The impact of new (orphan) drug approvals on premature mortality from rare diseases in the U.S. and France, 1999-2007

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Abstract

This paper investigates the impact of the introduction of new orphan drugs on premature mortality from rare diseases using longitudinal, disease-level data obtained from a number of major databases. The analysis is performed using data from two countries: the U.S. (during the period 1999-2006) and France (during the period 2000-2007). For both countries, we estimate models using two alternative definitions of premature mortality, several alternative criteria for inclusion in the set of rare diseases, and several values of the potential lag between new drug approvals and premature mortality reduction.

Both the U.S. and French estimates indicate that, overall, premature mortality from rare diseases is unrelated to the cumulative number of drugs approved 0-2 years earlier, but is significantly inversely related to the cumulative number of drugs approved 3-4 years earlier. This delay is not surprising, since most patients probably don't have access to a drug until several years after it has been launched. Although the estimates for the two countries are qualitatively similar, the estimated magnitudes of the U.S. coefficients are about four times as large as the magnitudes of the French coefficients. This may be partly due to greater errors in measuring dates of drug introduction in France.

Our estimates indicate that, in the U.S., potential years of life lost to rare diseases before age 65 (PYLL65) declined at an average annual rate of 3.3%, and that, in the absence of lagged new drug approvals, PYLL65 would have *increased* at a rate of 0.9%. Since the U.S. population age 0-64 was increasing at the rate of 1.0% per year, this means that PYLL65 per person under 65 would have remained approximately constant. The reduction in the U.S. growth rate of PYLL65 attributable to lagged new drug approvals was 4.2%.

In France, PYLL65 declined at an average annual rate of 1.8%. The estimates imply that, in the absence of lagged new drug approvals, it would have declined at a rate of 0.6%. The reduction in the French growth rate of PYLL65 attributable to lagged new drug approvals was 1.1%.

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The U.S. government, the European Union, and the governments of Japan and Australia have all enacted legislation to encourage pharmaceutical companies to develop drugs for diseases that have a small market. The Orphan Drug Act, passed in the United States in 1983, allows companies that develop drugs for disorders affecting fewer than 200,000 Americans to sell them without competition for seven years, and also allows them to get clinical trial tax incentives. The European Union has enacted similar legislation, Regulation (EC) No 141/2000.[1] Under the ODA and EU legislation, many orphan drugs have been developed, including drugs to treat glioma, multiple myeloma, cystic fibrosis, phenylketonuria, snake venom poisoning, and idiopathic thrombocytopenic purpura. In the USA, from January 1983 to June 2004, a total of 1,129 different orphan drug designations have been granted by the Office of Orphan Products Development (OOPD) and 249 orphan drugs have received marketing authorization. In contrast, the decade prior to 1983 saw fewer than ten such products come to market.

This paper will investigate the impact of the introduction of new orphan drugs on premature mortality from rare diseases using longitudinal, disease-level data obtained from a number of major databases. The analysis will be performed using data from two countries: the U.S. (using annual data during the period 1999-2006) and France (using annual data during the period 2000-2007).

In the next section, we describe the econometric model we will estimate. Data sources and descriptive statistics are discussed in Section II. Empirical results are presented in Section III. The final section contains a summary and conclusions.

I. Econometric model

To investigate the impact of the introduction of new orphan drugs on premature mortality from rare diseases, we will estimate models of the following form:

$$\begin{aligned} \ln(MORT_{it}) &= \beta \ln(DRUG\_STOCK_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{it} \\ &= \beta \ln\left(\sum_d IND_{di}\, APP_{d,t-k}\right) + \alpha_i + \delta_t + \varepsilon_{it} \qquad (1) \\ &\qquad (i = 1,\ldots, I;\ t = 1999,\ldots,2007) \end{aligned}$$

[1] The EU's definition of an orphan condition is broader than that of the USA, in that it also covers some tropical diseases that are primarily found in developing nations.

where

$MORT_{it}$ = an indicator of premature mortality from disease i in year t

$DRUG\_STOCK_{i,t-k} = \sum_d IND_{di}\ APP_{d,t-k}$

= the cumulative number of drugs approved by the beginning of year t-k that are used to treat disease i

IND_{di} = 1 if drug d is used to treat (indicated for) disease i

= 0 if drug d is not used to treat (indicated for) disease i

$APP_{d,t-k}$ = 1 if drug d has been approved by the beginning of year t-k

= 0 if drug d has not been approved by the beginning of year t-k

α_i = a fixed effect for disease i

δ_t = a fixed effect for year t

ε_{it} = a disturbance

In his model of endogenous technological change, Romer[2] hypothesized an aggregate production function such that an economy's output depends on the "stock of ideas" that have previously been developed, as well as on the economy's endowments of labor and capital. Eq. (1) may be considered a health production function, in which the mortality rate is an (inverse) indicator of health output or outcomes, and the cumulative number of drugs approved (DRUG_STOCK) is analogous to the stock of ideas.

Since the model includes disease and year fixed effects, it is a difference-in-differences model. Negative and significant estimates of β would indicate that, *ceteris paribus*, diseases with above-average increases in the lagged cumulative number of drugs approved had above-average declines in premature mortality. All models will be estimated via weighted least-squares, using appropriate weights. Clustered (within disease) standard errors will be reported.

We will analyze two measures of premature mortality: the number of potential years of life lost before ages 65 and 75:

$PYLL65_{it} = \Sigma_a \max(65 - a, 0)\ N\_DEATH_{ait}$

$PYLL75_{it} = \Sigma_a \max(75 - a, 0)\ N\_DEATH_{ait}$

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[2] Romer, Paul (1990), "Endogenous technical change," *Journal of Political Economy* 98, S71-S102.

where N_DEATH_{ait} is the number of deaths at age a from disease i in year t.

It would be ideal to control for changes in disease incidence or prevalence. For example, we would prefer to estimate the following model:

$$\ln(MORT_{it} / PREV_{it}) = \beta \ln(DRUG\_STOCK_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{it}$$

or this more general model:

$$\ln(MORT_{it}) = \beta \ln(DRUG\_STOCK_{i,t-k}) + \gamma \ln(PREV_{it}) + \alpha_i + \delta_t + \varepsilon_{it}$$

where $PREV_{it}$ = the prevalence of (number of people at risk to die from) disease i at the beginning of year t. If the growth in the stock of drugs were correlated across diseases with the growth in prevalence, failure to control for prevalence would cause estimates of β in eq. (1) to be biased. On theoretical grounds, one might expect the correlation across diseases between the growth in the stock of drugs and the growth in prevalence to be positive, e. g. because pharmaceutical companies are likely to develop more drugs for diseases with the largest (exogenous) increases in prevalence. If this is the case, failure to control for prevalence would cause estimates of β to be biased towards zero: the effect of pharmaceutical innovation on mortality would be underestimated.

Orphanet publishes some data on the prevalence of rare diseases,[3] but the data they publish are cross-sectional, rather than longitudinal. Longitudinal, disease-level U.S. data on *incidence* (the number of newly diagnosed cases) are available for a subset of orphan diseases: different types of cancer. These data are produced by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, an authoritative source of information on cancer incidence and survival in the United States.[4] We used these data to investigate whether the growth in the stock of

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[3] "Prevalence of rare diseases: Bibliographic data," Orphanet Report Series, *Rare Diseases collection*, May 2010, Number 1 : Listed in alphabetical order of diseases, http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

[4] The NCI's Cancer Prevalence Database (part of its Cancer Query System, http://srab.cancer.gov/prevalence/canques.html) provides data on cancer prevalence, by cancer site, but only for a single year (2007). The NCI's SEER*Stat statistical software provides longitudinal data on (limited-duration) prevalence, but not by ICD10 code.

drugs is correlated, across cancer sites (e.g. acute myelomonocytic leukemia or hepatoblastoma) with growth in the cumulative number of orphan drugs. We estimated the following model, using annual data on 34 cancer sites during the period 1975-2006:

$$\ln(\text{DRUG\_STOCK}_{it}) = \pi \ln(\text{INC}_{it}) + \alpha_i + \delta_t + \varepsilon_{it}$$

where INC_{it} = the number of people diagnosed with cancer at site i in SEER 9 registries in year t. The estimate of π was far from statistically significant: estimate = -.087, Z = 1.19, p-value = 0.24. There was not a significant correlation across cancer sites between growth in the stock of drugs and growth in incidence. This suggests that not controlling for changes in prevalence or incidence should result in little or no bias in our estimates of β.

