JOURNAL OF PHARMACEUTICAL POLICY AND PRACTICE
2024, VOL. 17, NO. 1, 2357604
https://doi.org/10.1080/20523211.2024.2357604

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RESEARCH ARTICLE

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Do newer drugs treat fewer diseases, controlling for time since launch? Evidence from France and the U.S.

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ABSTRACT

Background: More recently approved drugs have significantly fewer indications than drugs approved many years ago. One possible reason for this may be that, controlling for the number of years since approval or launch, more recently approved drugs have fewer indications (e.g. at the time of launch). The role of precision and personalised medicine has increased, and the goal of precision medicine is to provide a more precise approach for the prevention, diagnosis and treatment of disease. Drugs that have fewer indications may be 'more precise' than drugs that have many indications.

Methods: We use different kinds of data from two countries – France and the U.S. – to analyze the relationship across many drugs between the number of indications of a drug, the drug's vintage – i.e. the year in which the drug was first marketed or approved – and its age – the number of years it has been marketed.

Results: All the evidence from both countries indicates that, controlling for drug age, more recently approved drugs tend to have fewer indications than drugs approved many years ago. In the U.S., a 10-year increase in vintage is associated with a 10.7% decline in the effective number of indications of all drugs, and a 19.4% decline in the effective number of indications of drugs approved after 1989. In France, the positive effect on the number of indications of the increase in drug age was more than offset by the negative effect of the increase in drug vintage.

Conclusions: More recently approved drugs are less likely to be 'general-purpose technologies' (or even multi-purpose technologies) than older drugs. The relative importance of 'precision medicine' has increased in recent decades. Drugs that have fewer indications may be 'more precise' than drugs that have many indications.

KEYWORDS Pharmaceutical; innovation; precision medicine; disease; indication

JEL CODES I11; L65; O31

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Introduction

As noted by the European Medicines Agency (2024), if a drug is used to treat, prevent, or diagnose a medical condition or disease, that disease is considered to be an indication of the drug.

In the U.S., more recently approved drugs have significantly fewer indications than drugs approved many years ago. As shown in Figure 1, which is based on indications in 2023 of 1887 drugs approved by the FDA since its inception in 1939, the mean number of indications in 2023 of the 743 drugs approved before 1990 was 8.8, almost five times as high as the mean number of indications in 2023 of the 533 drugs approved since 2010: 1.8.

One reason why newer drugs have fewer indications may be that newer drugs have been on the market for less time, and that the number of indications of a drug tends to increase with respect to its length of time since approval. In a recent article, Vokinger et al. (2023) noted that,

> after the initial approval of a novel therapeutic agent, a company may seek authorization for the agent to be used to treat other conditions or illnesses … For example, pembrolizumab (Keytruda) was first approved for the treatment of advanced melanoma and subsequently approved for more than 30 supplemental indications by the US Food and Drug Administration (FDA) and more than 15 supplemental indications by the European Medicines Agency (EMA) … This trend is likely to continue given advancements in medicine, notably the growth of immunotherapies and gene therapies, which may be used to target multiple conditions.

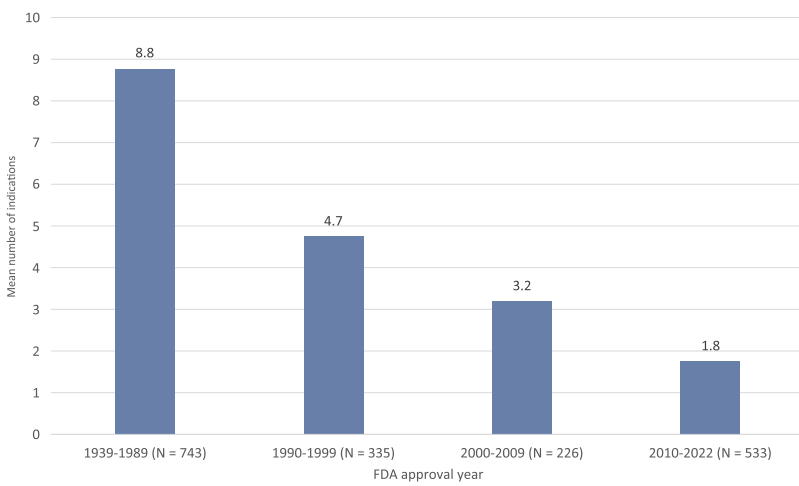

Figure 1. Mean number of indications in 2023 of drugs sold in U.S., by FDA approval year. Source: author's calculations based on data in DrugCentral 2023 database (https://drugcentral.org/).

