Study in support of the evaluation and impact assessment of the EU general pharmaceuticals legislation

Analytical Report

Written by Technopolis Group
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technopolis group

DG SANTE

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INTRODUCTION

The Analytical report focuses on reporting on secondary quantitative data analysis that was carried out as part of the the study in support of the Evaluation and Impact Assessment of the EU general pharmaceuticals legislation. It relies on existing proprietary and public databases and was used to populate pre-defined high-level indicators to assess relevant aspects of the 2004 revision of the general pharmaceutical legislation.

The empirical analyses revolve around various macroeconomic, environmental, social and technological indicators that may have been affected by the legislation. These quantitative indicators have been grouped in seven categories to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

These indicators provide trend analysis and comparison of pre- and post-legislative periods with respect to the implementation of the 2004 revision of the general pharmaceutical legislation. Reference data from other jurisdictions was also used to assess the impact of the EU legislation.

DATA ANALYSIS

We explore the evolution of various macro-level indicators relevant for the evaluation and impact assessment of the legislation and for the new objectives identified in the 2020 pharmaceutical strategy. Considering that the revision of the legislation was announced in 2004 and implemented in the following year, wherever data allows, we present longitudinal data covering the period 2000-2020, such that one can see the evolution of a given metric across a long enough period of time that includes a pre-event period of 5 years.

The final list of specific and measurable (SMART) indicators covers:

- 13 Industrial & Economic Competitiveness (IEC) indicators
- 9 Research & Innovation (RDI) indicators
- 10 Access indicators
- 6 Affordability and Single Market (ASM) indicators
- 3 indicators related to Efficiency
- 3 indicators specific to AMR (Antimicrobial Resistance)
- 7 indicators measuring the environmental impacts

For these indicators, when data allows, we compare the pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre- and post-legislative periods. Furthermore, in a few cases, we use difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation. More detailed methodology is provided where indicators are presented and data sources are available in Annex A.

1.1 INDUSTRIAL & ECONOMIC COMPETITIVENESS INDICATORS

The table below and in each of the following sections provide an overview of indicators analysed.

Indicator name	Indicator description
	International indicators:
IEC-1	Number of EU-origin medicines approved in the EU
IEC-2	Number of USA-origin medicines approved in the USA; Number of Japan-origin medicines approved in Japan; Number of Switzerland-origin medicines approved in Switzerland
IEC-3	Number of EU-origin medicines approved in one or more non-EU countries
IEC-4	Number of USA-origin medicines approved in the EU; Number of Japan-origin medicines approved in the EU; Number of Switzerland-origin medicines approved in the EU
IEC-5	Value of medicine exports EU to USA and USA to EU; Value of medicines exports EU to Japan and Japan to EU; Value of medicine exports EU to Switzerland and Switzerland to EU
IEC-6	Number of clinical trials performed in different geographies
	Internal EU indicators:
IEC-7	Employment in the pharmaceutical industry
IEC-8	GVA contribution of the pharmaceutical industry
IEC-9	Number of clinical trials conducted
IEC-10	Revenue generated by pharma companies
	Profitability of the sector:
IEC-11	Gross profit
	Additional IEC indicators:
IEC-12	Volumes of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics
IEC-13	Values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

IEC-1-4: Indicator definition and relevance with respect to the evaluation

Industrial and economic competitive indicators 1-4 are all related, measuring approvals of medicinal products with different geographic origins in different markets of interest.

If we consider competitiveness to mean the ability of a country or region to create welfare, taking into account the institutions, policies, and other factors which determine the level of productivity of a country or region, it is the intention of the IEC-1-4 indicators to measure changes in the ultimate output (productivity) of clinical research in the pharmaceutical industry, namely approved medicinal products both pre and post the implementation of the general pharmaceutical legislation. These approved products provide increased welfare in countries where they are approved, so the aim was to observe if the companies headquartered in the EU were able to be more productive (in terms of numbers of medicines approved) then competitors headquartered in

comparator countries, namely the USA, Japan, and Switzerland, which were assumed not to be influenced by the implementation of the general pharmaceutical legislation. In order to control for both the country of origin of the medicinal products (as defined by developer headquartered country) and for the region of approval, approvals of medicines with EU, USA, Japan, or Switzerland origin were compared in their respective home markets and the EU.

Methodology

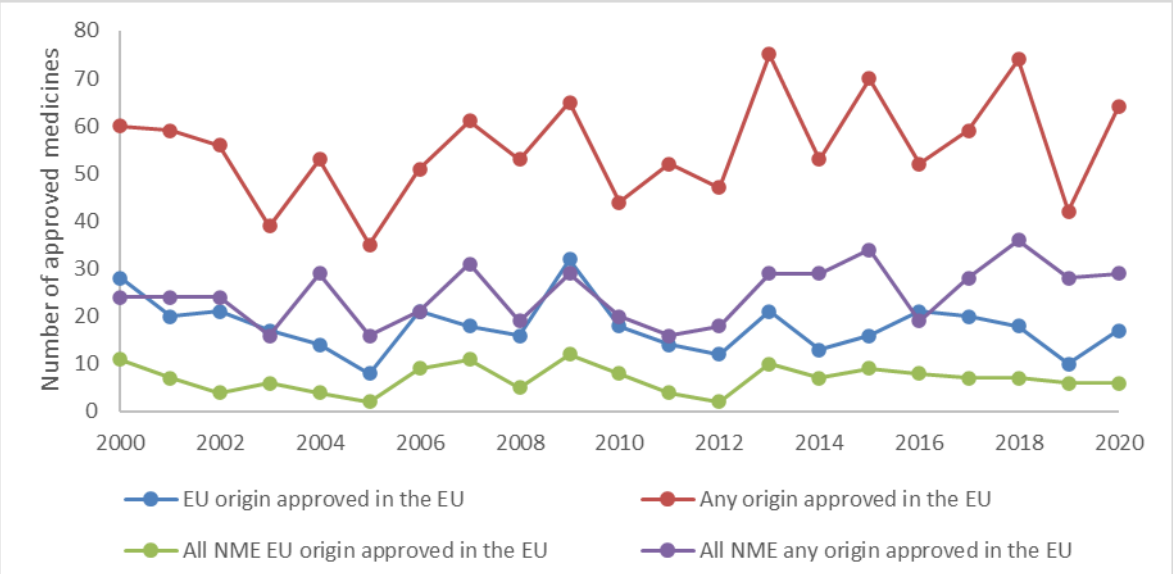
Throughout, all drug approval data are based on data contained within Pharmaprojects and Biomedtracker as of August 2021. The base data set for IEC-1-4 contained 4,981 products with a known approval date anywhere in the world. The approval year was set as first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. Therefore, in the case of approvals in the EU, no distinction is or can be made between drugs approved via the centralised or decentralised procedures using data from Pharmaprojects. Furthermore, all member states currently in the EU plus the UK were treated as having always been part of the EU for the entire analysis period. The scope of Pharmaprojects is also limited in that while the majority of medicinal products in development are covered, including biosimilars and reformulations relating to fixed dose combinations and route of administration reformulations by originator companies, approvals of generics or drug combinations are not recorded. The origin of the medical product was set by the HQ country of the originator company as recorded in Pharmaprojects. New molecular entity (NME) status as a definition of novel drug approvals was set by determining if products were recorded in Pharmaprojects as new chemical entities (NCEs) or new biologics (i.e., not recorded as a biosimilar or other generic). Pre and post refer to the analysis period before (pre defined as 2000-2004) or after (post defined as 2007-2020) the implementation of the general pharmaceutical legislation. Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) or non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. No post hoc or comparative analysis between indicators has been conducted. For all analyses, if the number of observations (in this case number of approved products) in an analysis period was less than 30, no statistical testing was performed or reported.

IEC-1: Number of EU-origin medicines approved in the EU

IEC-1 investigated approvals of EU-origin medicines in the EU in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. The number of approved products (via any authorisation route) were counted in each year between 2000 and 2020. Top level results comparing EU-origin medicines and medicines of any origin, split by new active substance status, are shown in Figure and Table IEC-1. While the average number of EU-origin medicines approved in the EU decreased in the post period, the difference was not statistically significant.[1] Analysis of the NME subset demonstrated that the average number of novel EU-origin medicines increased in the post period, but again the difference was not statistically significant. If the region of origin of the medicines is ignored, approvals for all products in the NME subset were shown to increase in the post period, but the difference was not statistically significant.

[1] Throughout this document, we show statistically significant differences between the pre and post periods by using **bold** p-value numbers in the analysis tables.

Figure IEC-1: EU-origin medicines approved in the EU and any origin medicines approved in the EU, split by all medicinal products or new active substances only.



Source: Pharmaprojects 2000-2020.

Table IEC-1 Descriptive statistics for EU-origin medicines approved in the EU and any origin medicines approved in the EU, split by all medicinal products or new active substances only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	EU	EU	Pre	18.429	5.827	12.601	24.256	100	0.759
All	EU	EU	Post	17.571	5.300	12.271	22.872	246	
All	All	EU	Pre	50.429	9.037	41.391	59.466	267	0.153
All	All	EU	Post	57.929	10.629	47.299	68.558	811	
New molecular entity	EU	EU	Pre	6.143	2.900	3.243	9.043	32	0.549
New molecular entity	EU	EU	Post	7.000	2.481	4.519	9.481	102	
New molecular entity	All	EU	Pre	22.000	4.375	17.625	26.375	117	0.164
New molecular entity	All	EU	Post	25.692	6.231	19.461	31.924	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

The data contained in Pharmaprojects facilitated the investigation of IEC-1 in more detail, both by therapy area and modality. The splits by therapy area for EU-origin medicines approved in the EU are shown in Table IEC1.2. In the post period, more oncology products were approved per year than in the pre period compared to the other therapy areas. No differences were observed for any other therapy area. In all cases, n

numbers were not sufficient for tests for statistical significance between the pre and post periods.

Table IEC1.2: Descriptive statistics for EU-origin medicines approved in the EU, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	EU	EU	Pre	3.571	1.498	2.073	5.070
Autoimmune/Inflammation	EU	EU	Post	2.857	1.542	1.315	4.399
Cardiovascular	EU	EU	Pre	2.286	1.750	0.536	4.035
Cardiovascular	EU	EU	Post	2.071	0.973	1.098	3.044
CNS	EU	EU	Pre	2.429	1.591	0.838	4.019
CNS	EU	EU	Post	2.786	2.162	0.624	4.948
Genitourinary	EU	EU	Pre	0.429	0.728	-0.300	1.157
Genitourinary	EU	EU	Post	0.714	0.738	-0.024	1.452
Infectious Disease	EU	EU	Pre	1.857	0.990	0.867	2.847
Infectious Disease	EU	EU	Post	1.143	1.406	-0.263	2.549
Metabolic/Endocrinology	EU	EU	Pre	3.857	1.959	1.898	5.816
Metabolic/Endocrinology	EU	EU	Post	3.214	1.961	1.253	5.175
Oncology	EU	EU	Pre	1.429	0.728	0.700	2.157
Oncology	EU	EU	Post	2.286	0.923	1.363	3.209
Ophthalmology	EU	EU	Pre	0.000	0.000	0.000	0.000
Ophthalmology	EU	EU	Post	0.214	0.421	-0.207	0.636
Vaccines	EU	EU	Pre	1.429	1.050	0.379	2.478
Vaccines	EU	EU	Post	1.786	2.044	-0.258	3.830

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Splits by modality are shown in Table IEC1. 3. In the post period, more antibody based products were approved than in the pre period. There were no differences observed related to any other modality investigated. Except for small molecules, n numbers were not sufficient in the pre analysis periods for tests for statistical significance between the pre and post periods, so such tests were not conducted.

Table IEC1. 3: Descriptive statistics for EU-origin medicines approved in the EU, split by modality

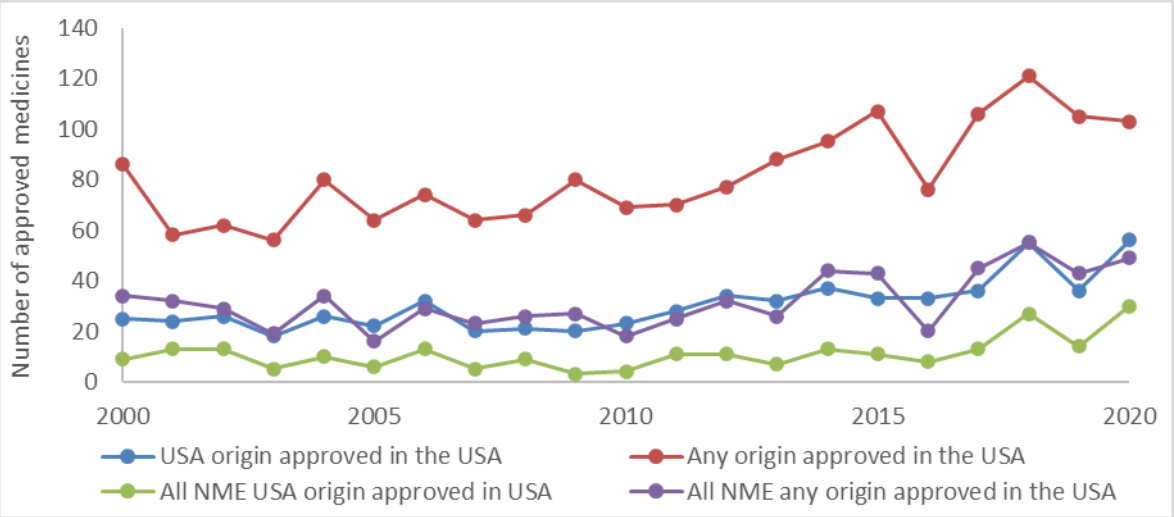
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	EU	Pre	13.43	4.30	9.12	17.73
Small molecule	EU	EU	Post	10.79	4.10	6.69	14.88
Antibody	EU	EU	Pre	0.29	0.45	-0.17	0.74
Antibody	EU	EU	Post	1.36	1.19	0.17	2.54
Cell therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	EU	Post	0.14	0.36	-0.22	0.50
Gene therapy	EU	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	EU	EU	Post	0.14	0.36	-0.22	0.50
RNA	EU	EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	EU	Post	0.07	0.27	-0.20	0.34
Peptide	EU	EU	Pre	0.14	0.35	-0.21	0.49
Peptide	EU	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Post	0.07	0.27	-0.20	0.34
Other biological	EU	EU	Pre	4.57	1.99	2.58	6.56
Other biological	EU	EU	Post	5.07	2.60	2.47	7.67

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

IEC-2: number of USA-origin medicines approved in the USA, Japan-origin medicines approved in Japan, and Switzerland-origin medicines approved in Switzerland

IEC-2 investigated approvals of USA-origin medicines in the USA, Japan-origin medicines in Japan, and Switzerland-origin medicines in Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing USA-origin medicines and medicines of any origin, split by NME status, are shown in Figure and Table IEC2.1. The average number of USA-origin medicines approved in the USA was found to significantly increase in the post period, as did the number of medicines of any origin. However, the analysis of the subset demonstrated that while the average number of novel USA-origin medicines increased in the post period, the difference was not statistically significant. As with the EU, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to increase in the post period, but the difference was not statistically significant.

Figure IEC2.1: USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by all medicinal products or new molecular entity only.



Source: Pharmaprojects 2000-2020.

Table IEC2.1: Descriptive statistics for USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by all medicinal products or new molecular entity only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	USA	USA	Pre	24.71	3.95	20.76	28.67	119	**0.015**
All	USA	USA	Post	33.14	10.63	22.51	43.78	464	
All	All	USA	Pre	68.57	10.68	57.90	79.25	342	**0.006**
All	All	USA	Post	87.64	17.11	70.53	104.76	1,227	
New molecular entity	USA	USA	Pre	9.86	3.14	6.72	12.99	50	0.333
New molecular entity	USA	USA	Post	12.38	7.60	4.78	19.99	166	
New molecular entity	All	USA	Pre	27.57	6.69	20.88	34.27	148	0.110
New molecular entity	All	USA	Post	34.85	11.61	23.23	46.46	476	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for USA-origin medicines approved in the USA, no differences relating to therapy area were observed (Table IEC2.2). Regarding modality, increases in the number of small molecule, antibody, and RNA drugs were observed in the post period compared to the pre period (Table IEC2.3). For the RNA drugs, the number involved is very small (0 in the pre period and 9 in the post period). N numbers were not sufficient for statistical comparisons between the pre and post periods.

