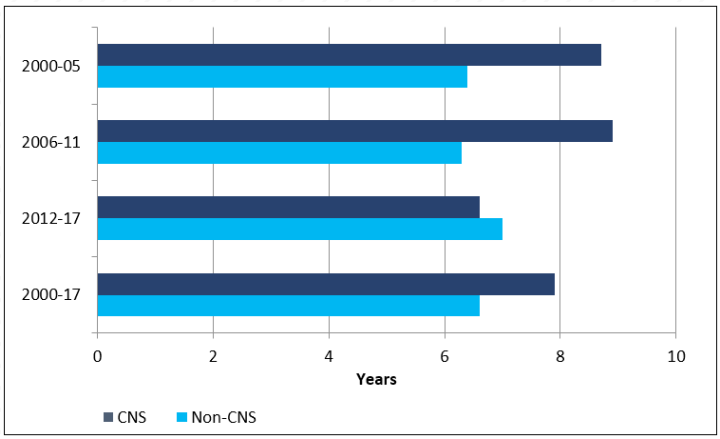


Source: Tufts Center for the Study of Drug Development

- The most prevalent disease areas among the 57 CNS drug approvals during 2000-17 were epilepsy and psychosis, each with 10 drug approvals.
- From 2000-08 to 2009-17, approval shares for three disease areas increased in prevalence: multiple sclerosis approvals rose from 0% to 15%; psychosis approvals increased from 13% to 21%; and epilepsy approvals increased from 17% to 18%.
- Four disease areas decreased in prevalence from the first half of the study period to the second half. The Alzheimer's share of approvals decreased from 13% to 0%; the Parkinson's share dropped from 13% to 3%; the sleep disorder share fell from 13% to 6%; and the depression share decreased from 8% to 6%.

Clinical development time for CNS drugs was 20% longer compared to non-CNS drugs

Mean clinical phase lengths for CNS vs. non-CNS drugs

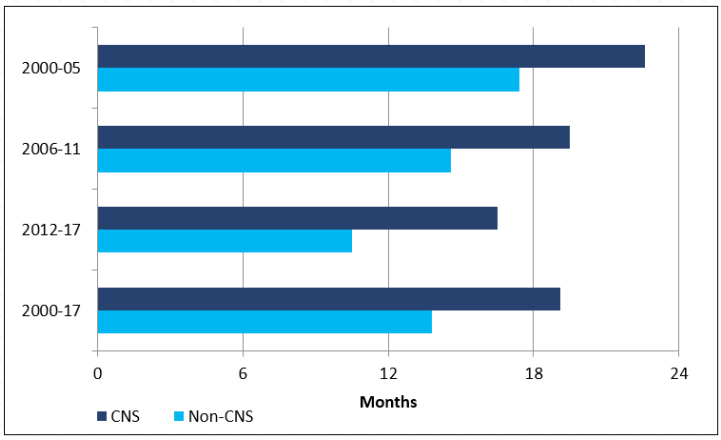


Source: Tufts Center for the Study of Drug Development

- Mean clinical development time for CNS approvals was 36% longer (2.3 years) than for non-CNS drugs in 2000-05, 41% longer (2.6 years) in 2006-11, but 6% shorter (0.4 years) in 2012-17.
- Similarly, median clinical development time was 31% longer (1.6 years) for CNS approvals in 2000-05, 16% longer (0.9 years) in 2006-11, and 5% shorter (0.3 years) in 2012-17.
- Mean clinical development time for CNS drugs decreased from a high of 8.9 years in 2006-11 to a low of 6.6 years in 2012-17, compared to a low of 6.3 years in 2006-11 and a high of 7.0 years in 2012-17 for non-CNS drugs.