O'Brien et al. (2023) argue that new indications, obtained by approximately a third of drugs, can reduce insurance-related barriers that patients face in accessing drugs for evidence-based off-label use.

A second possible reason why newer drugs have fewer indications may be that, controlling for the number of years since approval or launch, more recently approved drugs have fewer indications (e.g. at the time of launch). Krzyszczyk et al. (2018) document the 'growing role of precision and personalized medicine for cancer treatment.' The National Human Genome Research Institute (2024) says that 'the goal of precision medicine is to provide a more precise approach for the prevention, diagnosis and treatment of disease.' Drugs that have fewer indications may be 'more precise' than drugs that have many indications. However, the same genetic mutation may cause cancers at different sites and therefore the same drug may be approved to treat multiple different cancers thereby increasing the number of indications per drug.

In this study, we use different kinds of data from two countries – France and the U.S. – to analyze the relationship across many drugs between the number of indications of a drug, the drug's vintage – i.e. the year in which the drug was first marketed or approved – and its age – the number of years it has been marketed. We will analyze this relationship using different kinds of data from two different countries: France and the U.S. In the first analysis, we will use data on all drug products sold in France in the years 2012, 2017, and 2022. Those data indicate the active ingredient(s), approved indication(s), and marketing year of each product. In the second analysis, we will use annual data derived from a major U.S. survey of outpatient drug prescriptions sold during the period 1996–2015. Those data indicate the drug dispensed, the (patient-reported) medical condition for which it was used, and the drug's FDA approval year.

In a given year, the age of a drug is perfectly inversely correlated across drugs with the vintage of the drug. For example, in 2024, age = 2024 – vintage. So, if we only had data for a single year, we could not disentangle the effects of vintage and age on the number of indications. However, we have data on multiple years: 3 (2012, 2017, and 2022) in the case of France, and 20 (1996–2015) in the case of the U.S. Therefore, we will be able to separately identify the effects of vintage and age on the number of indications.

Methods

Number of indications of chemical substances sold in France in 2012, 2017, and 2022

Data on the approved indications in France of each active ingredient were obtained from the 2012, 2017, and 2022 editions of the Thériaque database**,**

produced by the Centre National Hospitalier d'Information sur le Médicament (2024). In 2022, this database contained information on over 30,000 drug products sold in France.[1] For each product, the database provides (1) the CAS Registry Number(s)[2] (CAS_RNs) of the substance(s) contained in the product, and (2) the ICD-10 codes of the product's approved indications. This enabled us to compute the approved indications of products containing each CAS_RN in 2012, 2017, and 2022. The database also provides the marketing date of each product, so we could determine the first year in which any product containing each substance was marketed.

Appendix Table 1 displays 2022 data on two substances to illustrate the data on indications by substance. There were 18 indications of clioquinol (CAS_RN 130-26-7), which was first marketed in 1968. There were 16 indications of infliximab (CAS 170277-31-3), which was first marketed in 2000.

Descriptive statistics, by year, are shown in Table 1. The 2012 edition of Thériaque contained data on 2455 substances. The number of indications ranged between 1 and 100; the mean number of indications was 6.1. The mean initial marketing year was 1972.6, so mean drug age was 39.5 years.

The 2017 edition of Thériaque contained data on 2625 substances. The mean number of indications was 6.0. The mean initial marketing year was 1975.3, so mean drug age was 41.7 years. The 2022 edition of Thériaque contained data on 2812 substances. The mean number of indications was again 6.0. The mean initial marketing year was 1978.2, so mean drug age was 43.8 years.