Table IEC2.2: Descriptive statistics for USA-origin medicines approved in the USA, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	USA	USA	Pre	4.14	1.88	2.26	6.03
Autoimmune/Inflammation	USA	USA	Post	5.00	2.09	2.91	7.09
Cardiovascular	USA	USA	Pre	2.14	1.25	0.90	3.39
Cardiovascular	USA	USA	Post	3.00	2.13	0.87	5.13
CNS	USA	USA	Pre	4.86	2.03	2.83	6.89
CNS	USA	USA	Post	6.43	2.30	4.13	8.73
Genitourinary	USA	USA	Pre	1.14	0.83	0.31	1.98
Genitourinary	USA	USA	Post	1.57	1.22	0.36	2.79
Infectious Disease	USA	USA	Pre	3.14	1.64	1.50	4.78
Infectious Disease	USA	USA	Post	3.93	3.16	0.77	7.09
Metabolic/Endocrinology	USA	USA	Pre	3.71	2.05	1.66	5.76
Metabolic/Endocrinology	USA	USA	Post	3.86	2.48	1.38	6.33
Oncology	USA	USA	Pre	2.71	1.67	1.05	4.38
Oncology	USA	USA	Post	5.93	5.20	0.73	11.13
Ophthalmology	USA	USA	Pre	0.57	0.49	0.08	1.07
Ophthalmology	USA	USA	Post	0.93	0.62	0.31	1.54
Vaccines	USA	USA	Pre	1.00	0.76	0.24	1.76
Vaccines	USA	USA	Post	0.64	0.92	-0.28	1.57

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

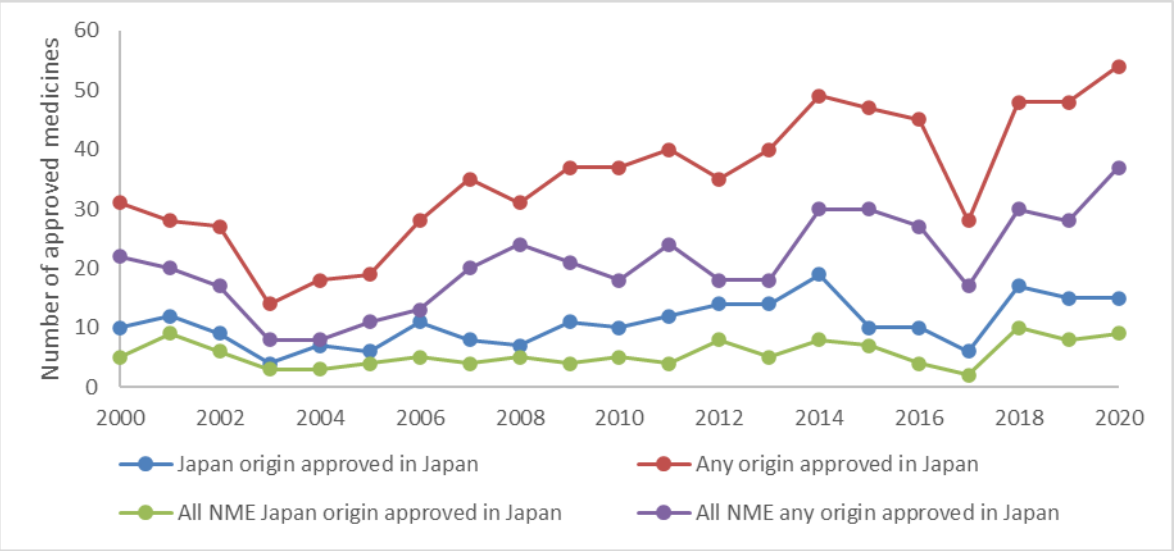
Table IEC2.3: Descriptive statistics for USA-origin medicines approved in the USA split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	USA	USA	Pre	17.86	3.87	13.99	21.73
Small molecule	USA	USA	Post	23.71	7.60	16.11	31.32
Antibody	USA	USA	Pre	0.71	0.70	0.01	1.41
Antibody	USA	USA	Post	3.21	2.53	0.68	5.74
Cell therapy	USA	USA	Pre	0.29	0.45	-0.17	0.74
Cell therapy	USA	USA	Post	0.71	0.62	0.09	1.34
Gene therapy	USA	USA	Pre	0.14	0.35	-0.21	0.49
Gene therapy	USA	USA	Post	0.71	0.82	-0.11	1.54
RNA	USA	USA	Pre	0.00	0.00	0.00	0.00
RNA	USA	USA	Post	0.64	0.91	-0.27	1.55
Peptide	USA	USA	Pre	0.00	0.00	0.00	0.00
Peptide	USA	USA	Post	0.14	0.36	-0.22	0.50
Fusion protein	USA	USA	Pre	0.14	0.35	-0.21	0.49
Fusion protein	USA	USA	Post	0.50	0.75	-0.25	1.25
Other biological	USA	USA	Pre	5.71	1.75	3.96	7.46
Other biological	USA	USA	Post	4.43	1.60	2.83	6.03

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Japan-origin medicines and medicines of any origin, split by NME status, are shown in Figure IEC2.2 and Table IEC2.4. The average number of Japan-origin medicines approved in Japan was found to significantly increase in the post period, as was the number of medicines of any origin. However, the analysis of the NME subset demonstrated that while the average number of novel Japan-origin medicines increased in the post period, no difference was observed and n numbers were insufficient for statistical analysis. In contrast to the EU and the USA, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to significantly increase in the post period compared to the pre period.

Figure IEC2.2: Japan-origin medicines approved in Japan and any origin medicines approved in Japan split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC2.4 Descriptive statistics for Japan-origin medicines approved in Japan and any origin medicines approved in Japan, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	Japan	Japan	Pre	8.43	2.66	5.76	11.09	42	**0.021**
All	Japan	Japan	Post	12.00	3.65	8.35	15.65	168	
All	All	Japan	Pre	23.57	5.97	17.60	29.54	118	**0.001**
All	All	Japan	Post	41.00	7.44	33.56	48.44	574	
New molecular entity	Japan	Japan	Pre	5.00	1.93	3.07	6.93	26	Not determined
New molecular entity	Japan	Japan	Post	6.08	2.30	3.77	8.38	88	
New molecular entity	All	Japan	Pre	14.14	5.22	8.92	19.36	75	**0.002**
New molecular entity	All	Japan	Post	24.77	5.95	18.82	30.72	342	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for Japan-origin medicines approved in Japan, increases in approvals for central nervous system, metabolic/endocrinology, and oncology products were observed in the post period (Table IEC2.5). Regarding modalities, differences were observed with other biological products increasing in the post period compared to the pre period (Table IEC2.6). In other cases, the number of approvals was too low to perform statistical analysis.

Table IEC2.5 Descriptive statistics for Japan-origin medicines approved in Japan, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Japan	Japan	Pre	2.29	2.43	-0.15	4.72
Autoimmune/Inflammation	Japan	Japan	Post	1.71	0.89	0.82	2.60
Cardiovascular	Japan	Japan	Pre	1.43	0.73	0.70	2.16
Cardiovascular	Japan	Japan	Post	1.50	1.50	0.00	3.00
CNS	Japan	Japan	Pre	0.57	0.49	0.08	1.07
CNS	Japan	Japan	Post	1.71	1.29	0.42	3.01
Genitourinary	Japan	Japan	Pre	0.57	0.73	-0.16	1.30
Genitourinary	Japan	Japan	Post	0.43	0.62	-0.20	1.05
Infectious Disease	Japan	Japan	Pre	1.29	1.03	0.26	2.32
Infectious Disease	Japan	Japan	Post	0.79	0.97	-0.19	1.76
Metabolic/Endocrinology	Japan	Japan	Pre	1.00	1.07	-0.07	2.07
Metabolic/Endocrinology	Japan	Japan	Post	2.86	1.07	1.79	3.93
Oncology	Japan	Japan	Pre	0.57	0.49	0.08	1.07
Oncology	Japan	Japan	Post	1.79	1.14	0.64	2.93
Ophthalmology	Japan	Japan	Pre	0.14	0.35	-0.21	0.49
Ophthalmology	Japan	Japan	Post	0.57	0.74	-0.17	1.31
Vaccines	Japan	Japan	Pre	0.29	0.70	-0.41	0.99
Vaccines	Japan	Japan	Post	0.43	0.62	-0.20	1.05

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

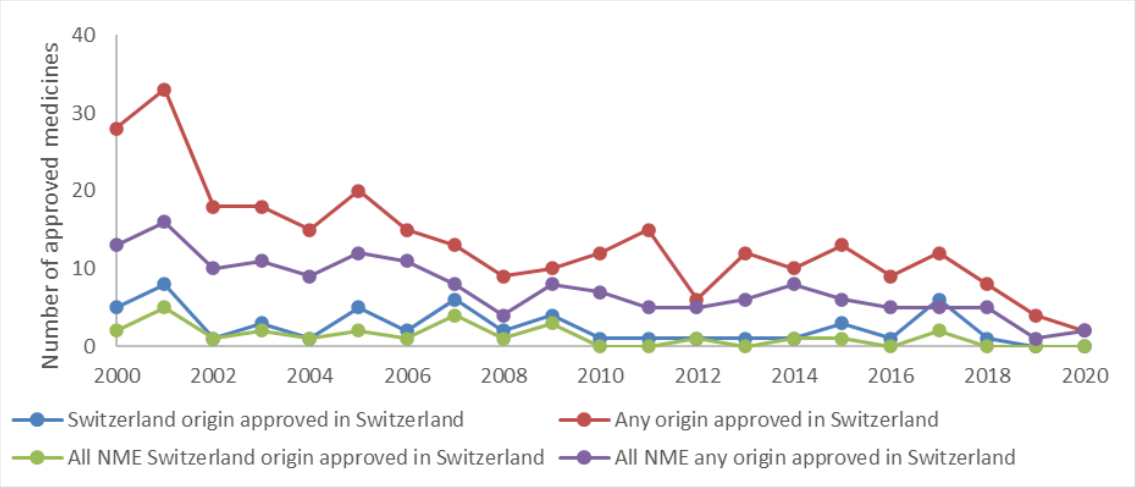
Table IEC2.6 Descriptive statistics for Japan-origin medicines approved in Japan, split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	Japan	Japan	Pre	7.71	2.05	5.66	9.76
Small molecule	Japan	Japan	Post	9.57	3.02	6.55	12.60
Antibody	Japan	Japan	Pre	0.14	0.35	-0.21	0.49
Antibody	Japan	Japan	Post	0.43	0.63	-0.21	1.06
Cell therapy	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Cell therapy	Japan	Japan	Post	0.21	0.42	-0.21	0.64
Gene therapy	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Gene therapy	Japan	Japan	Post	0.14	0.36	-0.22	0.50
RNA	Japan	Japan	Pre	0.00	0.00	0.00	0.00
RNA	Japan	Japan	Post	0.07	0.27	-0.20	0.34
Peptide	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Peptide	Japan	Japan	Post	0.00	0.00	0.00	0.00
Fusion protein	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Fusion protein	Japan	Japan	Post	0.00	0.00	0.00	0.00
Other biological	Japan	Japan	Pre	0.57	0.73	-0.16	1.30
Other biological	Japan	Japan	Post	1.71	1.00	0.71	2.72

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Switzerland-origin medicines and medicines of any origin, split by NME status, are shown in Figure IEC2.3 and Table IEC2.7. It should be noted that the n numbers in the Switzerland calculations are vastly reduced compared to the other analysis regions, as can be observed in the differences in the mean values for the pre and post periods, and they were not sufficient for statistical analysis. The average number of Switzerland-origin medicines approved in Switzerland was found to decrease in the post period. For the products of any origin, approvals were also shown to decrease in the post period compared to the pre period. The analysis of the NME subset demonstrated that the average number of novel Switzerland-origin medicines also decreased in the post period. In further contrast to the other analysis regions, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to decrease in the post period compared to the pre period.

Figure IEC2.3 Switzerland-origin medicines approved in Switzerland and any origin medicines approved in Switzerland split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC2.7 Descriptive statistics for Switzerland-origin medicines approved in Switzerland and any origin medicines approved in Switzerland, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
All	Switzerland	Switzerland	Pre	2.71	1.83	0.88	4.54
All	Switzerland	Switzerland	Post	2.07	1.29	0.78	3.36
All	All	Switzerland	Pre	16.00	5.90	10.10	21.90
All	All	Switzerland	Post	7.50	2.53	4.97	10.03
New molecular entity	Switzerland	Switzerland	Pre	1.86	1.64	0.22	3.50
New molecular entity	Switzerland	Switzerland	Post	0.69	0.82	-0.13	1.51
New molecular entity	All	Switzerland	Pre	8.86	2.75	6.11	11.61
New molecular entity	All	Switzerland	Post	3.23	1.53	1.70	4.76

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Regarding therapy area and modality splits for Switzerland-origin medicines approved in Switzerland, no significant differences were observed for either therapy area (Table IEC2.8) or modality (Table IEC2.9) In other cases, n numbers were not sufficient to report the results of statistical tests for significance.

Table IEC2.8 Descriptive statistics for Switzerland-origin medicines approved in Switzerland split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Switzerland	Switzerland	Pre	1.43	1.59	-0.16	3.02
Autoimmune/Inflammation	Switzerland	Switzerland	Post	0.29	0.61	-0.32	0.89
Cardiovascular	Switzerland	Switzerland	Pre	0.43	0.49	-0.07	0.92
Cardiovascular	Switzerland	Switzerland	Post	0.36	0.42	-0.06	0.78
CNS	Switzerland	Switzerland	Pre	0.00	0.00	0.00	0.00
CNS	Switzerland	Switzerland	Post	0.21	0.58	-0.36	0.79
Genitourinary	Switzerland	Switzerland	Pre	0.14	0.35	-0.21	0.49
Genitourinary	Switzerland	Switzerland	Post	0.21	0.58	-0.36	0.79
Infectious Disease	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Infectious Disease	Switzerland	Switzerland	Post	0.29	0.58	-0.29	0.86
Metabolic/Endocrinology	Switzerland	Switzerland	Pre	0.43	0.49	-0.07	0.92
Metabolic/Endocrinology	Switzerland	Switzerland	Post	0.36	0.46	-0.10	0.82
Oncology	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Oncology	Switzerland	Switzerland	Post	0.36	0.61	-0.25	0.96
Ophthalmology	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Ophthalmology	Switzerland	Switzerland	Post	0.00	0.00	0.00	0.00
Vaccines	Switzerland	Switzerland	Pre	0.00	0.00	0.00	0.00
Vaccines	Switzerland	Switzerland	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC2.9 Descriptive statistics for Switzerland-origin medicines approved in Switzerland split by modality

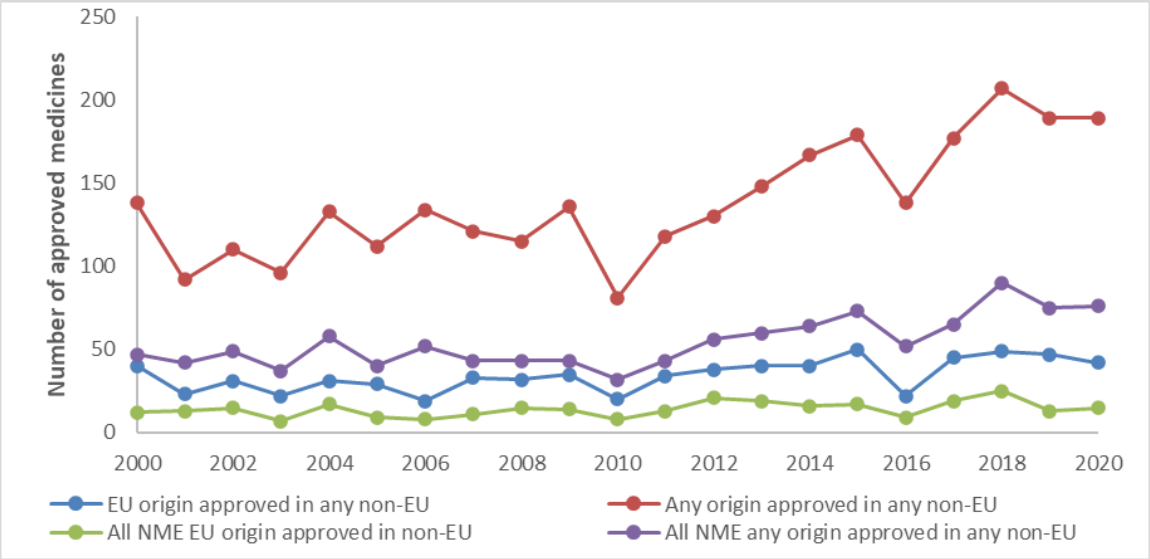
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	EU	Pre	2.14	1.81	0.34	3.95
Small molecule	EU	EU	Post	1.00	0.89	0.11	1.89
Antibody	EU	EU	Pre	0.29	0.45	-0.17	0.74
Antibody	EU	EU	Post	0.43	0.75	-0.32	1.17
Cell therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	EU	Post	0.00	0.00	0.00	0.00
Gene therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Gene therapy	EU	EU	Post	0.07	0.27	-0.20	0.34
RNA	EU	EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	EU	Post	0.00	0.00	0.00	0.00
Peptide	EU	EU	Pre	0.00	0.00	0.00	0.00
Peptide	EU	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Post	0.00	0.00	0.00	0.00
Other biological	EU	EU	Pre	0.29	0.70	-0.41	0.99
Other biological	EU	EU	Post	0.64	1.08	-0.43	1.72

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

IEC-3: Number of EU-origin medicines approved in one or more non-EU countries

IEC-3 investigated approvals of EU-origin medicines in one or more non-EU countries in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing EU-origin medicines and medicines of any origin, split by NME, are shown in Figure IEC-3.1 and Table IEC-3.1. The average number of EU-origin medicines approved in one or more non-EU countries was found to increase in the post period, but the difference was not significant. The number of medicines of any origin approved in one or more non-EU countries increased significantly in the post period. The analysis of the NME subset demonstrated that both the average number of novel EU-origin medicines and any origin medicines increased significantly in the post period. In the pre period, approximately 70% of medicines of EU origin were found to be approved both in the EU and outside the EU; this rose to almost 80% in the post period.