Regulatory approval phase time for CNS drugs was 38% longer vs. non-CNS drugs

Mean approval phase lengths for CNS vs. non-CNS drugs

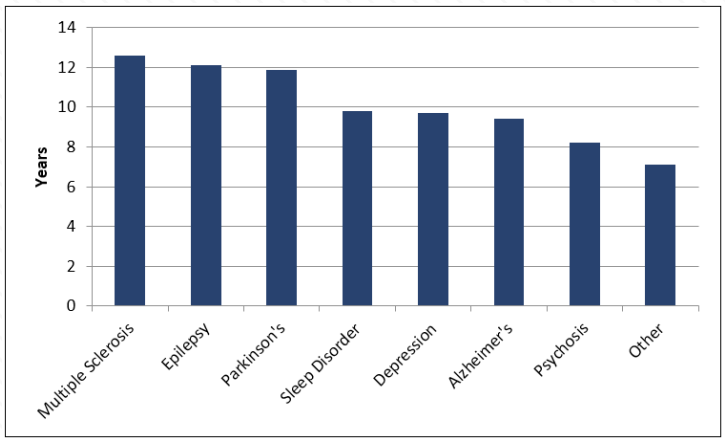


Source: Tufts Center for the Study of Drug Development

- During 2000-17, mean approval phase time for CNS drugs was 19.1 months, or 38%, longer than for non-CNS drugs.
- Mean approval phase time was 30% higher (5.2 months) for CNS compared to non-CNS approvals during 2000-05, 34% higher (4.9 months) for 2006-11 approvals, and 57% higher (6.0 months) for 2012-17 approvals.
- Mean CNS drug approval phase time decreased from a high of 22.6 months in 2000-05 to a low of 16.5 months in 2012-17, while mean approval phase time for non-CNS approvals decreased from a high of 17.4 months during 2000-05 to a low of 10.5 months in 2012-17. For approvals as whole, mean approval phase time was 17.9 months for 2000-05, 14.6 months for 2006-11, and 10.5 months for 2012-17.

Clinical development and approval phase times for CNS drugs varied widely by indication

U.S. total clinical plus approval phase times by CNS indication



Source: Tufts Center for the Study of Drug Development

- Mean total phase time (sum of clinical and approval phase lengths) for specific CNS diseases during 2000-17 ranged from 8.2 years for anti-psychotics to 12.6 years for multiple sclerosis, a 54% difference.
- The longest mean clinical development time for specific disease states (11.6 years for multiple sclerosis) was 73% higher than the shortest mean clinical development time (6.7 years for anti-psychotics).
- While multiple sclerosis approvals had the longest clinical development and total phases, they had the lowest average approval phase at 11.4 months, which was 50% lower than the highest average approval phase (22.6 months for Parkinson's approvals).

Since 2000, relatively few new CNS approvals received a priority rating or had orphan drug status

Approved CNS and non-CNS drugs by FDA priority rating and orphan drug designation

	Approved Priority Review Drugs		Approved Orphan Drug	
	CNS	Non-CNS	CNS	Non-CNS
2000-05	18.8%	46.3%	18.8%	24.3%
2006-11	22.2%	50.0%	16.7%	30.2%
2012-17	39.1%	56.2%	30.4%	42.2%
2000-17	28.1%	51.4%	22.8%	33.1%

Source: Tufts Center for the Study of Drug Development

- During 2000-17, 28.1% of CNS drug approvals received a priority rating from the FDA, compared to 51.4% for all non-CNS drugs.
- The share of CNS approvals that received a priority rating more than doubled over the study period, from 18.8% for 2000-05 to 39.1% for 2012-17. The share of non-CNS approvals with a priority rating also grew, but at a much lower rate (a 21% increase) from 2000-05 to 2012-17.
- During 2000-17, 22.8% of CNS approvals obtained an orphan drug designation for the original indication approved, compared to 33.1% for non-CNS approvals. The share of approvals with an orphan drug designation grew over the study period for CNS and non-CNS compounds, but at a lower rate for CNS compounds (62% vs. 74% from 2000-05 to 2012-17).

About this study

The findings summarized in this report were based on data on 509 new drugs and biologics, obtained from FDA and Tufts CSDD databases of approved drugs and biologics. For ease of exposition, this report refers to both small-molecule drugs and large-molecule biologics as drugs. Fifty-seven of the 509 drugs were in the CNS therapeutic class. A Tufts CSDD database of compounds approved for the first time in the United States from 2000 to 2017 was used to compare the percentage of approved drugs with priority ratings assigned by the FDA for CNS versus non-CNS drugs, the share of original approvals with an orphan drug designation for CNS versus non-CNS drugs, differences in mean clinical phase and approval phase lengths for CNS versus non-CNS drugs, and trends in the share of all new compound approvals accounted for by CNS and other therapeutic classes.

Joseph A. DiMasi, Ph.D., Director of Economic Analysis and Research Associate Professor at the Tufts Center for the Study of Drug Development, conducted the study.

Definition of terms

Approval phase time — The time from original NDA/BLA submission to NDA/BLA approval by the FDA.

Clinical phase time — The time from investigational new drug application (IND) filing to NDA/BLA submission.

IND — Investigational new drug application. Notification by a drug sponsor to the FDA of its intent to conduct clinical studies.

NDA/BLA — New drug application/biologics license application. An application to the FDA for a license to market a new drug or biological product, respectively.

Orphan drug — Drugs developed for rare diseases and conditions, which, in the U.S., affect fewer than 200,000 people, or, in the European Union, affect 5 per 10,000 people or fewer. Because sales of orphan drugs are likely to be small compared to their development costs, pharmaceutical companies are awarded exclusive rights to market these medicines for a period of time as an incentive to develop them.

Priority drugs — Priority new molecular entities (NMEs) are those considered by the FDA to offer high therapeutic value and are earmarked for expedited review

About the Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University provides data-driven analysis and strategic insight to help drug developers, regulators, and policy makers improve the efficiency and productivity of pharmaceutical R&D. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical development issues, offers professional development courses, and hosts symposia, workshops, and public forums.

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