To identify the effects of drug vintage and age on the number of indications, we will estimate the following model:

$$\ln(\text{n\_indications}_{dt}) = \beta_0 + \beta_1 \text{vintage}_d + \beta_2 \text{age\_drug}_{dt} + \varepsilon_{dt} \qquad (1)$$

where

$\text{n\_indications}_{dt}$ = the number of indications of drug d in year t (t = 2012, 2017, 2022)

vintage_d = the initial marketing year of drug d

age_drug_{dt} = the age of drug d in year t = t − vintage_d

ε_{dt} = a disturbance

[1]Some drug products (e.g., different generic manufacturers' versions of the same drug) have the same chemical substances.

[2]A CAS Registry Number (also referred to as CAS RN or informally CAS Number) is a unique identification number, assigned by the Chemical Abstracts Service (CAS) in the US to every chemical substance described in the open scientific literature, in order to index the substance in the CAS Registry. This registry includes all substances described since 1957, plus some substances from as far back as the early 1800s; it is a chemical database that includes organic and inorganic compounds, minerals, isotopes, alloys, mixtures, and nonstructurable materials (UVCBs, substances of unknown or variable composition, complex reaction products, or biological origin).

Table 1. Chemical substances sold in France: Summary statistics from 2012, 2017, and 2022 editions of Thériaque.

	all substances				substances first commercialized after 1989			
Variable	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max
	Thériaque 2012 (N = 2455)				**Thériaque 2012 (N = 652)**			
n_indications	6.13	8.65	1	100	3.38	3.68	1	38
ln(n_indications)	1.25	1.01	0.00	4.61	0.85	0.81	0.00	3.64
vintage	1972.55	23.86	1901	2011	1999.91	5.75	1990	2011
age_drug	39.45	23.86	1	111	12.09	5.75	1	22
	Thériaque 2017 (N = 2625)				**Thériaque 2017 (N = 823)**			
n_indications	5.99	8.55	1	102	3.31	3.43	1	30
ln(n_indications)	1.23	1.01	0.00	4.62	0.84	0.80	0.00	3.40
vintage	1975.28	25.10	1901	2017	2002.78	7.71	1990	2017
age_drug	41.72	25.10	0	116	14.22	7.71	0	27
	Thériaque 2022 (N = 2812)				**Thériaque 2022 (N = 1007)**			
n_indications	5.98	8.67	1	106	3.33	3.54	1	30
ln(n_indications)	1.22	1.02	0.00	4.66	0.83	0.81	0.00	3.40
vintage	1978.21	26.48	1901	2022	2005.75	9.48	1990	2022
age_drug	43.79	26.48	0	121	16.25	9.48	0	32

The disturbances of equation (1) will be clustered within drugs. β_1 indicates the effect of a drug's vintage on the number of indications, controlling for the drug's age.[3]

Effective number of indications of chemical substances sold in the U.S., 1996–2015

To our knowledge, comprehensive time-series data on the number of approved indications of each substance, available for France from Thériaque, are not available for the U.S.[4] However, by using annual data derived from a major U.S. survey of outpatient drug prescriptions sold during the period 1996–2015, we can calculate the 'effective number' of indications (defined below), by substance and year.

The 1996–2015 Medical Expenditure Panel Survey (MEPS) Prescribed Medicines Files (Agency for Healthcare Research and Quality, 2024) contain data on 3.9 million outpatient prescribed medicine events (prescriptions). Each record indicates (1) the generic name of the drug (Multum Lexicon RXDRGNAM), and (2) the household-reported medical condition associated with the event.[5] The medical conditions reported by the respondent were recorded by the interviewer as verbatim text, which were then coded to fully-specified ICD-9-CM codes. The ICD-9-CM condition codes were then

[3]If $\ln(n\_indications_{dt})$ depended only on the year in which the drug were sold (t), i.e. $\ln(n\_indications_{dt}) = \beta_0 + \beta\, t + \varepsilon_{dt} = \beta_0 + \beta\,(vintage_d + age\_drug_{dt}) + \varepsilon_{dt}$, the coefficients β_1 and β_2 in eq. (1) would be equal.

[4]The DrugCentral 2023 database contains comprehensive information on drug indications for only one year: 2023.