Figure IEC-3.1 EU-origin medicines approved in one or more non-EU countries and any origin medicines approved in one or more non-EU countries split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-3.1 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	EU	Non-EU	Pre	27.86	6.60	21.26	34.46	147	0.222
All	EU	Non-EU	Post	37.64	9.03	28.61	46.67	527	
All	All	Non-EU	Pre	116.43	17.42	99.01	133.85	569	**0.010**
All	All	Non-EU	Post	149.64	34.93	114.71	184.57	2095	
New molecular entity	EU	Non-EU	Pre	11.57	3.46	8.11	15.03	64	**0.048**
New molecular entity	EU	Non-EU	Post	15.69	4.48	11.21	20.17	215	
New molecular entity	All	Non-EU	Pre	46.43	6.78	39.65	53.21	233	**0.027**
New molecular entity	All	Non-EU	Post	59.38	15.97	43.41	75.36	815	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for EU-origin medicines approved in one or more non-EU countries, observable increases were seen for CNS and genitourinary in the post period compared to the pre period (Table IEC-3.2). Regarding modalities, observable increases were seen relating to approvals for small molecules, antibodies, and gene therapies (Table IEC-3.3).

Table IEC-3.2 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	EU	Non-EU	Pre	4.43	3.54	0.89	7.97
Autoimmune/Inflammation	EU	Non-EU	Post	8.29	3.45	4.83	11.74
Cardiovascular	EU	Non-EU	Pre	5.29	2.66	2.63	7.94
Cardiovascular	EU	Non-EU	Post	4.79	2.20	2.59	6.99
CNS	EU	Non-EU	Pre	3.57	0.73	2.84	4.30
CNS	EU	Non-EU	Post	5.50	2.06	3.44	7.56
Genitourinary	EU	Non-EU	Pre	0.71	0.45	0.26	1.17
Genitourinary	EU	Non-EU	Post	1.64	1.31	0.33	2.95
Infectious Disease	EU	Non-EU	Pre	3.14	1.25	1.90	4.39
Infectious Disease	EU	Non-EU	Post	3.64	2.58	1.07	6.22
Metabolic/Endocrinology	EU	Non-EU	Pre	3.57	1.92	1.65	5.49
Metabolic/Endocrinology	EU	Non-EU	Post	5.57	2.87	2.70	8.44
Oncology	EU	Non-EU	Pre	3.00	1.69	1.31	4.69
Oncology	EU	Non-EU	Post	3.64	1.44	2.20	5.09
Ophthalmology	EU	Non-EU	Pre	0.14	0.35	-0.21	0.49
Ophthalmology	EU	Non-EU	Post	0.64	0.82	-0.18	1.46
Vaccines	EU	Non-EU	Pre	2.29	1.83	0.46	4.12
Vaccines	EU	Non-EU	Post	2.57	1.94	0.63	4.51

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC-3.3 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries split by modality

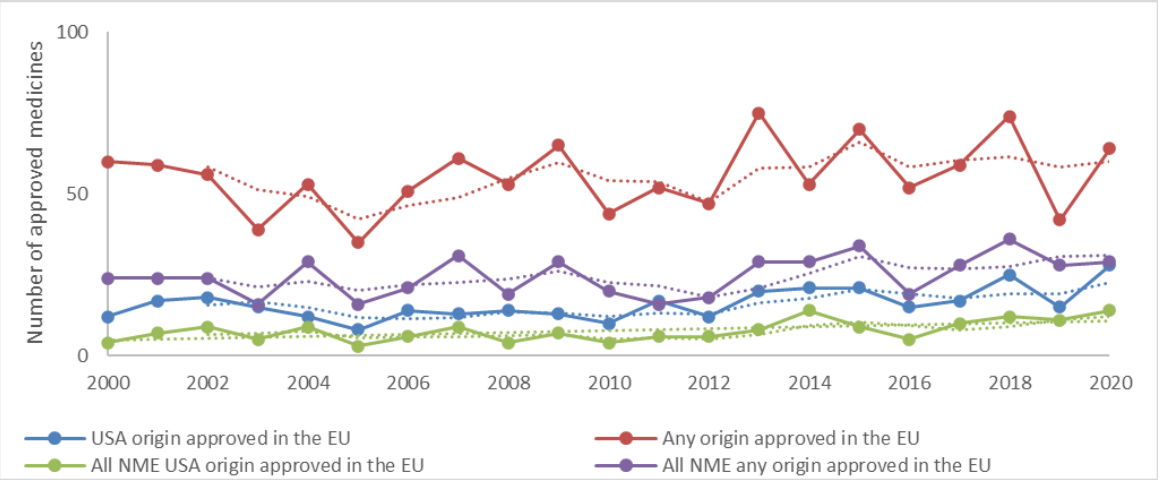
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	Non-EU	Pre	20.43	4.66	15.77	25.08
Small molecule	EU	Non-EU	Post	26.86	6.80	20.06	33.66
Antibody	EU	Non-EU	Pre	0.43	0.49	-0.07	0.92
Antibody	EU	Non-EU	Post	1.64	1.31	0.33	2.95
Cell therapy	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	Non-EU	Post	0.21	0.42	-0.21	0.64
Gene therapy	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Gene therapy	EU	Non-EU	Post	0.57	0.62	-0.05	1.20
RNA	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	Non-EU	Post	0.00	0.00	0.00	0.00
Peptide	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Peptide	EU	Non-EU	Post	0.07	0.27	-0.20	0.34
Fusion protein	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	Non-EU	Post	0.07	0.27	-0.20	0.34
Other biological	EU	Non-EU	Pre	7.00	2.98	4.02	9.98
Other biological	EU	Non-EU	Post	8.79	3.62	5.17	12.41

Source: Pharmaprojects (2021) and Biomedtracker (2021).

IEC-4: number of USA-origin medicines approved in the EU; number of Japan-origin medicines approved in the EU; number of Switzerland-origin medicines approved in the EU

IEC-4 investigated approvals of USA-origin medicines in the EU, Japan-origin medicines in the EU, and Switzerland-origin medicines in the EU in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing USA-origin medicines, split by NME status, are shown in Figure IEC-4.1 and Table IEC-4.1. For comparison, approval of medicines of any origin in the EU is shown. While in all cases the number of medicines approved was shown to increase in the post period compared to the pre period, differences were not significant.

Figure IEC-4.1 USA-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.1 Descriptive statistics for USA-origin medicines approved in the EU, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	USA	EU	Pre	22.00	3.96	18.04	25.96	74	0.065
All	USA	EU	Post	25.93	9.84	16.09	35.76	241	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	USA	EU	Pre	8.00	3.51	4.49	11.51	34	0.097
New molecular entity	USA	EU	Post	9.31	2.70	6.61	12.01	119	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	177	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

No differences were observed by therapy area (Table IEC-4.2), but for modality, approvals of antibody products and cell therapy products were shown to observably increase in the post period compared to the pre period (Table IEC-4.3).

Table IEC-4.2 Descriptive statistics for USA-origin medicines approved in the EU split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	USA	EU	Pre	2.14	1.73	0.42	3.87
Autoimmune/Inflammation	USA	EU	Post	2.64	1.60	1.04	4.24
Cardiovascular	USA	EU	Pre	1.14	0.83	0.31	1.98
Cardiovascular	USA	EU	Post	1.36	1.69	-0.34	3.05
CNS	USA	EU	Pre	2.43	1.68	0.75	4.11
CNS	USA	EU	Post	2.07	1.23	0.84	3.30
Genitourinary	USA	EU	Pre	0.14	0.35	-0.21	0.49
Genitourinary	USA	EU	Post	0.29	0.61	-0.32	0.89
Infectious Disease	USA	EU	Pre	0.71	0.70	0.01	1.41
Infectious Disease	USA	EU	Post	0.36	0.62	-0.27	0.98
Metabolic/Endocrinology	USA	EU	Pre	1.71	1.16	0.55	2.87
Metabolic/Endocrinology	USA	EU	Post	3.29	2.04	1.24	5.33
Oncology	USA	EU	Pre	1.86	1.25	0.61	3.10
Oncology	USA	EU	Post	2.36	1.69	0.66	4.05
Ophthalmology	USA	EU	Pre	2.00	1.07	0.93	3.07
Ophthalmology	USA	EU	Post	3.64	2.52	1.12	6.17
Vaccines	USA	EU	Pre	0.57	0.73	-0.16	1.30
Vaccines	USA	EU	Post	0.50	0.75	-0.25	1.25

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

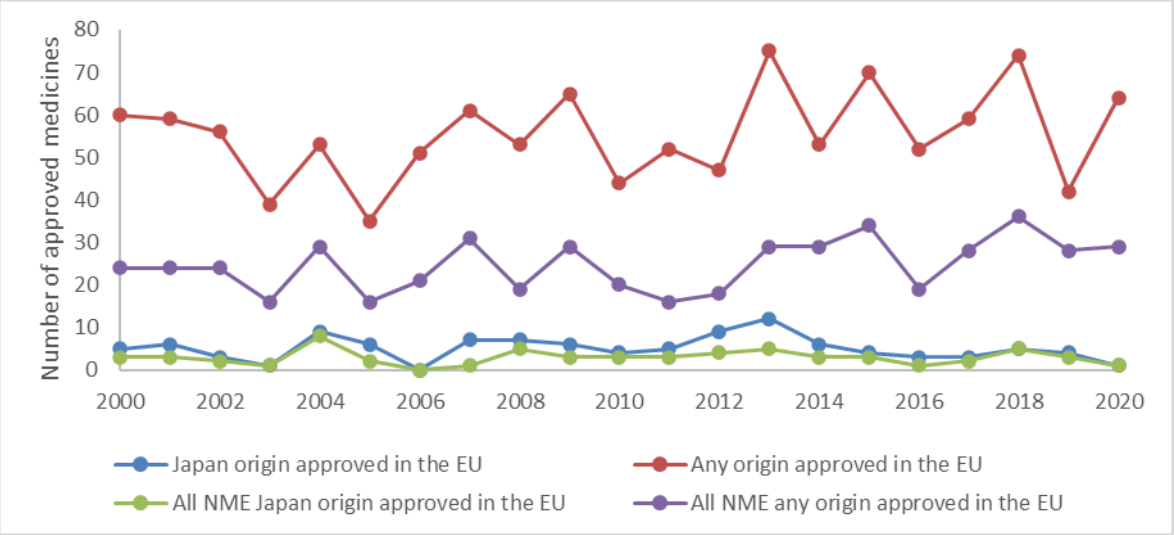
Table IEC-4.3 Descriptive statistics for USA-origin medicines approved in the EU split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	USA	EU	Pre	9.86	2.42	7.44	12.27
Small molecule	USA	EU	Post	10.64	3.03	7.62	13.67
Antibody	USA	EU	Pre	0.43	0.73	-0.30	1.16
Antibody	USA	EU	Post	2.57	2.43	0.14	5.00
Cell therapy	USA	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	USA	EU	Post	0.43	0.50	-0.07	0.93
Gene therapy	USA	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	USA	EU	Post	0.36	0.62	-0.27	0.98
RNA	USA	EU	Pre	0.00	0.00	0.00	0.00
RNA	USA	EU	Post	0.50	0.93	-0.43	1.43
Peptide	USA	EU	Pre	0.00	0.00	0.00	0.00
Peptide	USA	EU	Post	0.14	0.36	-0.22	0.50
Fusion protein	USA	EU	Pre	0.14	0.35	-0.21	0.49
Fusion protein	USA	EU	Post	0.64	0.62	0.02	1.27
Other biological	USA	EU	Pre	3.29	1.03	2.26	4.32
Other biological	USA	EU	Post	2.43	1.15	1.28	3.57

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Japan-origin medicines, split by NME status, are shown in Figure IEC-4.2 and Table IEC-4.4. For comparison, the previously calculated all origin approval in the EU is shown. Similar to the USA-origin medicines, while in all cases the number of medicines approved was shown to increase in the post period compared to the pre period, differences were not significant or could not be determined statistically due to low numbers.

Figure IEC-4.2: Japan-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.4 Descriptive statistics for Japan-origin medicines approved in the EU, split by all medicinal products or new molecular entities only

New molecular entity	**Origin of medicine**	**Region of approval**	**Pre or post**	**MEAN**	**STDEV**	**LOW**	**HIGH**	**N number**	**WELCH'S T-TEST (P-value)**
All	Japan	EU	Pre	4.29	2.91	1.37	7.20	24	Not determined
All	Japan	EU	Post	5.43	2.73	2.70	8.16	76	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	Japan	EU	Pre	2.71	2.37	0.34	5.09	17	Not determined
New molecular entity	Japan	EU	Post	3.15	1.29	1.86	4.45	42	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	117	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area splits, oncology products were shown to observably increase in the post period compared to the pre period (Table IEC-4.5). No differences were observed regarding modalities (Table IEC-4.6).

Table IEC-4.5 Descriptive statistics for USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Japan	EU	Pre	1.43	1.68	-0.25	3.11
Autoimmune/Inflammation	Japan	EU	Post	0.43	0.49	-0.06	0.92
Cardiovascular	Japan	EU	Pre	1.14	0.99	0.15	2.13
Cardiovascular	Japan	EU	Post	0.64	0.61	0.04	1.25
CNS	Japan	EU	Pre	0.29	0.45	-0.17	0.74
CNS	Japan	EU	Post	0.71	0.91	-0.20	1.62
Genitourinary	Japan	EU	Pre	0.29	0.45	-0.17	0.74
Genitourinary	Japan	EU	Post	0.21	0.42	-0.21	0.64
Infectious Disease	Japan	EU	Pre	0.00	0.00	0.00	0.00
Infectious Disease	Japan	EU	Post	0.43	0.62	-0.20	1.05
Metabolic/Endocrinology	Japan	EU	Pre	0.86	1.12	-0.27	1.98
Metabolic/Endocrinology	Japan	EU	Post	1.14	1.21	-0.06	2.35
Oncology	Japan	EU	Pre	0.29	0.45	-0.17	0.74
Oncology	Japan	EU	Post	1.36	0.84	0.52	2.19
Ophthalmology	Japan	EU	Pre	0.00	0.00	0.00	0.00
Ophthalmology	Japan	EU	Post	0.21	0.42	-0.21	0.64
Vaccines	Japan	EU	Pre	0.00	0.00	0.00	0.00
Vaccines	Japan	EU	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

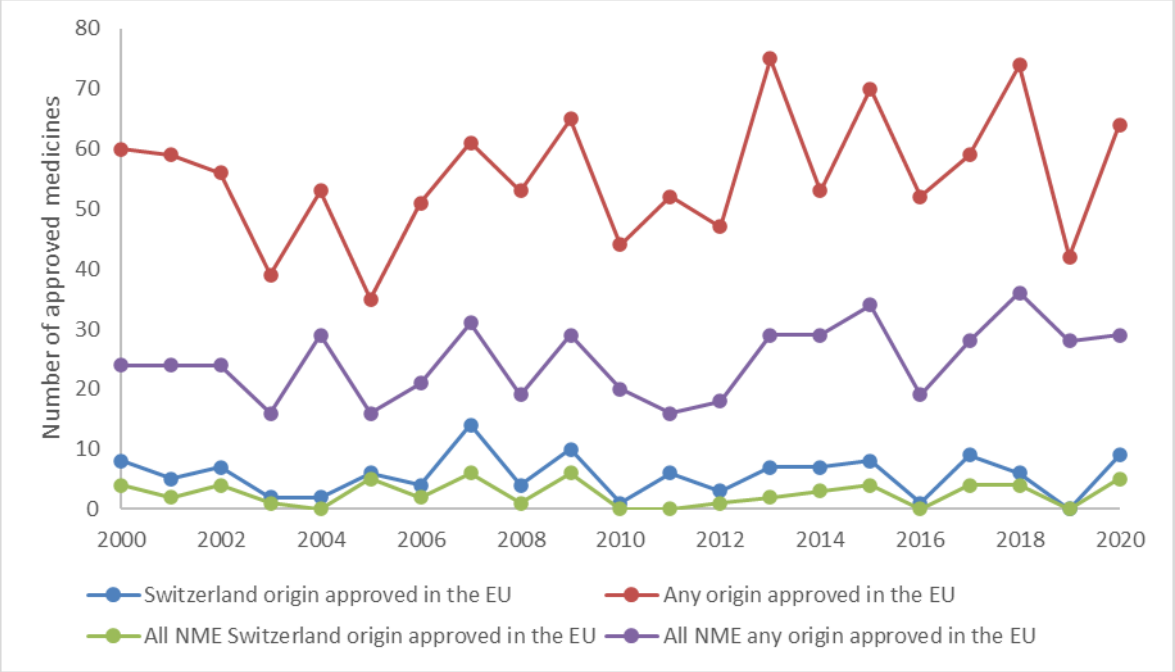
Table IEC-4.6 Descriptive statistics for Japan-origin medicines approved in the EU split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	WELCH'S T-TEST (P-value)
Small molecule	Japan	EU	Pre	3.86	2.85	1.01	6.71	0.637
Small molecule	Japan	EU	Post	4.57	2.73	1.84	7.31	
Antibody	Japan	EU	Pre	0.00	0.00	0.00	0.00	0.137
Antibody	Japan	EU	Post	0.36	0.84	-0.48	1.19	
Cell therapy	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Cell therapy	Japan	EU	Post	0.00	0.00	0.00	0.00	
Gene therapy	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Gene therapy	Japan	EU	Post	0.00	0.00	0.00	0.00	
RNA	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
RNA	Japan	EU	Post	0.00	0.00	0.00	0.00	
Peptide	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Peptide	Japan	EU	Post	0.00	0.00	0.00	0.00	
Fusion protein	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Fusion protein	Japan	EU	Post	0.00	0.00	0.00	0.00	
Other biological	Japan	EU	Pre	0.43	0.49	-0.07	0.92	0.861
Other biological	Japan	EU	Post	0.50	0.49	0.01	0.99	

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Switzerland-origin medicines, split by NME status, are shown in Figure IEC-4.3 and Table IEC-4.7. For comparison, the previously calculated all origin approval in the EU is shown. Similar to the USA-origin medicines and Japan-origin medicines, in all cases, no differences were observed, but n numbers were not sufficient for statistical analysis.