II. Data sources and descriptive statistics

Estimation of eq. (1) requires data on three variables: IND_{di} (which indicates whether drug d is used to treat (indicated for) disease i); $\text{APP}_{d,t-k}$ (which indicates whether drug d has been approved (in country c) by year t-k); and MORT_{it} (a measure of premature mortality (in country c) from disease i in year t).

Data on IND_{di}. Data on IND_{di} were obtained from Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), a consortium of European partners which maintains a database of information on rare diseases and orphan drugs. The list of orphan drugs in the Orphanet database includes all medicinal products that have received an orphan designation, as well as drugs without an orphan designation that have a marketing authorization and a specific indication for a rare disease. The lists are established using the information available at the relevant governmental agencies, and information provided by sponsors of medicinal products with an orphan designation when the product is not yet marketed.

A significant advantage of the Orphanet database is that drug indications have been carefully coded using ICD10 codes.[5] However, many orphan diseases do not have ICD10 codes that uniquely correspond to them. In that case, Orphanet assigns the ICD10 code of the broader disease category that includes the orphan disease. This is illustrated in Table 1, which lists top Orphanet diseases, ranked by the average annual number of U.S. deaths during the period 1999-2006 attributed to the ICD10 codes assigned by Orphanet to those diseases. The first disease listed is "Lung cancer, small cell." There is no specific code for small-cell lung cancer in the ICD10 classification, so Orphanet assigned the code C34.9 (which the World Health Organization (WHO) refers to as "Malignant neoplasm of bronchus or lung, unspecified") to this disease. But this is clearly not a rare disease: according to the Center for Disease Control's Compressed Mortality database (http://wonder.cdc.gov/controller/datarequest/D43) the average annual number of deaths from ICD10 code C34.9 during the period 1999-2006 was 155,838.

Similarly, the ICD10 code assigned by Orphanet to the disease "Colon cancer, familial nonpolyposis" was C18.9, which the World Health Organization (WHO) refers to as "Malignant neoplasm of colon, unspecified"; the average annual number of deaths from ICD10 code C18.9 during the period 1999-2006 was 44,841. And Orphanet assigned three different diseases ("Teratoma," "Ovarian germ cell malignant tumor," and "Ovarian tumor of sex cord-stromal origin") to the *same* ICD10 code—C56 (referred to by WHO as "Malignant neoplasm of ovary")—since more specific ICD10 codes do not exist.

Since there is not a distinct ICD10 code for every rare disease, in some cases the ICD10 codes assigned by Orphanet include a broader set of diseases, some of which are not rare. In these cases, the list of drugs contained in the Orphanet database is likely to be quite incomplete, and estimates of DRUG_STOCK would be subject to substantial measurement error. We will attempt to deal with this problem by restricting the sample to diseases with ICD10 codes that are unlikely to include non-rare diseases. In particular, we will exclude diseases that Orphanet has assigned ICD10 codes for which the average annual number of deaths is "large." Clearly, we should exclude "Lung cancer, small

[5] Other data sources, such as the FDA's List of Orphan Designations and Approvals (http://www.fda.gov/orphan/designat/list.htm), do not code rare diseases using ICD9 or ICD10 codes.

cell," because the average annual number of deaths from the ICD10 code assigned to this disease by Orphanet (C34.9) during the period 1999-2006 was 155,838. The question is, how large is too large to warrant inclusion in the sample?

In the U.S., a disease is considered rare if it afflicts fewer than 200,000 (about 1 in 1500) Americans. The crude mortality rate in the U.S. during the period 1999-2006 was 837.3 deaths per 100,000 population. Therefore, if the mortality rate of people with rare diseases were the same as the mortality rate of the general population, then a disease might be considered rare if it caused less than 1675 (= 2 * 837.3) deaths per year. However, this is surely too low a threshold, because people with rare diseases are subject to higher mortality rates than other people. Lichtenberg and Waldfogel (2009) demonstrated that the less prevalent a disease, the lower is mean age at death from that disease.[6] Further evidence is shown in Table 2, which contains data on cancer prevalence, number of cancer deaths, and the conditional mortality rate (number of deaths/prevalence), by cancer site, for the U.S. in 2007. The table contains data on 24 cancer sites. Eleven of these cancers would be considered "rare" (estimated prevalence below 200,000). The (weighted) average conditional mortality rate of the eleven rare cancers is over three times as high as the (weighted) average conditional mortality rate of the thirteen non-rare cancers:[7]

	Conditional mortality rate (number of deaths/prevalence)	Total prevalence
11 rare cancers (prev < 200K)	11.6%	1,031,710
13 common cancers (prev > 200K)	3.7%	10,162,919

We will estimate eq. (1) using three different threshold values of the maximum average annual number of deaths in each country (the U.S. and France). In the U.S., the three threshold values are 3200, 4800, and 6400 deaths per year. These are the maximum number of deaths from diseases with lower than 1/1500 prevalence that would occur if

[6] Frank R. Lichtenberg and Joel Waldfogel, *Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act* 15 Mich. Telecomm. Tech. L. Rev. 335 (2009), *available at* http://www.mttlr.org/volfifteen/lichtenberg&waldfogel.pdf

[7] In some cases, a disease has low prevalence *because* people who have the disease are subject to a high mortality rate.

mortality rates from these diseases were about 2 times, 3 times, and 4 times, respectively, the average mortality rate of Americans. In France, the three threshold values are 600, 900, and 1200 deaths per year, because the population of France is about one fifth that of the U.S.

Data on $APP_{d,t-k}$. Information about the date of market introduction of drugs (hence $APP_{d,t-k}$) in the U.S. was obtained from the FDA's Drugs@FDA database (http://www.fda.gov/cder/drugsatfda/datafiles/default.htm).[8]

Information about the date of market introduction of drugs in France was obtained from the Répertoire des Spécialités Pharmaceutiques of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS; http://afssaps.sante.fr/htm/1/amm/amm0.htm). These data do not appear to be completely reliable. For a subset of drugs, i.e. cancer drugs, we have data from another source--the Groupement pour l 'Elaboration et la Réalisation de Statistiques (GERS, http://www.gie-gers.fr/index.php3)--on the year each drug was first commercialized in France. Figure 1 shows the relationship across drugs between the AFSSAPS and GERS estimates of the year in which the drug was introduced in France. While there is a strong positive correlation between the two estimates (coefficient of correlation = .70), there are some large discrepancies. Random errors in $APP_{d,t-k}$ are likely to bias our estimates of the effect of new drug introductions on mortality (β) towards zero.

Mortality data. Data on every death that has occurred in the U.S. were obtained from the CDC's Multiple Cause-of-Death Public-Use Data Files (http://www.cdc.gov/nchs/products/elec_prods/subject/mortmcd.htm). The data are based on information abstracted from death certificates filed in vital statistics offices of each State and the District of Columbia. Causes of death were coded according to the International Classification of Diseases, Tenth Revision, during 1999-2006. These data were used to calculated $PYLL65_{it}$ and $PYLL75_{it}$.