[5]Most prescription drug databases do not contain information about the patient's medical condition.

aggregated into clinically meaningful, mutually exclusive categories, most of which are clinically homogeneous, using Clinical Classification Software (CCS).[6] This enables us to calculate:

n_rx_{dtc}	= the number of prescriptions of drug (chemical substance) d in year t for medical condition (CCS category) c[7]
$n\_rx_{dtc} / \sum_c n\_rx_{dtc}$	= the fraction of prescriptions of drug d in year t that were for medical condition c
$\sum_c \left[n\_rx_{dtc} / \sum_c n\_rx_{dtc}\right]^2$	= the medical condition (or disease) concentration index of drug d in year t = $disease\_concentration_{dt}$
$1 / \sum_c \left[n\_rx_{dtc} / \sum_c n\_rx_{dtc}\right]^2$	= the effective number of indications (diseases) of drug d in year t = $n\_effective\_indications_{dt}$

If all prescriptions of drug d in year t were for a single disease, $disease\_concentration_{dt} = 1^2 = 1$, and $n\_effective\_indications_{dt} = 1 / 1 = 1$.

If half of the prescriptions of drug d in year t were for disease A, and half were for disease B, $disease\_concentration_{dt} = 0.5^2 + 0.5^2 = 0.5$, and $n\_effective\_indications_{dt} = 1 / 0.5 = 2$.

However, if 90% of the prescriptions of drug d in year t were for disease A, and 10% were for disease B, $disease\_concentration_{dt} = 0.9^2 + 0.1^2 = 0.82$, and $n\_effective\_indications_{dt} = 1 / 0.82 = 1.22$.

Concentration indices like $disease\_concentration_{dt}$, and diversity indices like $n\_effective\_indications_{dt}$, have been used in economics, political science, and ecology. Economists and antitrust authorities assess the competitiveness of an industry by constructing the Herfindahl – Hirschman Index, a market concentration index equal to the sum of squared market shares of firms in the industry (U.S. Department of Justice, Antitrust Division, 2024). In political science, Laakso and Taagepera (1979) calculated the effective number of parties index as the reciprocal of the sum of squared party vote shares in an election.[8] Concentration and diversity indices calculated from sample data when the individuals of a population are classified are also used in ecology (Simpson, 1949).

The calculation of $disease\_concentration_{dt}$ and $n\_effective\_indications_{dt}$ is illustrated in Appendix Table 2. The top of the table shows the calculations for raloxifene, for which there were 197 MEPS prescriptions in 2012. Twelve patient-reported medical conditions were associated with these prescriptions. The most common one was osteoporosis, which accounted for 34% of the prescriptions. The effective number of diagnoses for raloxifene in 2012 was 5.34.

The bottom of the table shows the calculations for adalimumab, for which there were 301 MEPS prescriptions in 2015. Seven patient-reported medical

[6]MEPS Prescribed Medicines Files for the years 2016–2021 are also available, but the disease classification used in those years differs from that used in previous years.

[7]We estimate that about half of MEPS prescriptions are 'off-label', i.e., not used to treat approved indications.

[8]Data on the effective number of parties, by country, are presented in Wikipedia (2024).

conditions were associated with these prescriptions. The most common one was rheumatoid arthritis and related disease, which accounted for 59% of the prescriptions. The effective number of diagnoses for adalimumab in 2015 was 2.55.

To identify the effects of drug vintage and age on the effective number of indications, we will estimate the following model:

$$\ln(\text{n\_effective\_indications}_{dt}) = \beta_0 + \beta_1 \text{vintage}_d + \beta_2 \text{age\_drug}_{dt} + \varepsilon_{dt} \quad (2)$$

where

$\text{n\_effective\_indications}_{dt}$ = the effective number of indications of drug d in year t (t = 1996, 1997, … , 2015)

vintage_d = the FDA approval year of drug d[9]