Figure IEC-4.3 Switzerland-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.7 Descriptive statistics for Switzerland-origin medicines approved in the EU, split by all medicinal products or new molecular entity only

New molecular entity	**Origin of medicine**	**Region of approval**	**Pre or post**	**MEAN**	**STDEV**	**LOW**	**HIGH**	**N number**	**WELCH'S T-TEST (P-value)**
All	Switzerland	EU	Pre	4.29	2.91	1.37	7.20	24	Not determined
All	Switzerland	EU	Post	5.43	2.73	2.70	8.16	85	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	Switzerland	EU	Pre	2.71	2.37	0.34	5.09	11	Not determined
New molecular entity	Switzerland	EU	Post	3.15	1.29	1.86	4.45	36	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	117	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area splits, similar to Japan-origin medicines, oncology products were shown to increase in the post period compared to the pre period (Table IEC-4.8), but no differences were observed regarding modalities (Table IEC-4.9).

Table IEC-4.8 Descriptive statistics for Switzerland-origin medicines approved in the EU split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Switzerland	EU	Pre	1.71	1.58	0.14	3.29
Autoimmune/Inflammation	Switzerland	EU	Post	1.07	1.07	0.00	2.14
Cardiovascular	Switzerland	EU	Pre	0.71	1.03	-0.32	1.74
Cardiovascular	Switzerland	EU	Post	0.93	0.70	0.23	1.63
CNS	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
CNS	Switzerland	EU	Post	0.29	0.42	-0.14	0.71
Genitourinary	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Genitourinary	Switzerland	EU	Post	0.21	0.42	-0.21	0.64
Infectious Disease	Switzerland	EU	Pre	0.57	0.49	0.08	1.07
Infectious Disease	Switzerland	EU	Post	0.29	0.61	-0.32	0.89
Metabolic/Endocrinology	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Metabolic/Endocrinology	Switzerland	EU	Post	0.79	0.62	0.16	1.41
Oncology	Switzerland	EU	Pre	0.71	0.45	0.26	1.17
Oncology	Switzerland	EU	Post	1.86	1.64	0.22	3.50
Ophthalmology	Switzerland	EU	Pre	0.29	0.45	-0.17	0.74
Ophthalmology	Switzerland	EU	Post	0.50	0.62	-0.12	1.12
Vaccines	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
Vaccines	Switzerland	EU	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC-4.9 Descriptive statistics for Switzerland-origin medicines approved in the EU, split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	Switzerland	EU	Pre	3.29	1.16	2.13	4.45
Small molecule	Switzerland	EU	Post	3.79	2.46	1.32	6.25
Antibody	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Antibody	Switzerland	EU	Post	1.29	1.38	-0.09	2.67
Cell therapy	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	Switzerland	EU	Post	0.07	0.27	-0.20	0.34
Gene therapy	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	Switzerland	EU	Post	0.29	0.72	-0.44	1.01
RNA	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
RNA	Switzerland	EU	Post	0.00	0.00	0.00	0.00
Peptide	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Peptide	Switzerland	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	Switzerland	EU	Post	0.07	0.27	-0.20	0.34
Other biological	Switzerland	EU	Pre	1.00	0.76	0.24	1.76
Other biological	Switzerland	EU	Post	0.86	0.61	0.25	1.46

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Interpretation of possible causes for changes in IEC-1-4

In summary, there was no significant difference in the number of products approved in the EU that were developed by companies headquartered in the EU (EU-origin) following the implementation of the general pharmaceutical legislation compared to the period prior to implementation (IEC-1). However, it must be stated that no decline was observed, so companies were able to maintain the same level of productivity and welfare provision, despite well-known and widely discussed difficulties in successfully developing new medicinal products in the last 20 years. With that said, in the comparator countries, overall productivity for companies headquartered in the USA or Japan was seen to increase in their home markets as the number of drug approvals was demonstrated to increase (IEC-2). As a cross check, approvals of medicines of EU origin in countries outside the EU was investigated; again it was shown that companies headquartered in the EU were able to maintain, but not increase, productivity. This is evidence that it was not the approval procedure or at least any geographic factor that contributed to the overall numbers or change in numbers of approved products of EU-origin (IEC-3). The final set of observations was to look at the number of approved products in the EU from companies headquartered in the comparator regions. In all cases, productivity was maintained in the pre and post periods, demonstrating that the origin of the company was unlikely to be the driving factor behind the trends observed (IEC-4).

IEC-5.1: Value of medicine exports EU to Japan and Japan to EU

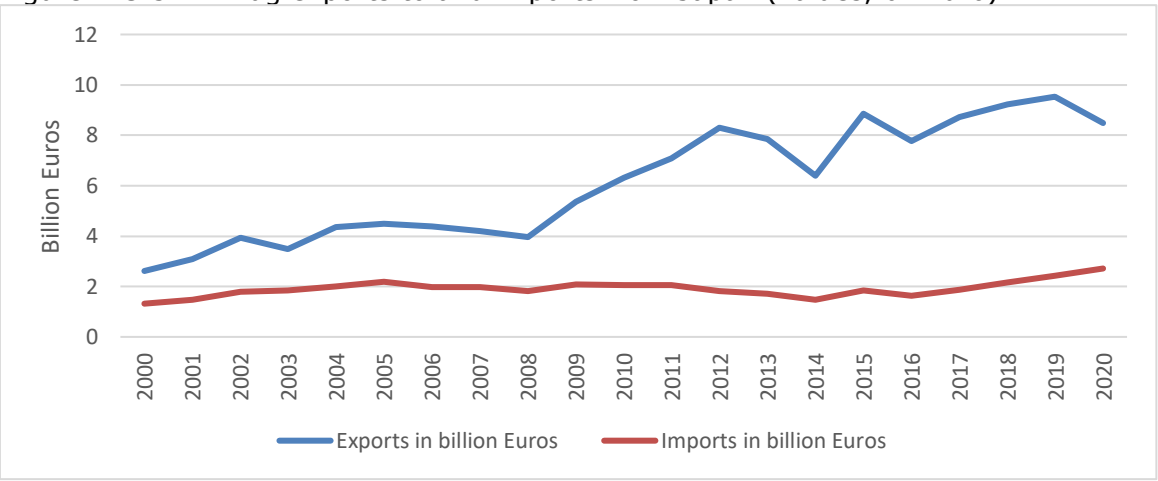
We have analysed the evolution of the EU's international trade in medicines, over the 20-year period from January 2000 to December 2020. We have run this analysis for several key trading partners, including Japan, Switzerland, and the US, each of which has been an important market for the EU pharmaceutical industry, as well as having its own strong domestic industry and regulatory frameworks. In each of these analyses,

we have used trade data from Eurostat. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types are categorised as Active Pharmaceutical Ingredients (APIs), Human Medicinal Products (HMPs), Finished Pharmaceutical Products (FPPs), Vaccines and Antibiotics (See the list of 126 product types in Annex B). The following graphs show medicinal products exports from EU27 countries and the UK (hereafter EU28) to Japan and Imports from Japan to EU28. For a breakdown of import/export trend figures for the various product types see additional IEC indicators IEC-12 and IEC-13 below.

The figures for the overall medicinal products show that exports from EU28 to Japan have grown strongly across the 20-year period, from around €2bn in 2000 to more than €8bn in 2020. The overall trend is characterised by several distinct phases, with exports remaining stable and close to €4bn a year during the period immediately following the introduction of the revised legislation (2004-2008), followed by double-digit annual growth in the period 2008-2012, reaching €8bn in 2012, notwithstanding the global financial crisis. Growth was more volatile in the subsequent 8-year period, with the value of exports in 2020 broadly equal to the value of exports in 2012. Interestingly, the EU-Japan Mutual Recognition Agreement, in force since 2004, does not seem to have had an immediate significant impact on EU28 exports of medicines to Japan, nor do the other elements of the EU's General Pharmaceutical legislation.

In comparison, EU28 imports from Japan have grown less strongly across the 20-year period, doubling in cash terms between 2000 and 2020, while EU exports to Japan had quadrupled in the same period. Moreover, the data show three phases, with clear growth in the 5-year period to 2005, followed by a weaker period, where imports were broadly flat or in decline, at around €2bn, across the 10-year period 2004-2014. In a third phase, the trade data show strong year-on-year growth in imports, from 2016 to 2020, outpacing EU exports.

Figure IEC-5.1: Drug exports to and imports from Japan (values, bn Euro)

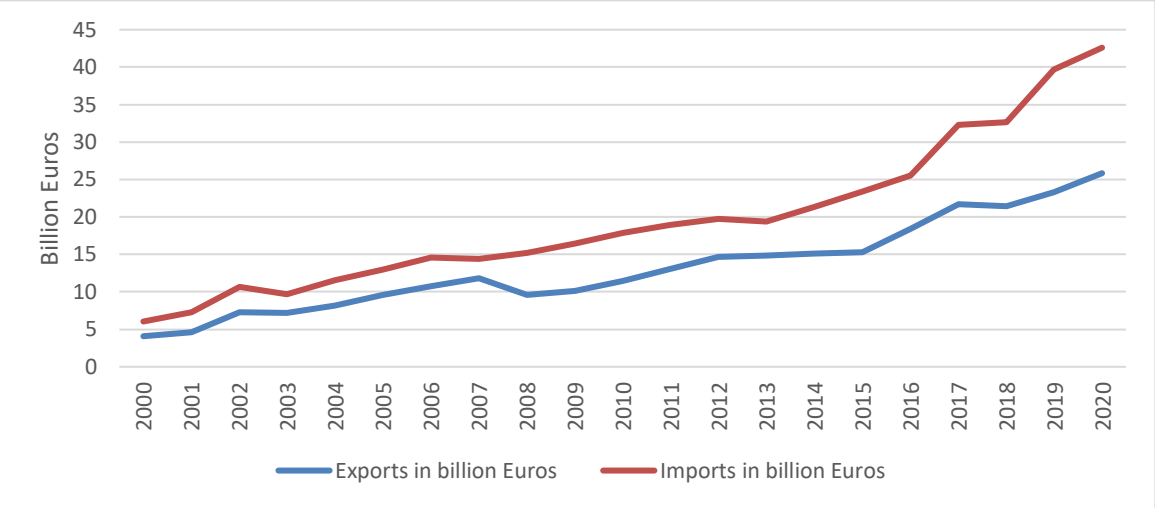


Source: Eurostat. The graph shows medicinal products exports from EU28 to Japan and Imports from Japan to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

IEC-5.2: Value of medicine exports EU to Switzerland and Switzerland to EU

The next graph shows medicines exports from EU28 countries to Switzerland and Imports from Switzerland to EU28 countries. The figures show that EU exports to Switzerland displayed consistent growth across the period 2000-2020, increasing fivefold, from close to €5bn in 2000 to close to €26bn in 2020. A similar change happened with EU28 imports from Switzerland, which grew sevenfold in the same period, from €6bn in 2000 to €42bn in 2020. These patterns could reflect the positive impact of the Mutual Recognition Agreement that has been in operation since June 2002.

Figure IEC-5.2: Drug exports to and imports from Switzerland (values, bln Euro)



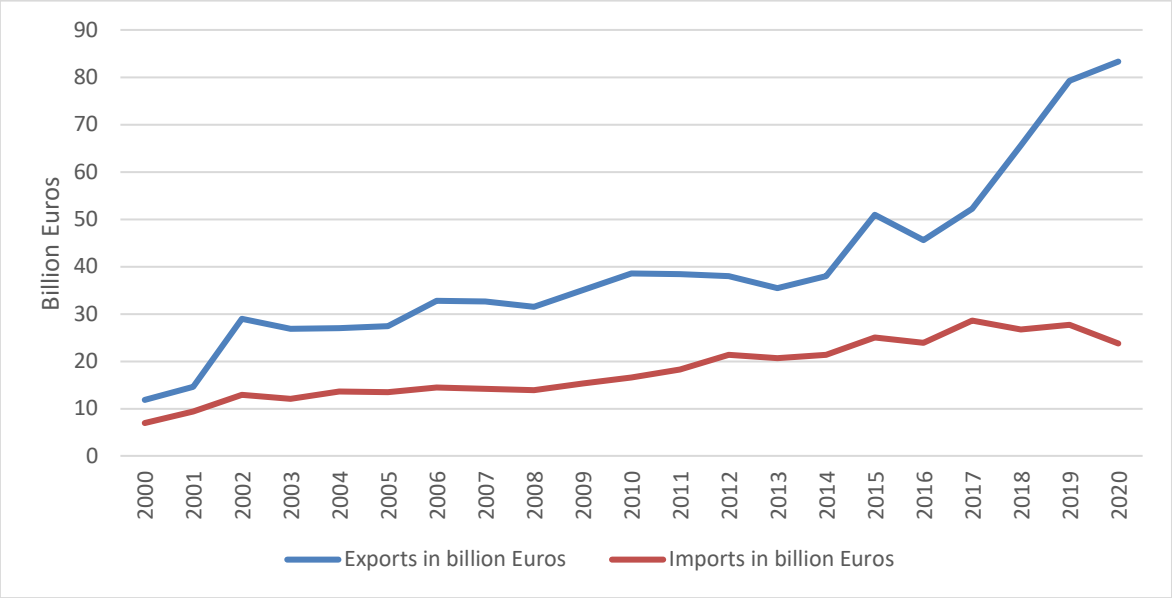
Source: Eurostat. The graph shows medicinal products exports from EU28 to Switzerland and Imports from Switzerland to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

IEC-5.3: Value of medicine exports EU to USA and USA to EU

The next graph shows medicines exports from EU28 countries to the US and Imports from the US to EU28 countries.

The figures show that EU28 medicines exports to the USA displayed moderate growth during the period 2003-2010 from €27 to €38 billion Euros in 2010 and faster growth during 2017-2020 going from €52bn to €83bn. This could be triggered by the Mutual Recognition Agreement that has been in operation since November 2017. By contrast, EU28 drug imports from the USA doubled in the first 2-3 years of the new century and then took another 10 years to double again, albeit with stronger growth during the period 2008-2017 when imports grew from €14bn in 2008 to €29bn in 2017. Recent performance has shown a marked reversal, with imports falling to around €23bn.

Figure IEC-5.3: Drug exports to and imports from the US (values, bn Euro)



Source: Eurostat. The graph shows medicinal products exports from EU28 to US and Imports from US to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

There is no obvious effect of the 2004 revision of the general pharmaceutical legislations in these trade data. The overall picture shows that EU trade with other key national and regional markets has grown across the 20-year period, before and after the implementation of the 2004 revisions. With exports and imports growing by 400-500% (in cash prices) across the period with each of the three trading blocs. Growth rates for both exports and imports were flatter in the 10 years or so following the introduction of the revised legislation, with growth in EU-USA trade noticeably slower in both directions during this middle-phase, before a significant strengthening of exports and slight weakening of imports in the last three years. Growth in EU-Japan trade has been more volatile, and weaker overall, but the last three years' trade figures are the inverse of the EU-US figures, with EU exports in decline and Japanese imports growing strongly.

IEC-6: Number of clinical trials performed in different geographies

Indicator definition and relevance with respect to the evaluation of IEC-6 and IEC-9

Industrial and economic competitiveness indicators 6 and 9 are related in that they measure the number of clinical trials starting in different countries of interest. As with IEC-1-4, if we consider competitiveness to mean the ability of a country or region to create welfare, taking into account the institutions, policies, and other factors that determine the level of productivity of a country or region, it is the intention of the IEC-6 and 9 indicators to measure changes in the intensity of clinical research (as a measure of productivity) in the pharmaceutical industry, both pre and post the implementation of the general pharmaceutical legislation. In order for a medicinal product to provide increased welfare in countries where it is approved, a product must successfully move through clinical research. Therefore, the aim was to observe if the EU demonstrated increased productivity following the implementation of the general pharmaceutical legislation, or if the USA, Japan, or Switzerland demonstrated increased productivity during the same period (these countries were of course assumed not to have been influenced by the implementation of the general pharmaceutical legislation). In addition, as in internal indicator for the EU, IEC-9 compares all nation states within the EU, to observe if any change in productivity was equally spread across the EU or not. In order to control for both the country of origin of the medicinal products (as defined by developer headquartered country) and for the region of approval, approvals of medicines with EU, USA, Japan, or Switzerland origin were compared in their respective home markets and the EU.