Data on all deaths that occurred in France, by ICD10 code, age group, and year, during the period 2000-2007 were obtained from the *Centre d'épidémiologie sur les causes médicales de décès* (CEPIDC, http://www.cepidc.vesinet.inserm.fr/).

[8] Many of the drugs included in the Orphanet database have not been approved in the U.S. (or other countries). Only about half of the drugs included in the Orphanet database that have been approved in the U.S. are classified as orphan drugs by the FDA.

Descriptive statistics. Descriptive statistics for the U.S. sample of diseases with fewer than 6400 U.S. deaths/year are shown in Table 3. The sample includes just over 100 diseases, which accounted for a total of about 38 thousand deaths (about 1.6% of all U.S. deaths), 232 thousand life-years lost before age 65, and 421 thousand life-years lost before age 75 per year. The U.S. population (below both age 65 and age 75) was increasing at the rate of 1.0% per year during this period. The number of life-years lost to these diseases before age 65 per 100,000 population age 0-64 declined at a 1.9% annual rate, and the number of life-years lost to these diseases before age 75 per 100,000 population age 0-74 declined at a 0.8% annual rate. The cumulative number of Orphanet drugs approved 3 years before increased from 119 in 1999 to 204 in 2006.[9]

Appendix Table 1 contains a list of drugs, in order of FDA approval year, for each disease with fewer than 6400 U.S. deaths/year.

III. Empirical results

Estimates of the effect of the cumulative number of drugs approved on premature mortality from rare diseases are shown in Table 4. Each estimate in the table comes from a separate model. Each model includes fixed disease effects and fixed year effects. We estimated 72 (=2 * 2 * 3 * 6) models: one for each country (U.S. or France), premature mortality measure (PYLL65 or PYLL75), maximum average annual number of deaths value (3200, 4800, and 6400 for the U.S.; 600, 900, and 1200 for France), and DRUG_STOCK lag (0-5 years). Each model was estimated via weighted least squares, where the weight was the mean of the disease's premature mortality measure during the entire sample period, e. g. $PYLL65_{i.} = (1/8) * \sum_t PYLL65_{it}$.

Estimates for the U.S., 1999-2006. In the first set of estimates (Set 1), we estimate the model using U.S. data, the premature mortality measure is the number of potential years of life lost before age 65, and the maximum average annual number of deaths is 3200. The coefficient on the contemporaneous drug stock is not statistically significant, which is not surprising, since most patients probably don't have access to a drug during the year

[9] In this calculation, if the same drug is used for N diseases, it is counted N times.

in which it is approved by the FDA.[10] However the coefficients on the DRUG_STOCK 1, 3, and 4 years earlier are negative and highly significant (although the coefficient on the DRUG_STOCK 2 years earlier is not). This signifies that premature mortality from a rare disease tends to decline 3 to 4 years after new drugs to treat the disease have been approved. The elasticity of premature mortality with respect to the cumulative stock of drugs 3-4 years earlier is about -.85.

The next two sets of estimates (Sets 2 and 3) show that increasing the maximum average annual number of deaths value from 3200 to either 4800 or 6400 has very little effect on the estimates. The next three sets of estimates (Sets 4, 5, and 6) show that changing the premature mortality measure from the number of potential years of life lost before age 65 to the number of potential years of life lost before age 75 also has very little effect on the estimates.

Estimates for France, 2000-2007. The remaining sets of estimates (Sets 7-12) examine the effect of the cumulative number of drugs approved on premature mortality from rare diseases in France. In Set 7, the premature mortality measure is the number of potential years of life lost before age 65, and the maximum average annual number of deaths is 600. The estimates indicate that premature mortality is not related to the DRUG_STOCK 0, 1, and 2 years earlier, but it is significantly inversely related to the DRUG_STOCK 3-5 years earlier. The next two sets of estimates (Sets 8 and 9) show that increasing the maximum average annual number of deaths value from 600 to either 900 or 1200 has very little effect on the estimates. The last three sets of estimates (Sets 10, 11, and 12) show that changing the premature mortality measure from the number of potential years of life lost before age 65 to the number of potential years of life lost before age 75 also has very little effect on the estimates.

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[10] Some patients may have access to drugs prior to marketing approval. According to Liu and Davis, "there are occasions when a clinical trial has ended and subjects are allowed to continue taking the investigational drug, benefiting from its use while the sponsor pursues marketing approval. This may be referred to as *compassionate use* of an investigational drug. Compassionate use of a drug may also be granted by the FDA when a drug that has been marketed or is under investigation in another country (but is not available in the U.S.) is the only reasonable and available treatment." Liu, Margaret, and Kate Davis, *A Clinical Trials Manual from the Duke Clinical Research Institute: Lessons from a Horse Named Jim* (Wiley, 2010, p. 25).

Both the U.S. and French estimates indicate that, overall, premature mortality from rare diseases is unrelated to the cumulative number of drugs approved 0-2 years earlier, but is inversely related to the cumulative number of drugs approved 3-4 years earlier. Although the estimates for the two countries are broadly similar in this respect, the magnitudes of the U.S. coefficients are about four times as large as the magnitudes of the French coefficients. This may be partly due to greater errors in measuring dates of drug introduction in France, as discussed above.

Our estimates enable us to calculate the extent to which new drug approvals have reduced premature mortality from rare diseases, i.e. to compare the actual decline in premature mortality to the (counterfactual) decline (or increase) that would have occurred in the absence of new drug approvals. The simplest way to perform this comparison is to compare the estimates of δ_{cond} and δ_{uncond} from the following two equations:

$$\ln(MORT_{it}) = \delta_{cond}\, t + \beta \ln(DRUG\_STOCK_{i,t-3}) + \alpha_i + \varepsilon_{it} \quad (2)$$

$$\ln(MORT_{it}) = \delta_{uncond}\, t + \alpha_i + \varepsilon_{it} \quad (3)$$

Eq. (2) is a modified version of eq. (1), in which fixed year effects have been replaced by a time trend,[11] and the DRUG_STOCK lag is set to 3 years, since the estimates in Table 4 indicate that this lag provides the best fit to the data. δ_{cond} in eq. (2) may be interpreted as the average annual growth rate of premature mortality, *holding constant* (or conditional on) the lagged stock of drugs, i.e. in the absence of new drug approvals. The drug stock variable is excluded from eq. (3), so δ_{uncond} may be interpreted as the actual (unconditional) growth rate of premature mortality. $(\delta_{uncond} - \delta_{cond})$ may be interpreted as the reduction in the growth rate of premature mortality attributable to lagged new drug approvals.[12]

These calculations are shown for the broadest definitions of rare diseases we have considered (max(mean_deaths) equal to 6400 in the U.S. and 1200 in France) in the following table.

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[11] Estimates of β hardly change when we replace fixed year effects by a time trend.

[12] $(\delta_{uncond} - \delta_{cond})$ is equivalent to β times the average annual growth rate of $DRUG\_STOCK_{i,t-3}$. The average annual growth rate of $DRUG\_STOCK_{i,t-3}$ was 4.8% in the U.S. and 5.7% in France.

Line	country	premature mortality measure	max(mean_deaths)	δ_{uncond}	δ_{cond}	$(\delta_{uncond} - \delta_{cond})$
1	US	PYLL65	6400	-3.3%	0.9%	-4.2%
2	US	PYLL75	6400	-2.4%	1.7%	-4.1%
3	France	PYLL65	1200	-1.8%	-0.6%	-1.1%
4	France	PYLL75	1200	-1.3%	-0.5%	-0.8%

Line 1 shows that, in the U.S., potential years of life lost to rare diseases before age 65 declined at an average annual rate of 3.3%. The estimates imply that, in the absence of lagged new drug approvals, PYLL65 would have *increased* at a rate of 0.9%. Since the U.S. population age 0-64 was increasing at the rate of 1.0% per year, this means that PYLL65 per person under 65 would have remained approximately constant. The reduction in the growth rate of PYLL65 attributable to lagged new drug approvals is 4.2%.