age_drug_{dt} = the age of drug d in year t = t − vintage_d

ε_{dt} = a disturbance

Results

Estimates of equation (1) based on French data

Estimates of several versions of equation (1) are provided in Table 2. Data on all 3094 substances were used to estimate the first 3 models. In model 1, the only regressor is vintage_d. The coefficient on this variable (β_1) is negative and highly significant, indicating that later-vintage drugs tended to have fewer indications. In model 2, the only regressor is age_drug_{dt}. The coefficient on this variable (β_2) is positive and highly significant, indicating that drugs that have been sold for more years tended to have more indications. In model 3, both regressors are included. Controlling for age_drug_{dt} reduces the magnitude of β_1 by 29%, but the estimate of β_1 is still negative and highly significant in model 3. Controlling for vintage_d reduces the magnitude of β_2 by 71%, but the estimate of β_2 is still positive and highly significant in model 3.

Table 2. Estimates of several versions of equation (1) based on French data: $\ln(\text{n\_indications}_{dt}) = \beta_0 + \beta_1\ \text{vintage}_d + \beta_2\ \text{age\_drug}_{dt} + \varepsilon_{dt}$.

Model	substances included	Regressor	Estimate	Std. Err.	Z	Pr > |Z|
1	all 3094 substances	vintage_d	−0.013	0.0007	−19.22	<.0001
2	all 3094 substances	age_drug_{dt}	0.0129	0.0007	19.19	<.0001
3	all 3094 substances	vintage_d	−0.0092	0.0009	−10.28	<.0001
		age_drug_{dt}	0.0038	0.0008	4.83	<.0001
4	1155 substances first commercialized after 1989	vintage_d	−0.0091	−0.0035	−3.17	0.0015
		age_drug_{dt}	0.0088	0.0124	4.78	<.0001

The disturbances of equation (1) are clustered within drugs.
N = 7892 in models 1, 2, and 3.
N = 2482 in model 4.

[9]Data on the FDA approval years of chemical substances were obtained from the DrugCentral 2023 database (Avram et al., 2023).

In model 4, both regressors are again included, but only data on the 1155 substances first marketed after 1989 were used to estimate this model. As in model 3, the estimate of β_1 is negative and highly significant, and the estimate of β_2 is positive and highly significant. The point estimates of β_1 in models 3 and 4 are virtually identical; the point estimate of β_2 in model 4 is 2.3 times as large as the point estimate of β_2 in model 3.

In addition to estimating equation (1) using data on all 3094 substances, we estimated equation (1) for each ATC main anatomical or pharmacological group.[10] These estimates, in which both regressors are included, are shown in Table 3. The coefficient on vintage_d (β_1) is negative and significant for 11 of the 14 main anatomical or pharmacological groups.

Estimates of equation (2) based on U.S. data

Estimates of several versions of equation (2) are provided in Table 4. Data on all 769 substances were used to estimate the first 3 models. In model 5, the only regressor is vintage_d. The coefficient on this variable (β_1) is negative and highly significant, indicating that later-vintage drugs tended to have fewer indications. In model 6, the only regressor is age_drug_{dt}. The coefficient on this variable (β_2) is positive and highly significant, indicating that drugs that have been sold for more years tended to have more indications. In model 7, both regressors are included. Controlling for age_drug_{dt} has no effect on the estimate of β_1. The estimate of β_2 is no longer significant when we control for vintage_d.

In model 8, both regressors are again included, but only data on the 336 substances first marketed after 1989 were used to estimate this model. The estimate of β_1 is again negative and highly significant, and the magnitude of the estimate is 81% larger in model 8 than it is in model 7. Also, the estimate of β_2 is positive and highly significant in model 8, when we confine the analysis to the 336 substances approved after 1989.

Discussion

Most of the evidence from both France and the U.S. indicates that, controlling for drug vintage, drugs that have been sold for many years tend to have more indications than drugs that have been sold for just a few years.[11] All of the evidence from both countries indicates that, controlling

[10] In the Anatomical Therapeutic Chemical (ATC) classification system, active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels. The system has fourteen main anatomical or pharmacological groups (1st level). An active substance may be included in more than one anatomical or pharmacological group.

[11] In the case of the U.S., this is true for drugs approved after 1989, but not for all drugs approved since 1939 – see models 7 and 8 in Table 3.