Methodology for IEC-6 and IEC-9

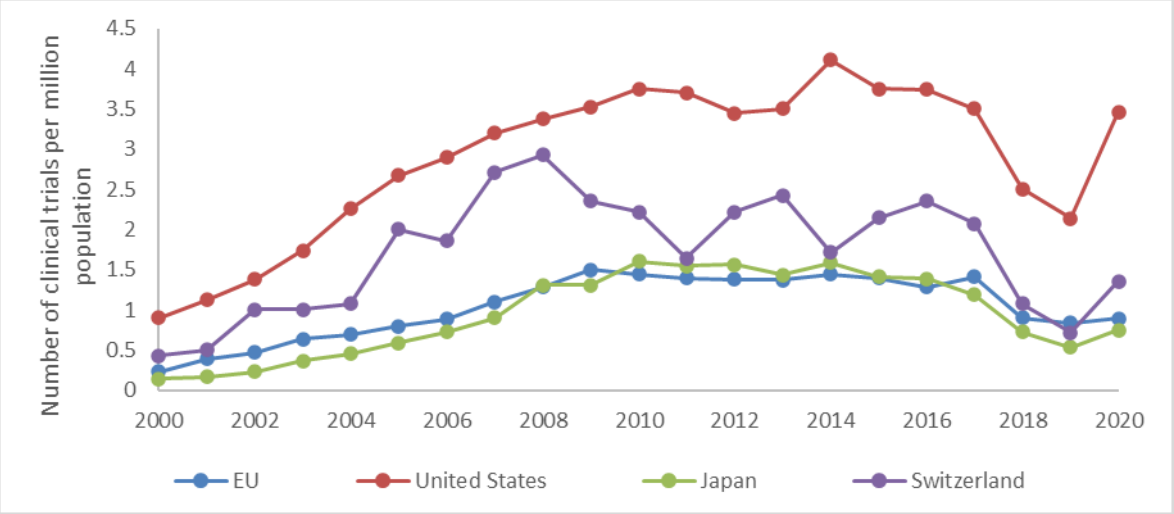
The base dataset for IEC-6 and 9 consists of over 172,000 Phase 1, Phase 2, and Phase 3 clinical trials contained in Trialtrove with start dates between 2000 and 2020. Each trial was assigned a development phase, an analysis region (USA, EU, Japan, Switzerland), and an analysis country (one of the EU28) based on the information contained in Trialtrove. In addition, only trials with known start dates and known or anticipated end dates were included. The countries in what was the EU28 were treated as always having been in the EU for the entire period of the analysis (2000-2020). Furthermore, the number of trials was adjusted based on the population of the analysis region or country in each year of the analysis period to facilitate more direct comparisons. The counts of clinical trials do not take into account the number of patients recruited in each region or country (such data are not available), so a trial with at least one site and therefore one or more patients per region or country is of necessity counted for that region or country. Trials conducted in multiple regions or countries are included as later phase trials are almost exclusively run globally or in at least two or more of the seven major pharmaceutical markets, making it impractical to exclude such trials. The mean number of clinical trials starting each year in each phase in each analysis region and country and standard deviations were determined for both the pre and post periods. As with IEC-1-4, Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post groups. For Phase 1 trials, Mann Whitney U tests are reported, as data were found not to fit a normal distribution. Parametric testing was preferred for Phase 2 and Phase 3, as data were found to fit a normal distribution. If the n number was lower than 30 completed trials in a phase for an analysis group, statistical analysis was not performed.

IEC-6

IEC-6 investigated the number of clinical trials starting in each year (adjusted for population) in each of the markets under investigation, namely the EU, the USA, Japan, and Switzerland, in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing each analysis region for trials in Phase 1 are shown in Figure IEC6-1 and Table IEC-6.1. In

all analysis regions, the number of Phase 1 trials starting in each year was found to significantly increase in the post period compared to the pre period. Per million of population, the number of Phase 1 trials conducted in the US and Switzerland was found to be double the number in the EU or Japan.

Figure IEC6-1 Number of Phase 1 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

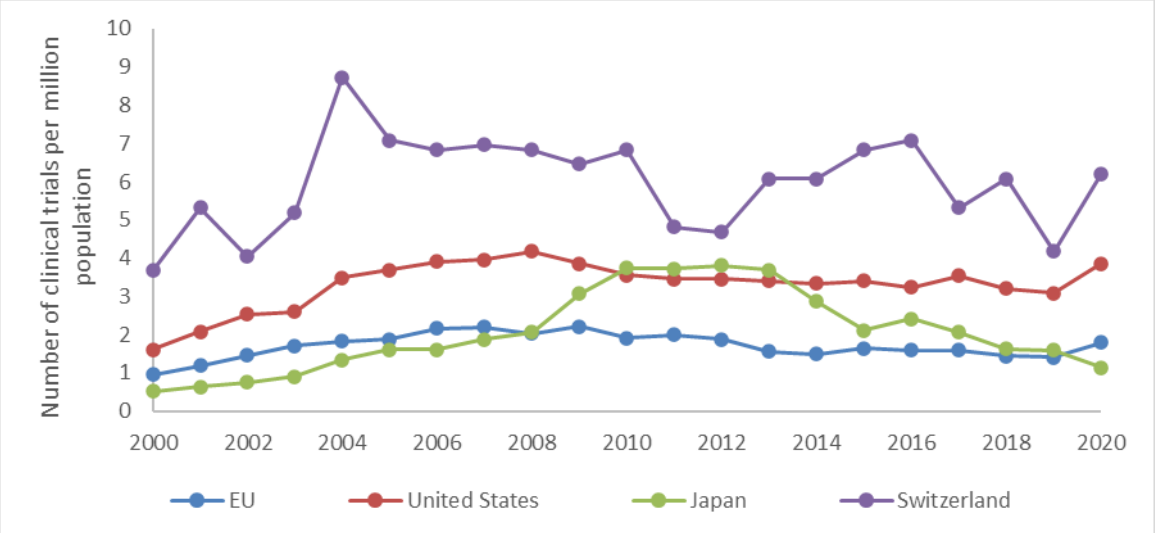
Table IEC-6.1 Descriptive statistics for the number of Phase 1 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted number of trials)	MANN-WHITNEY U TEST (P-value)
1	EU	Pre	0.58	0.22	0.37	0.80	1,058	**0.0009**
1	EU	Post	1.27	0.22	1.05	1.50	7,756	
1	USA	Pre	1.85	0.72	1.14	2.57	2,289	**0.001**
1	USA	Post	3.42	0.51	2.91	3.94	14,758	
1	Japan	Pre	0.38	0.21	0.18	0.59	173	**0.0005**
1	Japan	Post	1.26	0.35	0.91	1.60	2,206	
1	Switzerland	Pre	1.99	1.00	0.99	2.99	56	**0.014**
1	Switzerland	Post	3.44	1.04	2.39	4.48	391	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing each analysis region for trials in Phase 2 are shown in Figure IEC-6.2 and Table IEC-6.2. For Japan only, the number of Phase 2 trials starting in each year was found to significantly increase in the post period compared to the pre period. No other significant differences were observed. Furthermore, there were no observable differences between the analysis regions in terms of the number of Phase 2 trials per million of population.

Figure IEC-6.2 Number of Phase 2 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

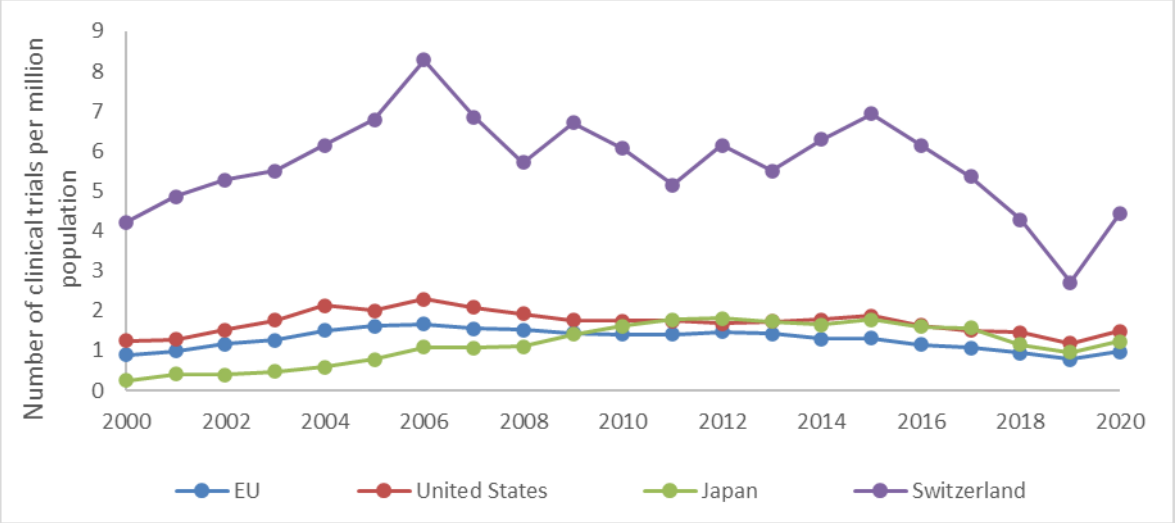
Table IEC-6.2 Descriptive statistics for the number of Phase 2 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted number of trials)	WELCH'S T-TEST (P-value)
2	EU	Pre	1.60	0.39	1.21	1.99	3,143	0.455
2	EU	Post	1.73	0.24	1.49	1.98	10,891	
2	USA	Pre	2.84	0.80	2.04	3.65	3,803	0.093
2	USA	Post	3.51	0.29	3.22	3.80	15,315	
2	Japan	Pre	1.06	0.43	0.63	1.48	553	**0.001**
2	Japan	Post	2.61	0.90	1.71	3.51	4,579	
2	Switzerland	Pre	5.84	1.67	4.17	7.51	213	0.875
2	Switzerland	Post	5.96	0.90	5.06	6.86	667	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing each analysis region for trials in Phase 3 are shown in Figure IEC-6.3 and Table IEC-6.3. **For Japan only, the number of Phase 3 trials starting in each year was found to significantly increase in the post period compared to the pre period. No other significant differences were observed. No difference in terms of the number of Phase 3 trials in the EU, the USA, and Japan was observed**, which is reflective of the global nature of Phase 3 development programs taking place simultaneously in the seven **major pharmaceutical markets**.

Figure IEC-6.3 Number of Phase 3 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

Table IEC-6.3 Descriptive statistics for the number of Phase 3 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
3	EU	Pre	1.30	0.28	1.02	1.58	2,564	0.672
3	EU	Post	1.24	0.23	1.01	1.47	7,102	
3	USA	Pre	1.75	0.39	1.36	2.13	2,450	0.585
3	USA	Post	1.65	0.19	1.46	1.84	7,275	
3	Japan	Pre	0.56	0.26	0.30	0.82	269	**0.002**
3	Japan	Post	1.49	0.28	1.21	1.76	2,609	
3	Switzerland	Pre	5.87	1.25	4.61	7.12	364	0.549
3	Switzerland	Post	5.49	1.10	4.39	6.60	996	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Table IEC-6.4 shows the splits by therapy area for each region for total trials, ignoring phase. Broadly similar trends in terms of the therapy areas with significant differences were observed between analysis regions, with numbers of trials for Autoimmune, CNS, Infectious disease, Metabolic, and Oncology all seeing significant differences between the pre and post periods.

Table IEC-6.4 Descriptive statistics for the number of clinical trials conducted in the EU, the USA, Japan, and Switzerland, split by therapy area

Therapy area	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
Autoimmune	EU	Pre	0.71	0.18	0.53	0.89	1,440	**0.009**
Autoimmune	EU	Post	1.07	0.12	0.95	1.20	6,622	
Autoimmune	USA	Pre	0.83	0.23	0.59	1.06	1,185	**0.003**
Autoimmune	USA	Post	1.33	0.12	1.21	1.46	5,759	
Autoimmune	Japan	Pre	0.31	0.15	0.16	0.47	174	**0.001**
Autoimmune	Japan	Post	1.14	0.24	0.90	1.37	1,969	
Autoimmune	Switzerland	Pre	1.83	0.71	1.13	2.54	115	0.579
Autoimmune	Switzerland	Post	2.03	0.34	1.69	2.38	397	
Cardiovascular	EU	Pre	0.49	0.18	0.32	0.67	955	0.089
Cardiovascular	EU	Post	0.71	0.15	0.56	0.86	4407	
Cardiovascular	USA	Pre	0.63	0.22	0.41	0.84	878	0.089
Cardiovascular	USA	Post	0.83	0.14	0.69	0.97	3648	
Cardiovascular	Japan	Pre	0.38	0.18	0.20	0.56	201	0.001
Cardiovascular	Japan	Post	1.05	0.36	0.69	1.41	1865	
Cardiovascular	Switzerland	Pre	1.61	0.55	1.06	2.16	102	0.144
Cardiovascular	Switzerland	Post	2.01	0.43	1.58	2.44	392	
CNS	EU	Pre	0.60	0.21	0.38	0.07	1162	**0.015**
CNS	EU	Post	0.97	0.18	0.78	0.16	6036	
CNS	USA	Pre	1.35	0.51	0.84	0.14	1906	**0.021**
CNS	USA	Post	2.10	0.09	2.00	0.31	9081	
CNS	Japan	Pre	0.19	0.08	0.11	0.06	104	**0.001**
CNS	Japan	Post	0.81	0.16	0.66	0.31	1422	
CNS	Switzerland	Pre	1.42	0.74	0.68	0.35	91	**0.022**
CNS	Switzerland	Post	2.08	0.44	1.64	0.49	409	
Genitourinary	EU	Pre	0.14	0.06	0.09	0.20	289	0.385
Genitourinary	EU	Post	0.18	0.04	0.13	0.22	1,096	
Genitourinary	USA	Pre	0.14	0.06	0.08	0.19	191	0.073
Genitourinary	USA	Post	0.20	0.05	0.15	0.25	867	
Genitourinary	Japan	Pre	0.05	0.02	0.03	0.07	30	Not determined
Genitourinary	Japan	Post	0.14	0.06	0.08	0.20	244	
Genitourinary	Switzerland	Pre	0.19	0.15	0.04	0.34	12	Not determined
Genitourinary	Switzerland	Post	0.20	0.12	0.08	0.32	42	
Infectious disease	EU	Pre	0.50	0.11	0.39	0.61	1011	**0.005**

Infectious disease	EU	Post	0.79	0.20	0.59	0.98	4,866	
Infectious disease	USA	Pre	0.69	0.21	0.48	0.90	967	**0.001**
Infectious disease	USA	Post	1.25	0.26	0.99	1.52	5,381	
Infectious disease	Japan	Pre	0.17	0.12	0.05	0.28	78	**0.001**
Infectious disease	Japan	Post	0.61	0.18	0.43	0.80	1,074	
Infectious disease	Switzerland	Pre	1.24	0.21	1.03	1.45	84	0.156
Infectious disease	Switzerland	Post	1.46	0.40	1.05	1.86	294	
Metabolic	EU	Pre	0.43	0.14	0.28	0.57	851	**0.035**
Metabolic	EU	Post	0.70	0.11	0.58	0.81	4,314	
Metabolic	USA	Pre	0.74	0.26	0.48	1.00	1,055	**0.017**
Metabolic	USA	Post	1.13	0.18	0.96	1.31	4,962	
Metabolic	Japan	Pre	0.27	0.18	0.09	0.44	130	**0.001**
Metabolic	Japan	Post	1.40	0.51	0.89	1.91	2,430	
Metabolic	Switzerland	Pre	1.32	0.61	0.71	1.93	82	0.781
Metabolic	Switzerland	Post	1.24	0.46	0.78	1.69	251	
Oncology	EU	Pre	1.32	0.25	1.07	1.57	2,808	0.408
Oncology	EU	Post	1.50	0.27	1.23	1.77	9,322	
Oncology	USA	Pre	2.70	0.61	2.10	3.31	3,888	**0.032**
Oncology	USA	Post	3.51	0.57	2.94	4.08	15,290	
Oncology	Japan	Pre	0.94	0.33	0.61	1.27	534	**0.001**
Oncology	Japan	Post	2.87	1.07	1.79	3.94	5,013	
Oncology	Switzerland	Pre	4.17	0.95	3.22	5.12	281	0.713
Oncology	Switzerland	Post	4.37	1.13	3.24	5.51	871	
Ophthalmology	EU	Pre	0.05	0.03	0.02	0.07	84	**0.006**
Ophthalmology	EU	Post	0.13	0.03	0.10	0.16	781	
Ophthalmology	USA	Pre	0.09	0.05	0.03	0.14	108	**0.001**
Ophthalmology	USA	Post	0.26	0.05	0.21	0.31	1127	
Ophthalmology	Japan	Pre	0.03	0.02	0.01	0.06	18	Not determined
Ophthalmology	Japan	Post	0.22	0.08	0.14	0.31	386	
Ophthalmology	Switzerland	Pre	0.17	0.19	-0.02	0.35	7	Not determined
Ophthalmology	Switzerland	Post	0.34	0.15	0.18	0.49	65	
Vaccines	EU	Pre	0.12	0.05	0.07	0.17	226	0.328
Vaccines	EU	Post	0.18	0.07	0.10	0.25	1140	
Vaccines	USA	Pre	0.17	0.09	0.08	0.26	214	**0.016**
Vaccines	USA	Post	0.31	0.06	0.25	0.36	1341	
Vaccines	Japan	Pre	0.02	0.02	0.00	0.04	5	Not determined
Vaccines	Japan	Post	0.13	0.05	0.08	0.18	229	