Line 2 shows that the reduction in the growth rate of potential years of life lost to rare diseases before age 75 attributable to lagged new drug approvals is almost identical: 4.1%. In this case, the estimates imply that, in the absence of new drug approvals, potential years of life lost before age 75 would have increased faster than the population age 0-74, but this difference is not statistically significant.

Line 3 shows that, in France, PYLL65 declined at an average annual rate of 1.8%. The estimates imply that, in the absence of lagged new drug approvals, it would have declined at a rate of 0.6%. The estimated reduction in the growth rate of PYLL65 attributable to lagged new drug approvals in France (1.1%) is about one-fourth the estimated reduction in the U.S. This is not surprising, since the magnitudes of the U.S. estimates of β are about four times as large as the magnitudes of the French estimates. Line 4 shows that, in France, PYLL75 declined at an average annual rate of 1.3%, and that the estimates imply that, in the absence of lagged new drug approvals, it would have declined at a rate of 0.5%.

IV. Summary and conclusions

This paper has investigated the impact of the introduction of new orphan drugs on premature mortality from rare diseases using longitudinal, disease-level data obtained from a number of major databases. The analysis was performed using data from two countries: the U.S. (during the period 1999-2006) and France (during the period 2000-2007). For both countries, we estimated models using two alternative definitions of premature mortality, several alternative criteria for inclusion in the set of rare diseases, and several values of the potential lag between new drug approvals and premature mortality reduction.

Both the U.S. and French estimates indicate that, overall, premature mortality from rare diseases is unrelated to the cumulative number of drugs approved 0-2 years earlier, but is significantly inversely related to the cumulative number of drugs approved 3-4 years earlier. This delay is not surprising, since most patients probably don't have access to a drug until several years after it has been launched. Although the estimates for the two countries are qualitatively similar, the estimated magnitudes of the U.S. coefficients are about four times as large as the magnitudes of the French coefficients. This may be partly due to greater errors in measuring dates of drug introduction in France.

Our estimates indicate that, in the U.S., potential years of life lost to rare diseases before age 65 declined at an average annual rate of 3.3%, and that, in the absence of lagged new drug approvals, PYLL65 would have *increased* at a rate of 0.9%. Since the U.S. population age 0-64 was increasing at the rate of 1.0% per year, this means that PYLL65 per person under 65 would have remained approximately constant. The reduction in the U.S. growth rate of PYLL65 attributable to lagged new drug approvals was 4.2%.

In France, PYLL65 declined at an average annual rate of 1.8%. The estimates imply that, in the absence of lagged new drug approvals, it would have declined at a rate of 0.6%. The reduction in the French growth rate of PYLL65 attributable to lagged new drug approvals was 1.1%.

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Table 1

Selected diseases in Orphanet database, ranked by average annual number of U.S. deaths of associated ICD10 codes

Orphanet disease name	Orphanet ICD10 code	WHO ICD10 name	average annual number of U.S. deaths during 1999-2006
Lung cancer, small cell	C34.9	Malignant neoplasm of bronchus or lung, unspecified	155,838
Colon cancer, familial nonpolyposis	C18.9	Malignant neoplasm of colon, unspecified	44,841
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy	F03	Unspecified dementia	43,597
Frontotemporal dementia	F03	Unspecified dementia	43,597
Breast cancer, familial	C50.9	Breast, unspecified	41,685
Prostate cancer, familial	C61	Malignant neoplasm of prostate	29,976
Parkinson disease, genetic types	G20	Parkinson's disease	17,259
Primary pulmonary lymphoma	C85.9	Non-Hodgkin's lymphoma, unspecified type	17,191
Teratoma	C56	Malignant neoplasm of ovary	14,475
Ovarian germ cell malignant tumor	C56	Malignant neoplasm of ovary	14,475
Ovarian tumor of sex cord-stromal origin	C56	Malignant neoplasm of ovary	14,475
Cirrhotic cardiomyopathy	K74.6	Other and unspecified cirrhosis of liver	13,850
Brachydactyly - arterial hypertension	I10	Essential (primary) hypertension	12,275
Nephroblastoma	C64	Malignant neoplasm of kidney, except renal pelvis	11,901
Renal cell carcinoma, familial	C64	Malignant neoplasm of kidney, except renal pelvis	11,901
Wilms tumour - radial bilateral aplasia	C64	Malignant neoplasm of kidney, except renal pelvis	11,901
Perlman syndrome	C64	Malignant neoplasm of kidney, except renal pelvis	11,901
Brain tumor	C71.9	Brain, unspecified	11,664
Pulmonary fibrosis, idiopathic	J84.1	Other interstitial pulmonary diseases with fibrosis	10,691
Myeloma, multiple	C90.0	Multiple myeloma	10,612
Atrial fibrillation, familial	I48	Atrial fibrillation and flutter	10,093

Table 2

U.S. cancer prevalence, number of deaths, and conditional mortality rate, by cancer site,

Cancer site	Estimated Complete Prevalence on 1/1/2007	Number of deaths in 2007	Number of deaths in 2007/Estimated Complete Prevalence on 1/1/2007
Breast	2,605,181	40,493	1.6%
Prostate	2,276,112	28,555	1.3%
Colon and Rectum	1,112,493	52,511	4.7%
Melanoma of the Skin	793,283	8,262	1.0%
Corpus and Uterus, NOS	575,108	7,406	1.3%
Urinary Bladder	535,236	13,550	2.5%
Non-Hodgkin Lymphoma	438,325	20,151	4.6%
Thyroid	434,256	1,635	0.4%
Lung and Bronchus	370,617	156,207	42.1%
Kidney and Renal Pelvis	281,490	12,552	4.5%
Oral Cavity and Pharynx	249,366	7,960	3.2%
Cervix Uteri	247,180	3,930	1.6%
Leukemia	244,272	21,608	8.8%
Testis	195,969	291	0.1%
Ovary	177,162	14,509	8.2%
Hodgkin Lymphoma	164,273	1,333	0.8%
Brain and Other Nervous System	126,329	13,033	10.3%
Larynx	90,438	3,524	3.9%
Stomach	65,639	11,236	17.1%
Myeloma	61,642	10,669	17.3%
Acute Lymphocytic Leukemia	60,783	1,333	2.2%
Pancreas	32,993	33,530	101.6%
Esophagus	28,729	13,361	46.5%
Liver and Intrahepatic Bile Duct	27,753	16,815	60.6%

Source: SEER Cancer Query System: Cancer Prevalence Database and US Mortality
http://srab.cancer.gov/prevalence/canques.html
http://seer.cancer.gov/canques/mortality.html

Table 3

Descriptive statistics, U.S. sample of diseases with fewer than 6400 U.S. deaths/year

Year	No. of diseases	Total number of deaths	Total number of life-years lost before age 65	Total number of life-years lost before age 75	Life-years lost before age 65 per 100,000 population age 0-64	Life-years lost before age 75 per 100,000 population age 0-74	Cumulative number of Orphanet drugs approved 3 years before	Population age 0-64	Population age 0-74
1999	100	36,130	234,433	411,316	96.0	156.6	119	244,242,327	262,661,236
2000	103	38,070	239,106	425,207	97.0	160.6	130	246,430,153	264,821,139
2001	102	38,731	240,889	430,716	96.5	160.8	146	249,505,945	267,819,168
2002	102	39,501	242,538	434,498	96.0	160.3	149	252,766,789	271,041,004
2003	102	38,203	229,775	416,597	90.1	152.5	155	254,891,606	273,228,650
2004	106	37,400	224,262	409,902	87.1	148.6	186	257,361,418	275,824,891
2005	105	38,795	228,372	421,085	88.0	151.3	195	259,620,291	278,260,104
2006	107	40,023	220,569	417,392	84.1	148.5	204	262,138,132	281,054,976