Table 3. Estimates of several versions of equation (1), by main ATC anatomical or pharmacological group, based on French data: $\ln(n\_indications_{dt}) = \beta_0 + \beta_1\ vintage_d + \beta_2\ age\_drug_{dt} + \varepsilon_{dt}$.

		$vintage_d$				age_drug_{dt}			
Main ATC anatomical or pharmacological group	No. of substances	Estimate	Std. Err.	Z	Pr > |Z|	Estimate	Std. Err.	Z	Pr > |Z|
A ALIMENTARY TRACT AND METABOLISM	578	**−0.0153**	**0.0016**	**−9.84**	**<.0001**	**0.0044**	**0.0013**	**3.42**	**0.0006**
B BLOOD AND BLOOD FORMING ORGANS	262	**−0.0097**	**0.0030**	**−3.22**	**0.0013**	**0.0074**	**0.0026**	**2.90**	**0.0038**
C CARDIOVASCULAR SYSTEM	307	**−0.0191**	**0.0025**	**−7.52**	**<.0001**	**0.0074**	**0.0021**	**3.52**	**0.0004**
D DERMATOLOGICALS	288	**−0.0176**	**0.0025**	**−6.91**	**<.0001**	−0.0014	0.0017	−0.83	0.4084
G GENITO URINARY SYSTEM AND SEX HORMONES	133	−0.0090	0.0059	−1.53	0.1257	0.0056	0.0036	1.56	0.1199
H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	77	−0.0122	0.0076	−1.61	0.1072	**0.0119**	**0.0050**	**2.39**	**0.0168**
J ANTIINFECTIVES FOR SYSTEMIC USE	300	**−0.0193**	**0.0035**	**−5.58**	**<.0001**	0.0042	0.0030	1.43	0.1533
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	316	−0.0068	0.0049	−1.39	0.1631	**0.0129**	**0.0050**	**2.59**	**0.0097**
M MUSCULO-SKELETAL SYSTEM	177	**−0.0133**	**0.0031**	**−4.29**	**<.0001**	0.0033	0.0023	1.41	0.159
N NERVOUS SYSTEM	450	**−0.0168**	**0.0019**	**−8.71**	**<.0001**	**0.0042**	**0.0016**	**2.59**	**0.0095**
P ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	77	**−0.0121**	**0.0055**	**−2.20**	**0.0279**	**0.0110**	**0.0047**	**2.33**	**0.0198**
R RESPIRATORY SYSTEM	320	**−0.0143**	**0.0022**	**−6.39**	**<.0001**	**0.0071**	**0.0017**	**4.11**	**<.0001**
S SENSORY ORGANS	209	**−0.0174**	**0.0028**	**−6.19**	**<.0001**	0.0039	0.0020	1.95	0.0511
V VARIOUS	295	**−0.0187**	**0.0021**	**−8.93**	**<.0001**	0.0027	0.0015	1.75	0.0794

Estimates in bold are statistically significant (p-value < .05).

Table 4. Estimates of several versions of equation (2) based on U.S. data: $\ln(\text{n\_effective\_indications}_{dt}) = \beta_0 + \beta_1\ \text{vintage}_d + \beta_2\ \text{age\_drug}_{dt} + \varepsilon_{dt}$.

Model	substances included	Regressor	Estimate	Std. Err.	Z	Pr > |Z|
5	all 769 substances	vintage_d	−0.0107	−0.0073	−6.24	<.0001
6	all 769 substances	age_drug_{dt}	0.0101	0.0134	6.12	<.0001
7	all 769 substances	vintage_d	−0.0107	−0.0059	−4.37	<.0001
		age_drug_{dt}	−0.0001	0.0041	−0.03	0.9773
8	336 substances approved after 1989	vintage_d	−0.0194	−0.0069	−3.04	0.0024
		age_drug_{dt}	0.0106	0.0172	3.14	0.0017

The disturbances of equation (2) are clustered within drugs.
N = 10,161 in models 1, 2, and 3.
N = 3892 in model 4.

for drug age, more recently approved drugs tend to have fewer indications than drugs approved many years ago. In France, a 10-year increase in vintage is associated with a 9.1% decline in the number of indications, of both all drugs and drugs marketed after 1989. In the U.S., a 10-year increase in vintage is associated with a 10.7% decline in the effective number of indications of all drugs, and a 19.4% decline in the effective number of indications of drugs approved after 1989.