Vaccines	Switzerland	Pre	0.20	0.13	0.07	0.33	11	Not determined
Vaccines	Switzerland	Post	0.71	0.18	0.53	0.89	1,440	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Interpretation of possible causes for changes in IEC-6

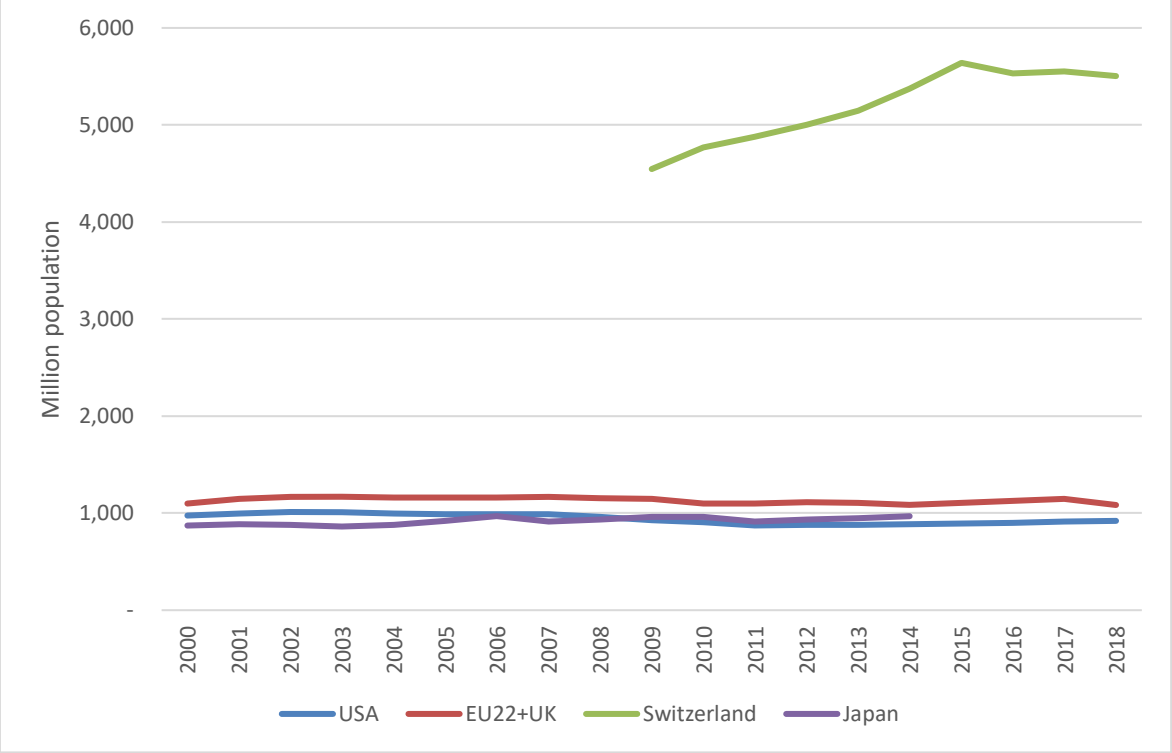
Regarding Phase 1 trials, all analysis regions were shown to increase in productivity (number of Phase 1 clinical trials starting each year), so it is unclear if the implementation of the general pharmaceutical legislation had an impact on increasing the productivity in the EU with regards to Phase 1 trials. At Phase 2 and Phase 3, only Japan saw an increase in productivity (number of trials starting in each year). This is possibly a function of the reduction in the "drug lag" between Japan and the other major pharmaceutical markets in the USA and Europe in terms of drug development over the last 20 years, but may also be an artefact of increasing data availability from Japan, which has also improved over the last 20 years.

IEC-7: Employment in the pharmaceutical industry

Statistics show that employment has grown only very slightly across the 20-year period under review, notwithstanding the stronger growth in trade and productivity figures. There is no evident major change in overall employment in the years following the implementation of the 2004 revision of the legislation, and the EU trend, such as it is, mirrors that of the industry in the USA.

The total number of employees in the pharmaceutical industry across the 22 EU countries that report this information in the OECD STAN database plus UK has remained stable over the period 2000-2020, averaging 1131 employees per million population. Something similar occurs with the US over this period and with Japan during 2000 - 2014, both countries with a close average of 942 and 921 employees per million population, respectively. In Switzerland, on the other hand, there has been a significant growth in this indicator during the period 2009-2015, from 4546 to 5640 employees per million population, followed by a slowdown in 2016-2018.

Figure IEC-7: Number of employees in the pharmaceutical sector per million population

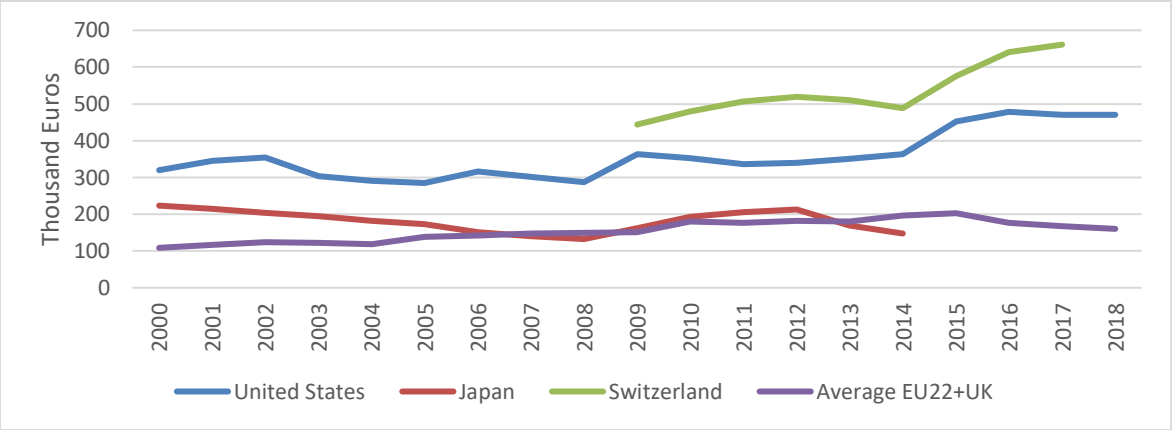


Source: OECD STAN database. The figure shows the number of employees in the pharmaceutical sector per million population in USA, Switzerland, Japan and the UK+ EU22 countries including: Austria, Belgium, Czech, Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain and Sweden.

IEC-8: GVA contribution of the pharmaceutical industry

The gross value added per employee (GVA/employee) in Europe displayed significant growth in the 5-year period 2005-2010, when it reached €181k per employee, followed by a slight decline in 2011-2013 and another period of growth during 2014-2015 and a slowdown in 2017-2018. In 2018, EU GVA/employee stood at €160k per employee. The US data mirror the trend in the EU figures although in general US workers productivity is on average 2.3 times higher during the complete period. Furthermore, since 2015 there is consistent growth in labour productivity which stands at €364k per employee in 2018. On this analysis, there has been no obvious loss or improvement in Europe's competitiveness vis a vis the pharmaceutical industry in the USA close to the time when the EU General Pharmaceutical legislation came into force in 2004-2005.

Figure IEC-8: Gross value added per employee in the pharmaceutical sector

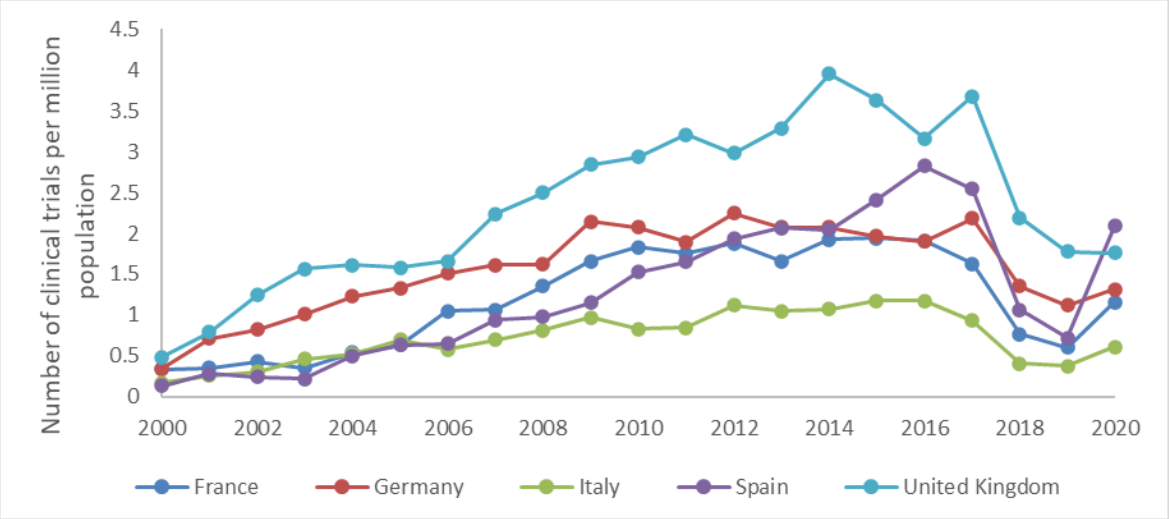


Source: OECD STAN database for indicators of value added in thousand euros and total employment in the pharmaceutical sector. GVA per employee was computed dividing GVA by the number of employees. The average for EU22 + UK is unweighted. Figures are not adjusted for inflation.

IEC-9: Number of clinical trials conducted in the European countries

IEC-9 investigated the number of clinical trials starting in each year in each phase of development in each of the EU28 countries in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the EU28 countries for trials in Phase 1 are shown in Table IEC-9.1, and illustrative data for the top 5 pharma markets in the EU are shown in Figure IEC-9.1. In all countries shown, the number of Phase 1 trials adjusted for population starting in each year was found to significantly increase in the post period compared to the pre period. Differences in trials at all phases by therapy area were also investigated. However, outside of the 5 major markets, n numbers found are too low to infer any significant differences, thus data for France, Germany, Italy, Spain, and the UK only are presented.

Figure IEC-9.1 Number of Phase 1 trials starting by year for top 5 largest pharma markets in the EU adjusted for population.



Source: Trialtrove 2000-2020.

Table IEC-9.1 Descriptive statistics for the number of Phase 1 clinical trials adjusted for population conducted in the EU28 countries

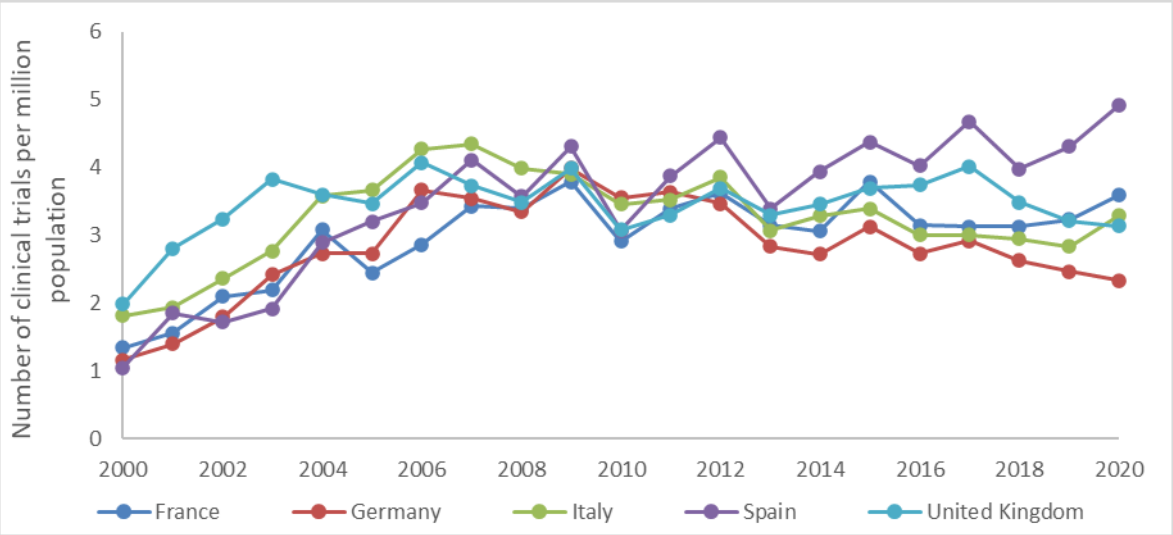
Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	MANN-WHITNEY U TEST (P-value)
1	France	Pre	0.53	0.23	0.29	0.76	131	**0.0004**
1	France	Post	1.54	0.43	1.11	1.97	1,373	
1	Germany	Pre	0.99	0.37	0.62	1.37	337	**0.001**
1	Germany	Post	1.84	0.35	1.49	2.20	2,097	
1	Italy	Pre	0.43	0.18	0.25	0.60	101	**0.0003**
1	Italy	Post	0.87	0.26	0.62	1.13	711	
1	Spain	Pre	0.38	0.20	0.18	0.58	63	**0.0004**
1	Spain	Post	1.77	0.63	1.14	2.40	1101	
1	United Kingdom	Pre	1.28	0.43	0.85	1.71	353	**0.0007**
1	United Kingdom	Post	2.92	0.67	2.25	3.58	2489	
1	Poland	Pre	0.15	0.11	0.04	0.26	20	Not determined
1	Poland	Post	0.59	0.15	0.43	0.74	314	
1	Romania	Pre	0.04	0.04	0.00	0.08	3	Not determined
1	Romania	Post	0.34	0.15	0.18	0.49	89	
1	Netherlands	Pre	1.73	0.78	0.95	2.51	119	**0.0006**
1	Netherlands	Post	5.01	0.97	4.04	5.99	1176	
1	Greece	Pre	0.23	0.12	0.12	0.35	12	Not determined
1	Greece	Post	0.54	0.22	0.32	0.76	81	
1	Czech Republic	Pre	0.31	0.28	0.03	0.59	14	Not determined
1	Czech Republic	Post	1.50	0.57	0.93	2.07	202	
1	Austria	Pre	0.86	0.48	0.37	1.34	25	Not determined
1	Austria	Post	2.25	0.65	1.60	2.90	250	
1	Belgium	Pre	2.03	0.98	1.04	3.01	84	**0.001**
1	Belgium	Post	6.78	1.48	5.30	8.25	1032	
1	Bulgaria	Pre	0.08	0.07	0.01	0.15	2	Not determined
1	Bulgaria	Post	1.29	0.52	0.77	1.81	120	
1	Croatia	Pre	0.21	0.16	0.05	0.37	3	Not determined
1	Croatia	Post	0.35	0.36	-0.01	0.71	19	
1	Cyprus	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Cyprus	Post	0.23	0.42	-0.19	0.65	3	
1	Denmark	Pre	1.67	1.16	0.51	2.82	30	Not determined
1	Denmark	Post	3.90	1.47	2.43	5.37	326	
1	Estonia	Pre	0.14	0.35	-0.21	0.49	1	Not determined
1	Estonia	Post	1.46	1.28	0.18	2.74	20	
1	Finland	Pre	0.63	0.47	0.16	1.10	11	Not determined
1	Finland	Post	1.83	0.64	1.19	2.47	122	
1	Hungary	Pre	0.23	0.17	0.05	0.40	7	Not determined
1	Hungary	Post	1.47	0.49	0.98	1.96	203	
1	Ireland	Pre	0.26	0.18	0.08	0.43	4	

1	Ireland	Post	1.05	0.56	0.49	1.61	76	Not determined
1	Latvia	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Latvia	Post	0.96	0.75	0.22	1.71	25	
1	Lithuania	Pre	0.05	0.12	-0.07	0.16	1	Not determined
1	Lithuania	Post	0.56	0.55	0.02	1.11	22	
1	Luxembourg	Pre	0.29	0.70	-0.41	0.99	1	Not determined
1	Luxembourg	Post	0.31	0.72	-0.41	1.03	2	
1	Malta	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Malta	Post	0.00	0.00	0.00	0.00	0	
1	Portugal	Pre	0.30	0.17	0.13	0.47	12	Not determined
1	Portugal	Post	0.29	0.17	0.12	0.47	47	
1	Slovakia	Pre	0.26	0.23	0.03	0.49	3	Not determined
1	Slovakia	Post	0.88	0.40	0.47	1.28	63	
1	Slovenia	Pre	0.14	0.23	-0.08	0.37	2	Not determined
1	Slovenia	Post	0.81	0.50	0.31	1.31	22	
1	Sweden	Pre	1.13	0.78	0.35	1.90	32	0.002
1	Sweden	Post	2.95	1.27	1.68	4.22	382	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing the EU28 countries for trials in Phase 2 are shown in Table IEC-9.2and illustrative data for the top 5 pharma markets in the EU28 are shown in Figure IEC-9.2. For France, Spain, Poland, Romania, Greece, and the Czech Republic, the number of Phase 2 trials starting in each year was found to significantly increase in the post period compared to the pre period.

Figure IEC-9.2 Number of Phase 2 trials starting by year for top 5 largest pharma markets in the EU.



Source: Trialtrove 2000-2020.