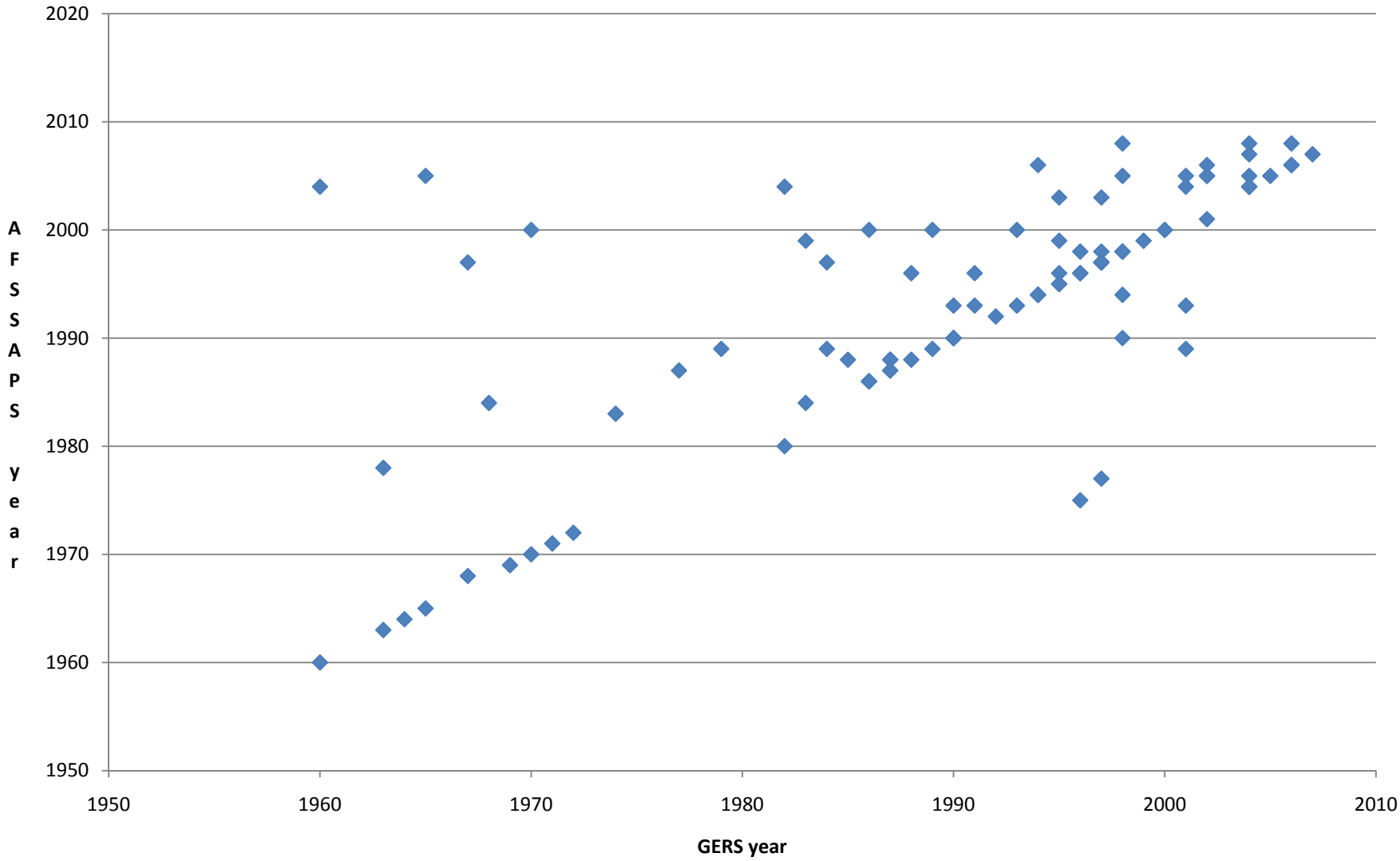
Table 4

Estimates of the effect of the cumulative number of drugs approved on premature mortality from rare diseases

Regressor	Estimate	Z	Pr > |Z|		Estimate	Z	Pr > |Z|		Estimate	Z	Pr > |Z|
	Set 1: USA, PYLL65, max(mean_deaths)=3200				Set 2: USA, PYLL65, max(mean_deaths)=4800				Set 3: USA, PYLL65, max(mean_deaths)=6400		
$\ln(DRUG\_STOCK_{i,t})$	-0.825	-1.49	0.137		-0.824	-1.48	0.138		-0.895	-1.67	0.095
$\ln(DRUG\_STOCK_{i,t-1})$	-1.063	-2.02	0.043		-1.063	-2.02	0.043		-1.091	-2.16	0.031
$\ln(DRUG\_STOCK_{i,t-2})$	-0.412	-1.49	0.137		-0.412	-1.48	0.138		-0.448	-1.67	0.095
$\ln(DRUG\_STOCK_{i,t-3})$	-0.848	-3.21	0.001		-0.849	-3.21	0.001		-0.864	-3.36	0.001
$\ln(DRUG\_STOCK_{i,t-4})$	-0.916	-2.88	0.004		-0.916	-2.88	0.004		-0.902	-2.74	0.006
$\ln(DRUG\_STOCK_{i,t-5})$	-0.858	-1.76	0.079		-0.858	-1.76	0.079		-0.622	-1.30	0.193
	Set 4: USA, PYLL75, max(mean_deaths)=3200				Set 5: USA, PYLL75, max(mean_deaths)=4800				Set 6: USA, PYLL75, max(mean_deaths)=6400		
$\ln(DRUG\_STOCK_{i,t})$	-0.925	-1.67	0.094		-0.926	-1.67	0.095		-0.987	-1.85	0.065
$\ln(DRUG\_STOCK_{i,t-1})$	-1.162	-2.23	0.026		-1.164	-2.24	0.025		-1.179	-2.36	0.018
$\ln(DRUG\_STOCK_{i,t-2})$	-0.462	-1.67	0.094		-0.463	-1.67	0.095		-0.493	-1.85	0.065
$\ln(DRUG\_STOCK_{i,t-3})$	-0.902	-3.54	0.000		-0.902	-3.55	0.000		-0.913	-3.67	0.000
$\ln(DRUG\_STOCK_{i,t-4})$	-0.954	-2.94	0.003		-0.954	-2.94	0.003		-0.934	-2.75	0.006
$\ln(DRUG\_STOCK_{i,t-5})$	-0.856	-1.66	0.097		-0.856	-1.66	0.097		-0.580	-1.19	0.233
	Set 7: France, PYLL65, max(mean_deaths)=600				Set 8: France, PYLL65, max(mean_deaths)=900				Set 9: France, PYLL65, max(mean_deaths)=1200		
$\ln(DRUG\_STOCK_{i,t})$	-0.079	-0.60	0.546		-0.078	-0.60	0.550		-0.071	-0.57	0.567
$\ln(DRUG\_STOCK_{i,t-1})$	-0.041	-0.25	0.802		-0.040	-0.24	0.807		-0.029	-0.19	0.852
$\ln(DRUG\_STOCK_{i,t-2})$	-0.040	-0.60	0.546		-0.039	-0.60	0.550		-0.036	-0.57	0.567
$\ln(DRUG\_STOCK_{i,t-3})$	-0.223	-2.60	0.009		-0.223	-2.60	0.009		-0.218	-2.59	0.010
$\ln(DRUG\_STOCK_{i,t-4})$	-0.206	-2.44	0.015		-0.206	-2.44	0.015		-0.206	-2.44	0.015
$\ln(DRUG\_STOCK_{i,t-5})$	-0.179	-1.98	0.048		-0.179	-1.98	0.048		-0.179	-1.98	0.048
	Set 10: France, PYLL75, max(mean_deaths)=600				Set 11: France, PYLL75, max(mean_deaths)=900				Set 12: France, PYLL75, max(mean_deaths)=1200		
$\ln(DRUG\_STOCK_{i,t})$	-0.117	-1.05	0.293		-0.115	-1.04	0.299		-0.087	-0.85	0.393
$\ln(DRUG\_STOCK_{i,t-1})$	-0.068	-0.52	0.604		-0.066	-0.51	0.610		-0.054	-0.46	0.643
$\ln(DRUG\_STOCK_{i,t-2})$	-0.058	-1.05	0.293		-0.058	-1.04	0.299		-0.044	-0.85	0.393
$\ln(DRUG\_STOCK_{i,t-3})$	-0.173	-2.34	0.020		-0.173	-2.34	0.020		-0.164	-2.31	0.021
$\ln(DRUG\_STOCK_{i,t-4})$	-0.165	-2.05	0.040		-0.165	-2.05	0.040		-0.165	-2.05	0.040
$\ln(DRUG\_STOCK_{i,t-5})$	-0.152	-1.96	0.050		-0.152	-1.96	0.050		-0.152	-1.96	0.050