As shown in Table 1, between 2012 and 2022, the mean age of all substances sold in France increased by 4.3 years, from 39.5 years to 43.8 years. Despite this increase, the mean number of drug indications declined by about 3.6%.[12] The positive effect on the number of indications of the 4.3-year increase in drug age was more than offset by the negative effect of the 5.66-year increase in drug vintage, from 1972.6–1978.2. The net effect of the changes in drug vintage and age on Δmean(ln(n_indications)) was $\beta_1\ \Delta\text{mean(vintage)} + \beta_2\ \Delta\text{mean(age\_drug)} = (-.0092\ *\ 5.66) + (.0038\ *\ 4.33) = -.036 = -3.6\%$.[13]

Although drugs that have been sold for many years tend to have more indications than drugs that have been sold for just a few years, and the mean age of drugs sold has increased, the mean number of indications of drugs sold in France has declined. Controlling for the number of years since approval or launch, more recently approved (later-vintage) drugs tend to have fewer indications. More recently approved drugs are less likely to be 'general-purpose technologies' (Helpman, 1998) (or even multi-purpose technologies) than older drugs. The positive effect on the number of indications of the increase in drug age was more than offset by the negative effect of the increase in drug vintage.

[12]The 2012–2022 change in the mean of ln(n_indications) was −.036 = 1.217 − 1.253.

[13]When we confine the analysis to substances first marketed after 1989, it is also the case that the positive effect on the number of indications of the increase in drug age was more than offset by the negative effect of the increase in drug vintage. The net effect of the changes in drug vintage and age on $\Delta\text{mean(ln(n\_indications))}$ was $\beta_1\ \Delta\text{mean(vintage)} + \beta_2\ \Delta\text{mean(age\_drug)} = (-.0091\ *\ 5.84) + (.0088\ *\ 4.15) = -.017 = -1.7\%$.

The growing role of precision and personalised medicine may not be the only reason why more recently approved drugs tend to have fewer indications than drugs approved many years ago. Regulatory standards may have changed, and increasing research costs may inhibit companies from looking for new indications. Also, the diseases treated by recently-approved drugs differ from the diseases treated by older drugs. For example, Lichtenberg (2018) reported that the number of new cancer drugs launched worldwide during 2005–2014 (76) was 77% larger than the number launched during 1985–1994 (43), while the number of new drugs for other diseases (e.g. cardiovascular and infectious diseases) launched during 2005–2014 (242) was 42% *lower* than the number launched during 1985–1994 (417).[14]

Limitations

Since the U.S. data we analyzed covered outpatient prescriptions only, indications of drugs used only in hospitals were not accounted for.

Conclusions

If newer drugs have fewer indications than older drugs, the market size (number of prescriptions) of newer drugs may be smaller. (Also, the entry of new drugs will affect competition in fewer markets.) A reduction in market size could reduce the expected returns on investment in new drugs. However, if newer drugs are more 'precise' than older drugs, and therefore more effective, the reduction in market size could be offset by an increase in drug prices.

More recently approved drugs tend to have fewer indications than drugs approved many years ago. Some analysts have argued that the U.S. Inflation Reduction Act (IRA) of 2022 may accelerate this decline. O'Brien et al. (2023) argue that the IRA's price-setting timeline has the potential to reduce the probability of investing in research to generate additional evidence or support additional indications. Goldman et al. (2023) argue that absent reform, the IRA may result in a decline in new drug innovation as well as a decline in research on new indications and evidence generation for long-term effectiveness and safety outcomes. They recommend that innovators be granted delays in the start of the price-setting period when new indications are approved to incentivize research on new indications.

Author contributions

All work on the article was performed by the sole author.

[14]However, as shown in Table 3, for cancer (ATC group L) drugs, the vintage coefficient is not statistically significant.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

All data and computer programs will be made available upon request.