Table IEC-9.2 Descriptive statistics for the number of Phase 2 clinical trials conducted in the EU28 countries

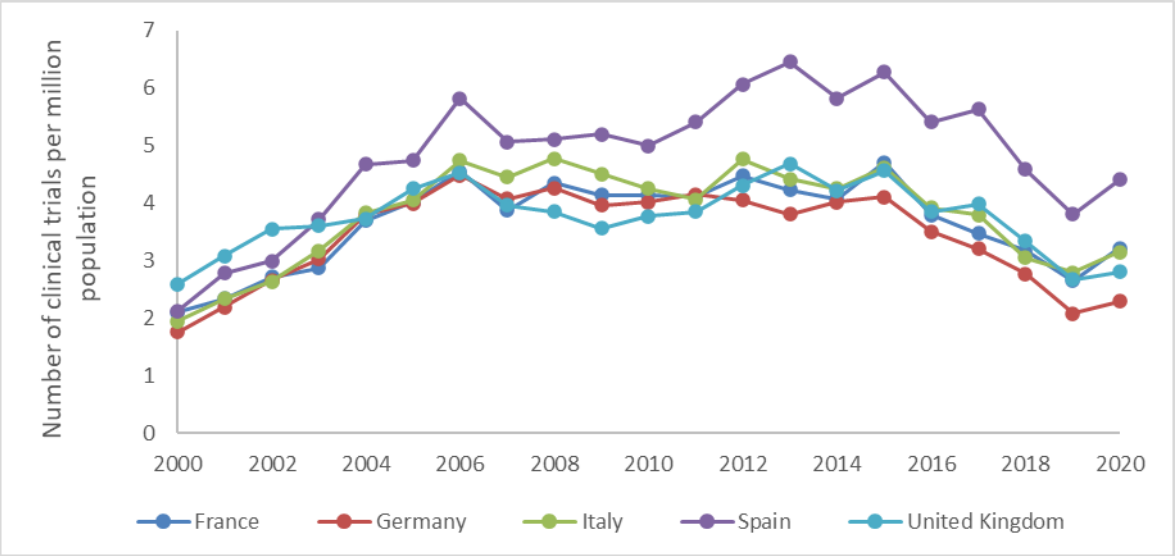
Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
2	France	Pre	2.22	0.59	1.63	2.81	893	**0.003**
2	France	Post	3.33	0.28	3.05	3.60	3,538	
2	Germany	Pre	2.27	0.81	1.46	3.08	1,101	0.06
2	Germany	Post	3.05	0.48	2.57	3.54	4,128	
2	Italy	Pre	2.91	0.87	2.04	3.78	822	0.273
2	Italy	Post	3.35	0.37	2.98	3.72	3,354	
2	Spain	Pre	2.30	0.83	1.47	3.13	750	**0.001**
2	Spain	Post	4.06	0.50	3.57	4.56	3,416	
2	United Kingdom	Pre	3.28	0.65	2.63	3.93	1,027	0.454
2	United Kingdom	Post	3.50	0.29	3.21	3.80	3,315	
2	Poland	Pre	1.42	0.71	0.71	2.12	540	**0.0002**
2	Poland	Post	3.19	0.51	2.68	3.71	3,004	
2	Romania	Pre	1.10	0.74	0.36	1.84	165	**0.005**
2	Romania	Post	2.35	0.69	1.65	3.04	1,583	
2	Netherlands	Pre	5.24	1.70	3.54	6.93	615	0.051
2	Netherlands	Post	6.93	0.79	6.14	7.72	2,083	
2	Greece	Pre	1.87	0.65	1.22	2.52	231	**0.003**
2	Greece	Post	3.08	0.61	2.47	3.70	1,027	
2	Czech Republic	Pre	3.61	2.51	1.10	6.13	375	**0.004**
2	Czech Republic	Post	8.08	1.06	7.02	9.13	2,188	
2	Austria	Pre	11.09	4.87	6.22	15.96	379	**0.045**
2	Austria	Post	14.04	2.96	11.08	17.00	1,611	

2	Belgium	Pre	11.88	4.77	7.12	16.65	570	**0.013**
2	Belgium	Post	15.69	2.81	12.88	18.50	2,400	
2	Bulgaria	Pre	4.39	3.08	1.31	7.46	105	**0.001**
2	Bulgaria	Post	13.85	2.87	10.98	16.71	1,313	
2	Croatia	Pre	5.71	3.13	2.58	8.85	86	0.041
2	Croatia	Post	10.44	2.93	7.51	13.37	583	
2	Cyprus	Pre	5.86	11.92	-6.06	17.78	38	Not determined
2	Cyprus	Post	1.46	1.01	0.45	2.47	22	
2	Denmark	Pre	13.26	4.96	8.30	18.22	329	**0.003**
2	Denmark	Post	16.19	2.87	13.32	19.06	1,367	
2	Estonia	Pre	30.71	16.10	14.61	46.82	118	**0.015**
2	Estonia	Post	45.46	10.30	35.16	55.76	641	
2	Finland	Pre	15.74	4.59	11.16	20.33	343	**0.777**
2	Finland	Post	13.72	3.90	9.83	17.62	982	
2	Hungary	Pre	8.94	3.59	5.36	12.53	360	**0.001**
2	Hungary	Post	15.95	3.12	12.83	19.08	2,219	
2	Ireland	Pre	7.11	1.87	5.24	8.98	153	**0.005**
2	Ireland	Post	9.51	2.42	7.09	11.93	666	
2	Latvia	Pre	11.64	7.00	4.64	18.65	85	**0.005**
2	Latvia	Post	22.31	4.94	17.36	27.25	620	
2	Lithuania	Pre	10.86	6.83	4.03	17.68	112	**0.017**
2	Lithuania	Post	17.03	4.95	12.08	21.97	724	
2	Luxembourg	Pre	4.00	2.83	1.17	6.83	11	0.591
2	Luxembourg	Post	5.38	2.76	2.62	8.15	37	
2	Malta	Pre	1.71	2.71	-1.00	4.42	1	Not determined
2	Malta	Post	1.69	3.22	-1.53	4.91	14	
2	Portugal	Pre	5.47	1.86	3.61	7.33	229	0.080
2	Portugal	Post	6.82	1.24	5.58	8.05	948	
2	Slovakia	Pre	8.91	4.23	4.69	13.14	168	0.060
2	Slovakia	Post	14.98	4.45	10.53	19.44	1054	
2	Slovenia	Pre	6.21	1.56	4.66	7.77	55	**0.001**
2	Slovenia	Post	7.92	2.62	5.31	10.54	221	
2	Sweden	Pre	11.35	3.29	8.06	14.64	460	**0.005**
2	Sweden	Post	11.95	3.41	8.54	15.35	1531	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing the EU28 countries by population for trials in Phase 3 are shown in Table IEC-9.3 and illustrative data for the top 5 pharma markets in the EU are shown in Figure IEC-9.3. For Spain, Poland, Romania, Greece, and the Czech Republic, the number of Phase 3 trials starting in each year was found to significantly increase in the post period compared to the pre period.

Figure IEC-9.3 Number of Phase 3 trials starting by year for top 5 largest pharma markets in the EU.



Source: Trialtrove 2000-2020.

Table IEC-9.3 Descriptive statistics for the number of Phase 3 clinical trials conducted in the EU28 countries

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
3	France	Pre	3.19	0.85	2.34	4.03	893	0.1
3	France	Post	3.89	0.57	3.32	4.46	3,538	
3	Germany	Pre	3.13	0.93	2.20	4.06	1,101	0.345
3	Germany	Post	3.56	0.71	2.85	4.27	4,128	
3	Italy	Pre	3.25	0.93	2.31	4.18	822	0.098
3	Italy	Post	4.03	0.64	3.39	4.67	3,354	
3	Spain	Pre	3.84	1.21	2.63	5.05	750	**0.024**
3	Spain	Post	5.32	0.58	4.74	5.90	3,416	
3	United Kingdom	Pre	3.62	0.61	3.01	4.23	1,027	0.548
3	United Kingdom	Post	3.81	0.58	3.23	4.39	3,315	
3	Poland	Pre	3.48	1.30	2.18	4.77	540	**0.005**
3	Poland	Post	5.67	0.92	4.75	6.59	3,004	
3	Romania	Pre	2.36	1.44	0.92	3.80	165	**0.001**
3	Romania	Post	5.69	1.82	3.87	7.51	1,583	
3	Netherlands	Pre	8.13	1.75	6.38	9.87	615	0.492
3	Netherlands	Post	8.73	1.59	7.14	10.32	2,083	
3	Greece	Pre	4.82	1.39	3.43	6.20	231	**0.019**
3	Greece	Post	6.66	1.26	5.40	7.92	1,027	
3	Czech Republic	Pre	9.63	4.19	5.44	13.82	375	**0.012**
3	Czech Republic	Post	15.64	2.84	12.80	18.48	2,188	
3	Austria	Pre	11.09	4.87	6.22	15.96	379	0.213

3	Austria	Post	14.04	2.96	11.08	17.00	1,611	
3	Belgium	Pre	11.88	4.77	7.12	16.65	570	0.051
3	Belgium	Post	15.69	2.81	12.88	18.50	2,400	
3	Bulgaria	Pre	4.39	3.08	1.31	7.46	105	**0.001**
3	Bulgaria	Post	13.85	2.87	10.98	16.71	1,313	
3	Croatia	Pre	5.71	3.13	2.58	8.85	86	**0.005**
3	Croatia	Post	10.44	2.93	7.51	13.37	583	
3	Cyprus	Pre	5.86	11.92	-6.06	17.78	38	0.737
3	Cyprus	Post	1.46	1.01	0.45	2.47	22	
3	Denmark	Pre	13.26	4.96	8.30	18.22	329	0.219
3	Denmark	Post	16.19	2.87	13.32	19.06	1,367	
3	Estonia	Pre	30.71	16.10	14.61	46.82	118	0.071
3	Estonia	Post	45.46	10.30	35.16	55.76	641	
3	Finland	Pre	15.74	4.59	11.16	20.33	343	0.591
3	Finland	Post	13.72	3.90	9.83	17.62	982	
3	Hungary	Pre	8.94	3.59	5.36	12.53	360	**0.002**
3	Hungary	Post	15.95	3.12	12.83	19.08	2,219	
3	Ireland	Pre	7.11	1.87	5.24	8.98	153	**0.035**
3	Ireland	Post	9.51	2.42	7.09	11.93	666	
3	Latvia	Pre	11.64	7.00	4.64	18.65	85	**0.009**
3	Latvia	Post	22.31	4.94	17.36	27.25	620	
3	Lithuania	Pre	10.86	6.83	4.03	17.68	112	0.080
3	Lithuania	Post	17.03	4.95	12.08	21.97	724	
3	Luxembourg	Pre	4.00	2.83	1.17	6.83	11	Not determined
3	Luxembourg	Post	5.38	2.76	2.62	8.15	37	
3	Malta	Pre	1.71	2.71	-1.00	4.42	1	Not determined
3	Malta	Post	1.69	3.22	-1.53	4.91	14	
3	Portugal	Pre	5.47	1.86	3.61	7.33	229	0.144
3	Portugal	Post	6.82	1.24	5.58	8.05	948	
3	Slovakia	Pre	8.91	4.23	4.69	13.14	168	**0.015**
3	Slovakia	Post	14.98	4.45	10.53	19.44	1,054	
3	Slovenia	Pre	6.21	1.56	4.66	7.77	55	0.101
3	Slovenia	Post	7.92	2.62	5.31	10.54	221	
3	Sweden	Pre	11.35	3.29	8.06	14.64	460	0.725
3	Sweden	Post	11.95	3.41	8.54	15.35	1,531	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Table IEC-9.4 shows splits by therapy area for each region for total trials adjusted for population, ignoring phase, in the top 5 largest pharmaceutical markets in the EU. In terms of trends, only trials for Autoimmune diseases significantly increased in all countries in the post period compared to the pre period. Cardiovascular trials significantly increased in Spain and the UK, CNS trials in France, Italy, and Spain, Infectious disease trials in France, Spain, and the UK, and Oncology trials in France, Spain, and the UK. N numbers were not sufficient in any country to perform statistical tests for Ophthalmology or Vaccines.

Table IEC-9.4 Descriptive statistics for the number of clinical trials conducted in France, Germany, Italy, Spain, and the UK, split by therapy area

Therapy area	Analysis country	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
Autoimmune	France	Pre	1.13	0.30	0.83	1.42	320	**0.002**
Autoimmune	France	Post	1.72	0.22	1.50	1.93	1551	
Autoimmune	Germany	Pre	1.40	0.49	0.90	1.89	467	**0.005**
Autoimmune	Germany	Post	2.23	0.32	1.91	2.55	2571	
Autoimmune	Italy	Pre	1.10	0.38	0.72	1.48	267	**0.016**
Autoimmune	Italy	Post	1.62	0.24	1.38	1.86	1349	
Autoimmune	Spain	Pre	1.20	0.41	0.78	1.61	225	**0.001**
Autoimmune	Spain	Post	2.26	0.37	1.89	2.63	1441	
Autoimmune	United Kingdom	Pre	1.96	0.38	1.58	2.33	561	**0.008**
Autoimmune	United Kingdom	Post	2.56	0.39	2.17	2.95	2197	
Cardiovascular	France	Pre	0.88	0.26	0.62	1.14	251	0.123
Cardiovascular	France	Post	1.08	0.20	0.88	1.29	991	
Cardiovascular	Germany	Pre	1.12	0.39	0.72	1.51	368	0.793
Cardiovascular	Germany	Post	1.18	0.34	0.85	1.52	1379	
Cardiovascular	Italy	Pre	1.14	0.36	0.78	1.50	290	0.265
Cardiovascular	Italy	Post	1.34	0.34	1.00	1.69	1124	
Cardiovascular	Spain	Pre	1.08	0.37	0.71	1.46	203	**0.038**
Cardiovascular	Spain	Post	1.49	0.23	1.26	1.73	952	
Cardiovascular	United Kingdom	Pre	1.13	0.34	0.78	1.47	302	0.086
Cardiovascular	United Kingdom	Post	1.44	0.28	1.16	1.71	1252	
CNS	France	Pre	0.99	0.44	0.55	1.43	254	**0.017**
CNS	France	Post	1.58	0.26	1.32	1.84	1450	
CNS	Germany	Pre	1.17	0.51	0.66	1.68	383	0.254
CNS	Germany	Post	1.45	0.41	1.05	1.86	1717	
CNS	Italy	Pre	0.93	0.48	0.45	1.42	200	**0.086**
CNS	Italy	Post	1.34	0.15	1.20	1.49	1140	
CNS	Spain	Pre	1.19	0.50	0.69	1.69	215	**0.016**
CNS	Spain	Post	1.85	0.23	1.63	2.08	1202	
CNS	United Kingdom	Pre	1.67	0.34	1.33	2.00	480	0.209
CNS	United Kingdom	Post	1.89	0.33	1.56	2.22	1657	
Genitourinary	France	Pre	0.18	0.06	0.12	0.24	49	0.775
Genitourinary	France	Post	0.17	0.07	0.10	0.24	157	
Genitourinary	Germany	Pre	0.26	0.10	0.16	0.36	91	0.287
Genitourinary	Germany	Post	0.20	0.10	0.10	0.30	248	

Genitourinary	Italy	Pre	0.19	0.07	0.12	0.26	52	0.101
Genitourinary	Italy	Post	0.26	0.10	0.16	0.35	212	
Genitourinary	Spain	Pre	0.25	0.16	0.08	0.41	41	0.070
Genitourinary	Spain	Post	0.40	0.06	0.33	0.46	257	
Genitourinary	United Kingdom	Pre	0.31	0.11	0.21	0.42	85	0.151
Genitourinary	United Kingdom	Post	0.23	0.09	0.14	0.33	209	
Infectious disease	France	Pre	0.86	0.16	0.70	1.02	250	**0.007**
Infectious disease	France	Post	1.23	0.35	0.88	1.58	1109	
Infectious disease	Germany	Pre	0.80	0.26	0.54	1.06	270	0.220
Infectious disease	Germany	Post	0.97	0.28	0.69	1.25	328	
Infectious disease	Italy	Pre	0.87	0.24	0.63	1.12	216	0.162
Infectious disease	Italy	Post	1.09	0.39	0.70	1.48	908	
Infectious disease	Spain	Pre	1.24	0.26	0.98	1.50	265	**0.016**
Infectious disease	Spain	Post	1.73	0.53	1.21	2.26	1108	
Infectious disease	United Kingdom	Pre	1.03	0.21	0.82	1.23	284	**0.004**
Infectious disease	United Kingdom	Post	1.44	0.32	1.13	1.76	1251	
Metabolic	France	Pre	0.81	0.33	0.48	1.13	214	0.442
Metabolic	France	Post	0.92	0.18	0.74	1.11	851	
Metabolic	Germany	Pre	0.96	0.47	0.49	1.43	308	0.112
Metabolic	Germany	Post	1.33	0.27	1.06	1.60	1540	
Metabolic	Italy	Pre	0.84	0.42	0.42	1.25	200	0.217
Metabolic	Italy	Post	1.08	0.17	0.91	1.25	896	
Metabolic	Spain	Pre	0.98	0.40	0.58	1.37	189	0.136
Metabolic	Spain	Post	1.27	0.26	1.01	1.52	835	
Metabolic	United Kingdom	Pre	1.28	0.35	0.93	1.63	353	0.194
Metabolic	United Kingdom	Post	1.50	0.24	1.27	1.74	1318	
Oncology	France	Pre	2.37	0.59	1.78	2.97	687	**0.001**
Oncology	France	Post	3.87	0.77	3.10	4.64	3487	
Oncology	Germany	Pre	2.15	0.49	1.66	2.64	808	0.058
Oncology	Germany	Post	2.69	0.59	2.10	3.28	3075	
Oncology	Italy	Pre	2.93	0.72	2.21	3.66	755	0.078
Oncology	Italy	Post	3.64	0.78	2.86	4.42	3030	
Oncology	Spain	Pre	2.38	0.75	1.64	3.13	460	**0.001**
Oncology	Spain	Post	4.63	1.10	3.52	5.73	2944	
Oncology	United Kingdom	Pre	2.51	0.56	1.95	3.07	703	**0.020**
Oncology	United Kingdom	Post	3.35	0.80	2.55	4.14	2895	
Ophthalmology	France	Pre	0.10	0.07	0.04	0.17	26	Not determined
Ophthalmology	France	Post	0.21	0.04	0.17	0.25	184	
Ophthalmology	Germany	Pre	0.10	0.07	0.03	0.17	30	Not determined
Ophthalmology	Germany	Post	0.21	0.06	0.15	0.27	238	
Ophthalmology	Italy	Pre	0.13	0.10	0.03	0.23	23	