Each estimate in the table comes from a separate model. Each model includes fixed disease effects and fixed year effects. Each model was estimated via weighted least squares, where the weight was the mean of the disease's premature mortality measure during the entire sample period, e. g. $PYLL65_{i.} = (1/8) * \sum_t PYLL65_{it}$. Standard errors are clustered within diseases.

Figure 1
AFSSAPS vs. GERS data on
year in which cancer drugs were introduced in France



Appendix Table 1

Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
A07.2	Cryptosporidiosis	NITAZOXANIDE	2002
A78	Q fever	DOXYCYCLINE HYCLATE	1967
B22.2	HIV disease resulting in wasting syndrome	SOMATROPIN RECOMBINANT	1987
B54	Unspecified malaria	CHLOROQUINE HYDROCHLORIDE	1949
B54	Unspecified malaria	MEFLOQUINE HYDROCHLORIDE	1989
B54	Unspecified malaria	HALOFANTRINE HYDROCHLORIDE	1992
B54	Unspecified malaria	ARTEMETHER	2009
B59	Pneumocystosis	DAPSONE	1979
B59	Pneumocystosis	PENTAMIDINE ISETHIONATE	1984
B59	Pneumocystosis	ATOVAQUONE	1992
B59	Pneumocystosis	TRIMETREXATE GLUCURONATE	1993
C22.0	Liver cell carcinoma	IMATINIB MESYLATE	2001
C22.2	Hepatoblastoma	IMATINIB MESYLATE	2001
C26.9	Ill-defined sites within the digestive system	IMATINIB MESYLATE	2001
C26.9	Ill-defined sites within the digestive system	SUNITINIB MALATE	2006
C37	Malignant neoplasm of thymus	OCTREOTIDE ACETATE	1988
C40.9	Bone and articular cartilage of limb, unspecified	LEUCOVORIN CALCIUM	1952
C40.9	Bone and articular cartilage of limb, unspecified	METHOTREXATE SODIUM	1953
C40.9	Bone and articular cartilage of limb, unspecified	GEMCITABINE HYDROCHLORIDE	1996
C40.9	Bone and articular cartilage of limb, unspecified	IMATINIB MESYLATE	2001
C40.9	Bone and articular cartilage of limb, unspecified	PEGINTERFERON ALFA-2B	2001
C40.9	Bone and articular cartilage of limb, unspecified	OXALIPLATIN	2002
C49.9	Connective and soft tissue, unspecified	DOXORUBICIN HYDROCHLORIDE	1974
C49.9	Connective and soft tissue, unspecified	IFOSFAMIDE	1988
C49.9	Connective and soft tissue, unspecified	IMATINIB MESYLATE	2001
C69.2	Retina	IMATINIB MESYLATE	2001
C71.8	Overlapping lesion of brain	CARMUSTINE	1977
C71.8	Overlapping lesion of brain	DEXRAZOXANE HYDROCHLORIDE	1995
C71.8	Overlapping lesion of brain	IRINOTECAN HYDROCHLORIDE	1996
C71.8	Overlapping lesion of brain	TEMOZOLOMIDE	1999
C71.8	Overlapping lesion of brain	IMATINIB MESYLATE	2001
C71.8	Overlapping lesion of brain	GEFITINIB	2003
C71.8	Overlapping lesion of brain	BEVACIZUMAB	2004
C71.8	Overlapping lesion of brain	CETUXIMAB	2004
C72.3	Optic nerve	CARMUSTINE	1977
C72.3	Optic nerve	IMATINIB MESYLATE	2001
C73	Malignant neoplasm of thyroid gland	THYROTROPIN ALFA	1998
C74.0	Cortex of adrenal gland	MITOTANE	1970
C74.1	Medulla of adrenal gland	IOBENGUANE SULFATE I-131	1994
C74.1	Medulla of adrenal gland	IMATINIB MESYLATE	2001
C83.1	Small cleaved cell (diffuse)	BORTEZOMIB	2003
C83.7	Burkitt's tumour	VINBLASTINE SULFATE	1965
C83.7	Burkitt's tumour	INTERFERON ALFA-2A	1986
C83.7	Burkitt's tumour	RITUXIMAB	1997
C83.7	Burkitt's tumour	ALEMTUZUMAB	2001
C83.7	Burkitt's tumour	IMATINIB MESYLATE	2001
C84.0	Mycosis fungoides	METHOXSALEN	1954