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Appendices

Appendix Table 1. Indications in France in 2022 of products containing 2 substances.

Clioquinol (CAS 130-26-7; commercialized 1968)
I831 Varices des membres inférieurs, avec inflammation
L20 Dermite atopique
L20-L30 Dermatoses et eczémas
L200 Prurigo de Besnier
L21 Dermite séborrhéique
L23 Dermite allergique de contact
L24 Dermite irritante de contact
L25 Dermite de contact, sans précision
L280 Lichen simplex chronique
L281 Prurigo nodulaire de Hyde
L282 Autres formes de prurigo
L301 Dyshidrose [pompholyx]
L40 Psoriasis
L43 Lichen plan
L44 Autres lésions papulo-squameuses
L900 Lichen scléreux et atrophique
L920 Granulome annulaire
L93 Lupus érythémateux

Infliximab (CAS 170277-31-3; commercialized 2000)
H209 Iridocyclite, sans précision
H309 Choriorétinite, sans précision
K50 Maladie de Crohn [entérite régionale]
K51 Recto-colite hémorragique [colite ulcéreuse]
K52 Autres gastro-entérites et colites non infectieuses
L40 Psoriasis
L88 Pyodermite gangréneuse
M05 Polyarthrite rhumatoïde séropositive
M06 Autres polyarthrites rhumatoïdes
M070 Arthropathie psoriasique distale interphalangienne (L40.5)
M071 Arthrite mutilante (L40.5)
M072 Spondylite psoriasique (L40.5)
M073 Autres arthropathies psoriasiques (L40.5)
M314 Syndrome de la crosse aortique [Takayasu]
M352 Syndrome de Behçet
M45 Spondylarthrite ankylosante

Source: Theriaque 2022 edition.

Appendix Table 2. Calculation of the effective number of diagnoses for raloxifene in 2012 and adalimumab in 2015.

RALOXIFENE, 2012 Medical condition (c)	n_rx_c	$n\_rx_c / \sum_c n\_rx_c$	$(n\_rx_c / \sum_c n\_rx_c)^2$
206 Osteoporosis	67	34.0%	0.1157
203 Osteoarthritis	40	20.3%	0.0412
212 Other bone disease and musculoskeletal deformities	22	11.2%	0.0125
98 Essential hypertension	18	9.1%	0.0083
24 Cancer of breast	13	6.6%	0.0044
167 Nonmalignant breast conditions	9	4.6%	0.0021
140 Gastritis and duodenitis	6	3.0%	0.0009
173 Menopausal disorders	5	2.5%	0.0006
104 Other and ill-defined heart disease	5	2.5%	0.0006
204 Other non-traumatic joint disorders	4	2.0%	0.0004
202 Rheumatoid arthritis and related disease	4	2.0%	0.0004
51 Other endocrine disorders	2	1.0%	0.0001
134 Other upper respiratory disease	1	0.5%	0.0000
53 Disorders of lipid metabolism	1	0.5%	0.0000
SUM	197	100.0%	0.1874
Effective no. of diagnoses = $1 / [\sum_c (n\_rx_c / \sum_c n\_rx_c)^2]$			5.34

ADALIMUMAB, 2015 Medical condition (c)	n_rx_c	$n\_rx_c / \sum_c n\_rx_c$	$(n\_rx_c / \sum_c n\_rx_c)^2$
202 Rheumatoid arthritis and related disease	177	58.8%	0.3458
144 Regional enteritis and ulcerative colitis	50	16.6%	0.0276
198 Other inflammatory condition of skin	29	9.6%	0.0093
204 Other non-traumatic joint disorders	27	9.0%	0.0080
49 Diabetes mellitus without complication	13	4.3%	0.0019
41 Cancer; other and unspecified primary	4	1.3%	0.0002
232 Sprains and strains	1	0.3%	0.0000
SUM	301	100.0%	0.3928
Effective no. of diagnoses = $1 / [\sum_c (n\_rx_c / \sum_c n\_rx_c)^2]$			2.55

Source: author's calculations based on 2012 and 2015 Medical Expenditure Panel Survey Prescribed Medicines Files.