Appendix Table 1

Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
C84.4	Peripheral T-cell lymphoma	ALEMTUZUMAB	2001
C85.1	B-cell lymphoma, unspecified	VINBLASTINE SULFATE	1965
C85.1	B-cell lymphoma, unspecified	INTERFERON ALFA-2A	1986
C85.1	B-cell lymphoma, unspecified	RITUXIMAB	1997
C91.0	Acute lymphoblastic leukaemia	METHOTREXATE SODIUM	1953
C91.0	Acute lymphoblastic leukaemia	VINBLASTINE SULFATE	1965
C91.0	Acute lymphoblastic leukaemia	CYTARABINE	1969
C91.0	Acute lymphoblastic leukaemia	INTERFERON ALFA-2A	1986
C91.0	Acute lymphoblastic leukaemia	ASPARAGINASE	1994
C91.0	Acute lymphoblastic leukaemia	PEGASPARGASE	1994
C91.0	Acute lymphoblastic leukaemia	RITUXIMAB	1997
C91.0	Acute lymphoblastic leukaemia	IMATINIB MESYLATE	2001
C91.0	Acute lymphoblastic leukaemia	CLOFARABINE	2004
C91.0	Acute lymphoblastic leukaemia	NELARABINE	2005
C91.0	Acute lymphoblastic leukaemia	DASATINIB	2006
C91.0	Acute lymphoblastic leukaemia	NILOTINIB HYDROCHLORIDE MONOHYDRATE	2007
C91.4	Hairy-cell leukaemia	INTERFERON ALFA-2B	1986
C91.4	Hairy-cell leukaemia	CLADRIBINE	1993
C92.1	Chronic myeloid leukaemia	BUSULFAN	1954
C92.1	Chronic myeloid leukaemia	INTERFERON ALFA-2A	1986
C92.1	Chronic myeloid leukaemia	INTERFERON ALFA-2B	1986
C92.1	Chronic myeloid leukaemia	IMATINIB MESYLATE	2001
C92.1	Chronic myeloid leukaemia	DASATINIB	2006
C92.1	Chronic myeloid leukaemia	NILOTINIB HYDROCHLORIDE MONOHYDRATE	2007
C92.4	Acute promyelocytic leukaemia	ARSENIC TRIOXIDE	2000
C92.4	Acute promyelocytic leukaemia	GEMTUZUMAB OZOGAMICIN	2000
C92.4	Acute promyelocytic leukaemia	IMATINIB MESYLATE	2001
C92.4	Acute promyelocytic leukaemia	AZACITIDINE	2004
C92.4	Acute promyelocytic leukaemia	SORAFENIB TOSYLATE	2005
C92.5	Acute myelomonocytic leukaemia	MITOXANTRONE HYDROCHLORIDE	1987
C92.5	Acute myelomonocytic leukaemia	IDARUBICIN HYDROCHLORIDE	1990
C92.5	Acute myelomonocytic leukaemia	GEMTUZUMAB OZOGAMICIN	2000
C92.5	Acute myelomonocytic leukaemia	IMATINIB MESYLATE	2001
C92.5	Acute myelomonocytic leukaemia	AZACITIDINE	2004
C92.5	Acute myelomonocytic leukaemia	SORAFENIB TOSYLATE	2005
C92.7	Other myeloid leukaemia	MITOXANTRONE HYDROCHLORIDE	1987
C92.7	Other myeloid leukaemia	IDARUBICIN HYDROCHLORIDE	1990
C92.7	Other myeloid leukaemia	GEMTUZUMAB OZOGAMICIN	2000
C92.7	Other myeloid leukaemia	IMATINIB MESYLATE	2001
C92.7	Other myeloid leukaemia	AZACITIDINE	2004
C92.7	Other myeloid leukaemia	SORAFENIB TOSYLATE	2005
C94.0	Acute erythraemia and erythroleukaemia	MITOXANTRONE HYDROCHLORIDE	1987
C94.0	Acute erythraemia and erythroleukaemia	IDARUBICIN HYDROCHLORIDE	1990
C94.0	Acute erythraemia and erythroleukaemia	GEMTUZUMAB OZOGAMICIN	2000
C94.0	Acute erythraemia and erythroleukaemia	IMATINIB MESYLATE	2001
C94.0	Acute erythraemia and erythroleukaemia	AZACITIDINE	2004
C94.0	Acute erythraemia and erythroleukaemia	SORAFENIB TOSYLATE	2005
C94.2	Acute megakaryoblastic leukaemia	MITOXANTRONE HYDROCHLORIDE	1987
C94.2	Acute megakaryoblastic leukaemia	IDARUBICIN HYDROCHLORIDE	1990
C94.2	Acute megakaryoblastic leukaemia	GEMTUZUMAB OZOGAMICIN	2000
C94.2	Acute megakaryoblastic leukaemia	IMATINIB MESYLATE	2001

Appendix Table 1

Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
C94.2	Acute megakaryoblastic leukaemia	AZACITIDINE	2004
C94.2	Acute megakaryoblastic leukaemia	SORAFENIB TOSYLATE	2005
C96.2	Malignant mast cell tumour	IMATINIB MESYLATE	2001
C96.2	Malignant mast cell tumour	NILOTINIB HYDROCHLORIDE MONOHYDRATE	2007
D12.6	Colon, unspecified	CELECOXIB	1998
D12.6	Colon, unspecified	CETUXIMAB	2004
D27	Benign neoplasm of ovary	METHOTREXATE SODIUM	1953
D27	Benign neoplasm of ovary	THIOTEPA	1959
D27	Benign neoplasm of ovary	MELPHALAN	1964
D27	Benign neoplasm of ovary	DOXORUBICIN HYDROCHLORIDE	1974
D27	Benign neoplasm of ovary	CISPLATIN	1978
D27	Benign neoplasm of ovary	PACLITAXEL	1992
D27	Benign neoplasm of ovary	TOPOTECAN HYDROCHLORIDE	1996
D44.5	Pineal gland	IMATINIB MESYLATE	2001
D45	Polycythaemia vera	INTERFERON ALFA-2A	1986
D46.7	Other myelodysplastic syndromes	INFLIXIMAB	1998
D46.7	Other myelodysplastic syndromes	IMATINIB MESYLATE	2001
D46.7	Other myelodysplastic syndromes	AZACITIDINE	2004
D46.7	Other myelodysplastic syndromes	LENALIDOMIDE	2005
D46.7	Other myelodysplastic syndromes	DECITABINE	2006
D46.9	Myelodysplastic syndrome, unspecified	IMATINIB MESYLATE	2001
D47.1	Chronic myeloproliferative disease	THALIDOMIDE	1998
D47.3	Essential (haemorrhagic) thrombocythaemia	ANAGRELIDE HYDROCHLORIDE	1997
D66	Hereditary factor VIII deficiency	DESMOPRESSIN ACETATE	1978
D67	Hereditary factor IX deficiency	DESMOPRESSIN ACETATE	1978
D68.0	Von Willebrand's disease	DESMOPRESSIN ACETATE	1978
D69.3	Idiopathic thrombocytopenic purpura	AZATHIOPRINE	1968
D69.3	Idiopathic thrombocytopenic purpura	RITUXIMAB	1997
D69.3	Idiopathic thrombocytopenic purpura	ELTROMBOPAG OLAMINE	2008
D69.4	Other primary thrombocytopenia	RITUXIMAB	1997
D69.5	Secondary thrombocytopenia	LEPIRUDIN RECOMBINANT	1998
D71	Functional disorders of polymorphonuclear neutrophils	INTERFERON GAMMA-1B	1999
D72.1	Eosinophilia	IMATINIB MESYLATE	2001
D72.1	Eosinophilia	NILOTINIB HYDROCHLORIDE MONOHYDRATE	2007
D76.0	Langerhans' cell histiocytosis, not elsewhere classified	VINBLASTINE SULFATE	1965
D76.0	Langerhans' cell histiocytosis, not elsewhere classified	IMATINIB MESYLATE	2001
D81.3	Adenosine deaminase [ADA] deficiency	PEGADEMASE BOVINE	1990
E22.0	Acromegaly and pituitary gigantism	OCTREOTIDE ACETATE	1988
E22.0	Acromegaly and pituitary gigantism	PEGVISOMANT	2003
E22.0	Acromegaly and pituitary gigantism	LANREOTIDE ACETATE	2007
E22.8	Other hyperfunction of pituitary gland	LEUPROLIDE ACETATE	1985
E22.8	Other hyperfunction of pituitary gland	NAFARELIN ACETATE	1990
E22.8	Other hyperfunction of pituitary gland	HISTRELIN ACETATE	1991
E23.0	Hypopituitarism	SOMATROPIN RECOMBINANT	1987
E23.2	Diabetes insipidus	DESMOPRESSIN ACETATE	1978
E23.3	Hypothalamic dysfunction, not elsewhere classified	SOMATROPIN RECOMBINANT	1987
E70.2	Disorders of tyrosine metabolism	NITISINONE	2002

Appendix Table 1

Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
E71.3	Disorders of fatty-acid metabolism	RILUZOLE	1995
E72.0	Disorders of amino-acid transport	TIOPRONIN	1988
E72.0	Disorders of amino-acid transport	CYSTEAMINE BITARTRATE	1994
E72.2	Disorders of urea cycle metabolism	SODIUM PHENYLBUTYRATE	1996
E74.3	Other disorders of intestinal carbohydrate absorption	SACROSIDASE	1998
E75.2	Other sphingolipidosis	ALGLUCERASE	1991
E75.2	Other sphingolipidosis	IMIGLUCERASE	1994
E75.2	Other sphingolipidosis	AGALSIDASE BETA	2003
E75.2	Other sphingolipidosis	MIGLUSTAT	2003
E76.0	Mucopolysaccharidosis, type I	LARONIDASE	2003
E76.2	Other mucopolysaccharidoses	MIGLUSTAT	2003
E83.0	Disorders of copper metabolism	PENICILLAMINE	1970
E83.0	Disorders of copper metabolism	ZINC ACETATE	1980
E83.0	Disorders of copper metabolism	TRIENTINE HYDROCHLORIDE	1985
E85.0	Non-neuropathic heredofamilial amyloidosis	COLCHICINE	1961
G11.1	Early-onset cerebellar ataxia	RILUZOLE	1995
G11.8	Other hereditary ataxias	RILUZOLE	1995
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]	VALPROATE SODIUM	1996
G12.1	Other inherited spinal muscular atrophy	RILUZOLE	1995
G12.2	Motor neuron disease	SOMATROPIN RECOMBINANT	1987
G12.2	Motor neuron disease	RILUZOLE	1995
G12.2	Motor neuron disease	VALPROATE SODIUM	1996
G12.2	Motor neuron disease	MEMANTINE	2010
G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]	DONEPEZIL HYDROCHLORIDE	1996
G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]	VALPROATE SODIUM	1996
G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]	RIVASTIGMINE	2007
G30.8	Other Alzheimer's disease	DONEPEZIL HYDROCHLORIDE	1996
G35	Multiple sclerosis	BACLOFEN	1977
G35	Multiple sclerosis	MITOXANTRONE HYDROCHLORIDE	1987
G35	Multiple sclerosis	INTERFERON BETA-1B	1993
G35	Multiple sclerosis	RILUZOLE	1995
G35	Multiple sclerosis	GLATIRAMER ACETATE	1996
G35	Multiple sclerosis	INTERFERON BETA-1A	1996
G35	Multiple sclerosis	NATALIZUMAB	2004
G35	Multiple sclerosis	MEMANTINE	2010
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	VALPROATE SODIUM	1996
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	LEVETIRACETAM	1999
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	PREGABALIN	2004
G40.1	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	VIGABATRIN	2009

Appendix Table 1

Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
G40.3	Generalized idiopathic epilepsy and epileptic syndromes	VALPROATE SODIUM	1996
G40.3	Generalized idiopathic epilepsy and epileptic syndromes	LEVETIRACETAM	1999
G40.3	Generalized idiopathic epilepsy and epileptic syndromes	PREGABALIN	2004
G40.4	Other generalized epilepsy and epileptic syndromes	FELBAMATE	1993
G40.4	Other generalized epilepsy and epileptic syndromes	LAMOTRIGINE	1994
G40.4	Other generalized epilepsy and epileptic syndromes	VALPROATE SODIUM	1996
G40.4	Other generalized epilepsy and epileptic syndromes	RUFINAMIDE	2008
G47.4	Narcolepsy and cataplexy	MODAFINIL	1998
G47.4	Narcolepsy and cataplexy	SODIUM OXYBATE	2002
G70.0	Myasthenia gravis	TACROLIMUS	1994
G70.0	Myasthenia gravis	MYCOPHENOLATE MOFETIL	1995
G90.3	Multi-system degeneration	MIDODRINE HYDROCHLORIDE	1996
I27.0	Primary pulmonary hypertension	EPOPROSTENOL SODIUM	1995
I27.0	Primary pulmonary hypertension	SILDENAFIL CITRATE	1998
I27.0	Primary pulmonary hypertension	NITRIC OXIDE	1999
I27.0	Primary pulmonary hypertension	BOSENTAN	2001
I27.0	Primary pulmonary hypertension	ESCITALOPRAM OXALATE	2002
I27.0	Primary pulmonary hypertension	TREPROSTINIL SODIUM	2002
I27.0	Primary pulmonary hypertension	ILOPROST	2004
I27.0	Primary pulmonary hypertension	AMBRISENTAN	2007
K22.7	Barrett's esophagus	PORFIMER SODIUM	1995
K22.7	Barrett's esophagus	SUNITINIB MALATE	2006
K74.3	Primary biliary cirrhosis	BUDESONIDE	1994
K75.4	Autoimmune hepatitis	AZATHIOPRINE	1968
L10.0	Pemphigus vulgaris	AZATHIOPRINE	1968
L12.0	Bullous pemphigoid	METHOTREXATE SODIUM	1953
L12.0	Bullous pemphigoid	DAPSONE	1979
L12.0	Bullous pemphigoid	CLOBETASOL PROPIONATE	1985
L13.0	Dermatitis herpetiformis	DAPSONE	1979
M08.0	Juvenile rheumatoid arthritis	RITUXIMAB	1997
M08.0	Juvenile rheumatoid arthritis	ETANERCEPT	1998
M08.0	Juvenile rheumatoid arthritis	ADALIMUMAB	2002
M08.2	Juvenile arthritis with systemic onset	SOMATROPIN RECOMBINANT	1987
M08.2	Juvenile arthritis with systemic onset	ANAKINRA	2001
M08.2	Juvenile arthritis with systemic onset	ADALIMUMAB	2002
M08.2	Juvenile arthritis with systemic onset	ABATACEPT	2005
M30.0	Polyarteritis nodosa	CYCLOPHOSPHAMIDE	1959
M30.0	Polyarteritis nodosa	AZATHIOPRINE	1968
M30.1	Polyarteritis with lung involvement [Churg-Strauss]	CYCLOPHOSPHAMIDE	1959
M30.1	Polyarteritis with lung involvement [Churg-Strauss]	AZATHIOPRINE	1968
M30.1	Polyarteritis with lung involvement [Churg-Strauss]	INFLIXIMAB	1998
M31.3	Wegener's granulomatosis	CYCLOPHOSPHAMIDE	1959
M31.3	Wegener's granulomatosis	AZATHIOPRINE	1968

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Drugs listed in order of FDA approval year for diseases with fewer than 6400 U.S. deaths/year

icd10	Cause of death	activeingred	fda_year
M31.3	Wegener's granulomatosis	INFLIXIMAB	1998
M31.8	Other specified necrotizing vasculopathies	CYCLOPHOSPHAMIDE	1959
M31.8	Other specified necrotizing vasculopathies	AZATHIOPRINE	1968
M31.8	Other specified necrotizing vasculopathies	INFLIXIMAB	1998
M33.1	Other dermatomyositis	AZATHIOPRINE	1968
M33.2	Polymyositis	AZATHIOPRINE	1968
M35.0	Sicca syndrome [Sjogren]	PILOCARPINE	1974
M35.0	Sicca syndrome [Sjogren]	RITUXIMAB	1997
M35.2	Behcet's disease	COLCHICINE	1961
M35.2	Behcet's disease	THALIDOMIDE	1998
M45	Ankylosing spondylitis	CELECOXIB	1998
M45	Ankylosing spondylitis	ETANERCEPT	1998
M45	Ankylosing spondylitis	INFLIXIMAB	1998
M45	Ankylosing spondylitis	ADALIMUMAB	2002
M94.1	Relapsing polychondritis	DAPSONE	1979
N04.9	Nephrotic syndrome, unspecified	LEVAMISOLE HYDROCHLORIDE	1990
N04.9	Nephrotic syndrome, unspecified	MYCOPHENOLATE MOFETIL	1995
Q25.0	Patent ductus arteriosus	INDOMETHACIN	1965
Q25.0	Patent ductus arteriosus	IBUPROFEN	1974
Q25.0	Patent ductus arteriosus	IBUPROFEN LYSINE	2006
Q77.4	Achondroplasia	SOMATROPIN RECOMBINANT	1987
Q82.2	Mastocytosis	METHOXSALEN	1954
Q87.1	Congenital malformation syndromes predominantly associated with short stature	SOMATROPIN RECOMBINANT	1987