Ophthalmology	Italy	Post	0.25	0.05	0.20	0.31	207	Not determined
Ophthalmology	Spain	Pre	0.13	0.08	0.05	0.22	24	Not determined
Ophthalmology	Spain	Post	0.31	0.06	0.25	0.36	194	
Ophthalmology	United Kingdom	Pre	0.15	0.06	0.09	0.20	37	**0.001**
Ophthalmology	United Kingdom	Post	0.28	0.08	0.20	0.36	242	
Vaccines	France	Pre	0.11	0.05	0.06	0.16	26	Not determined
Vaccines	France	Post	0.16	0.09	0.07	0.25	147	
Vaccines	Germany	Pre	0.22	0.10	0.12	0.32	68	0.852
Vaccines	Germany	Post	0.21	0.10	0.11	0.31	256	
Vaccines	Italy	Pre	0.13	0.06	0.07	0.19	29	Not determined
Vaccines	Italy	Post	0.13	0.09	0.05	0.22	117	
Vaccines	Spain	Pre	0.13	0.06	0.07	0.18	30	Not determined
Vaccines	Spain	Post	0.25	0.07	0.17	0.32	163	
Vaccines	United Kingdom	Pre	0.22	0.11	0.11	0.33	53	0.049
Vaccines	United Kingdom	Post	0.34	0.11	0.23	0.45	301	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Interpretation of possible causes for changes in IEC-9

In summary, IEC-9 aims to assess differences in productivity across the EU following the implementation of the general pharmaceutical legislation with regards to the number of clinical trials conducted. For Phase 1 trials, the vast majority of countries were shown to increase in productivity (number of Phase 1 clinical trials starting each year), so any impact of the implementation of the general pharmaceutical legislation seems to have been evenly distributed across the EU with regards to Phase 1 trials. However, Phase 1 trials tend to take place in a single country, and sometimes at single sites, in a small number of healthy volunteers to establish safety, so they should be considered the least important measure of productivity, as drug efficacy is not established in such trials. At Phase 2 and Phase 3, the majority of the larger countries in the EU saw significant increases in the numbers of trials started each year in the post period compared to the pre period, and the remaining countries saw comparative numbers. This is most likely due to the favouring of the larger, more attractive markets for initial approval (whether a drug is approved via the centralised or decentralised procedure), and the fact that larger countries are more attractive for recruiting patients for larger trials due to the expected higher numbers of eligible patients.

IEC-10: Revenue generated by pharma companies

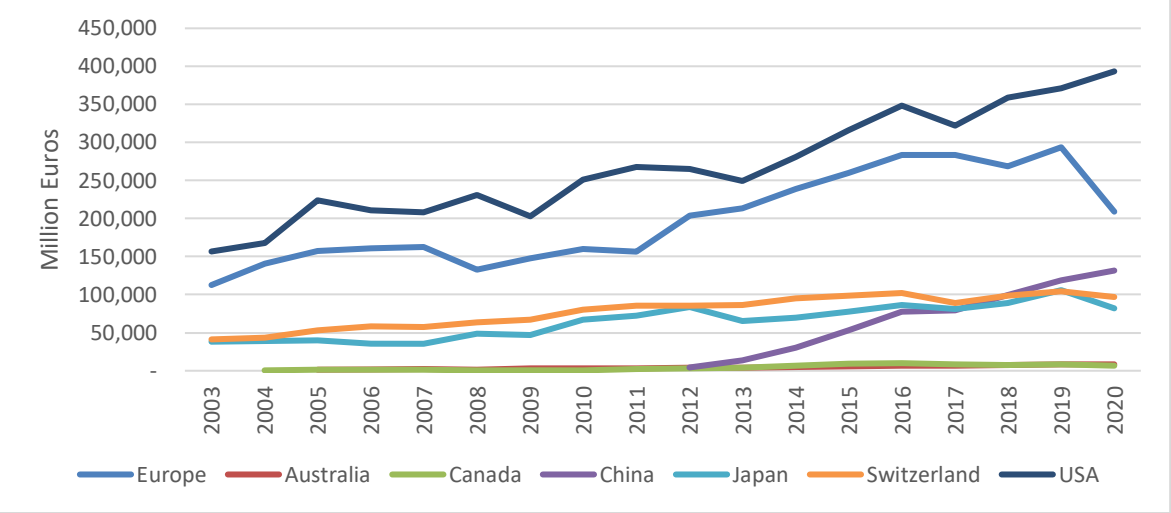
Indicators IEC-10 and IEC-11 are constructed from the EU and World Industrial R&D Investment Scoreboard (IRI, available at https://iri.jrc.ec.europa.eu/data) data. The EU Industrial R&D Investment Scoreboard, compiled by the European Commission's Joint Research Centre, collects data on the largest corporate R&D investors, based on the companies' annual reports. The latest data covers top 1000 companies (across all sectors) in the EU Industrial R&D Investment Scoreboard and top 2500 companies (across all sectors) in World Industrial R&D Investment Scoreboard

Since our focus is on pharmaceutical companies, we only analysed data on the subset

of firms in the sector "Pharmaceuticals & Biotechnology". Figure IEC-10 and Figure IEC-11 are based on an average of 120 Europe based companies that reported information during 2003-2020 and 183 companies based on Australia (1%), Canada(2%), China(17%), Japan(13%), Switzerland(4%), and USA(71%). Pharmaceutical companies constitute around 13% of the world's largest spenders on research. The largest companies in terms of total R&D spending in the data are Roche, Johnson & Johnson, Pfizer, Novartis, and GlaxoSmithKline.

Figure IEC-10 plots the total annual revenues of pharmaceutical companies in the respective regions (without adjustment for inflation). The differences in the level of total revenues mainly reflect size effects due to the different numbers of firms included. Differences in level of revenues aside, the growth rates of Europe, China and US are the highest and similar in particular since 2013 when there is data available for China. The average annual growth rate is 4.6% for Europe during the entire period and 6.1% for the US. Switzerland and Japan also follow similar paths with more moderate growth rates than the first three jurisdictions. Finally, Canada and Australia experience the lowest growth rates across all jurisdictions. Overall, there is no evidence that the reforms introduced by the EU General Pharmaceutical Legislation had an impact on the trend observed for pharmaceutical revenues after 2005.

Figure IEC-10: Revenue generated by pharma companies

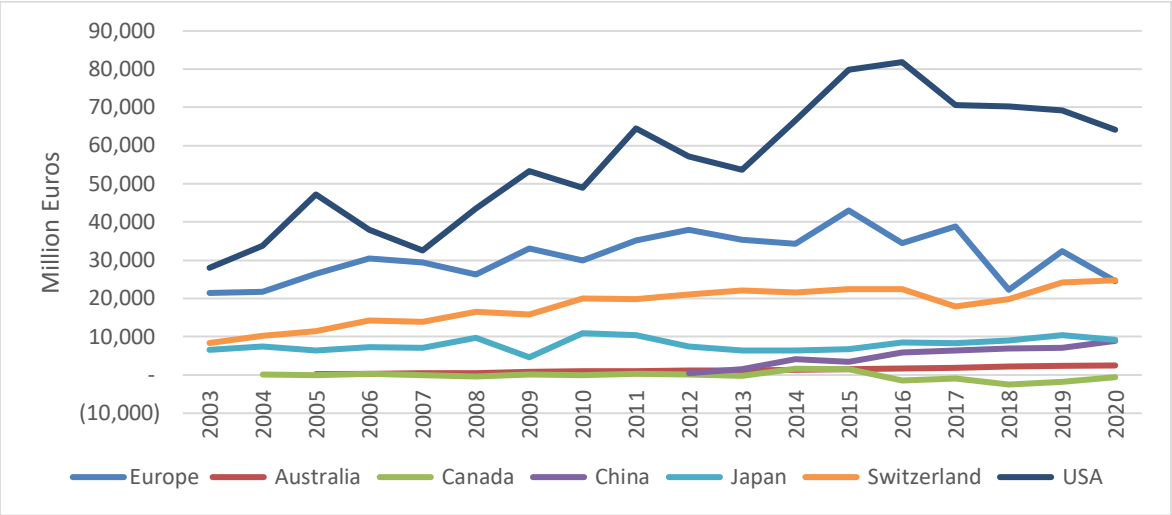


Source: EU and World Industrial R&D Investment Scoreboard. The latest data covers top 1000 companies in the EU Industrial R&D Investment Scoreboard and top 2500 companies in World Industrial R&D Investment Scoreboard. Figures have not been adjusted by inflation.

IEC-11: Gross profit

Figure IEC-11 plots the aggregated annual profits of pharmaceutical companies in the respective regions. The US and Europe appear on top with US experiencing average annual growth rates of 6.6% in profits during 2003-2020 relative to 3.1% in Europe. The lower growth rates in Europe are influenced by a marked reduction in profits during 2016-2020. This extended period of decline in Europe is not observed in Switzerland or Japan. While Canadian companies reported negative profits during the same period (2016-2020). Just as with Figure IEC-10, there is no evidence that the reforms introduced by the EU General Pharmaceutical Legislation had an impact on the trend observed for pharmaceutical profits after 2005.

Figure IEC-11: Profits generated by pharma companies

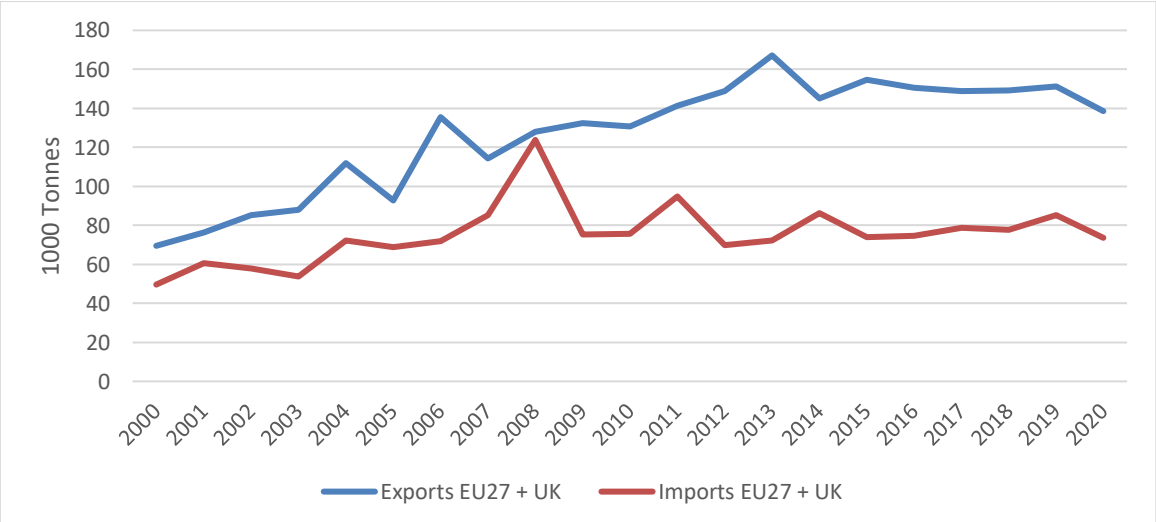


Source: EU and World Industrial R&D Investment Scoreboard. The latest data covers top 1000 companies in the EU Industrial R&D Investment Scoreboard and top 2500 companies in World Industrial R&D Investment Scoreboard. Figures have not been adjusted by inflation.

IEC-12: Volumes of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

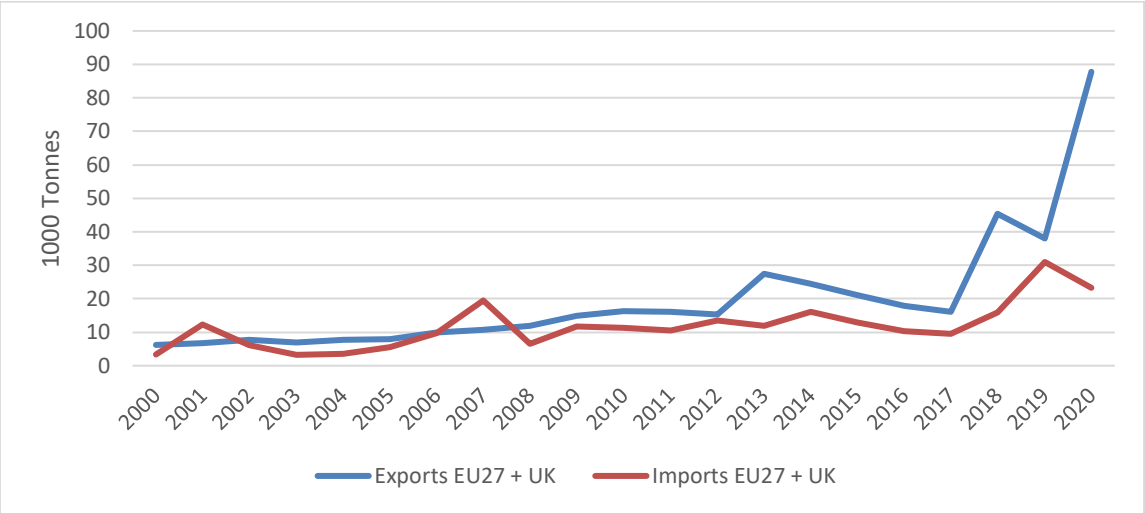
In terms of **antibiotics finished pharmaceutical products** (FPPs), EU28 export volumes have shown a steady growth from 2000 until 2013 when they seem to have stalled (Figure IEC-12.1). On the other hand, EU28 imports volume for antibiotics FPPs had a significant growth in 2007 and 2008 where they reached the highest point during the period 2000-2020. Something similar happened with the volume of EU28 **vaccines** imports, which peaked in 2007 and then again in 2019, while exports peaked in 2020 probably due to the COVID-19 pandemic (Figure IEC-12.2). On the other hand, import volumes of EU28 **finished pharmaceutical products** (FPPs) peaked in 2004 and 2009 (Figure IEC-12.3). Finally, EU28 **APIs** exports and imports from and to all countries of the world both displayed constant growth during 2000-2020 without any major changes in their trends (Figure IEC-12.4).

Figure IEC-12.1: Antibiotics FPPs exports and imports (volumes, tonnes)



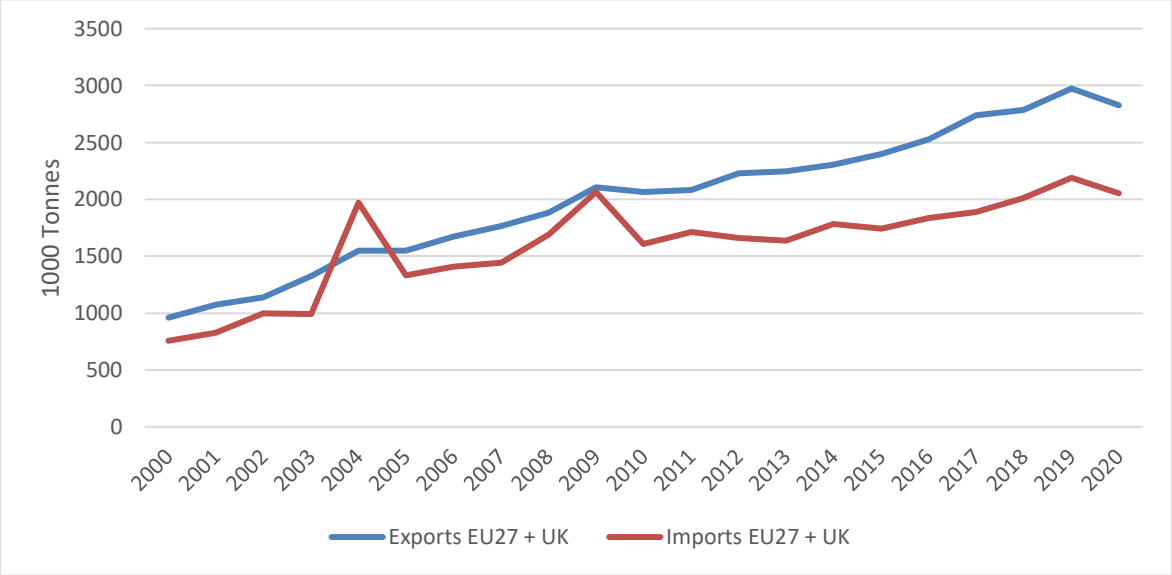
Source: Eurostat. EU28 (EU27 and UK) antibiotics exports (imports) to (from) all countries of the world. Antibiotics FPPs correspond the 2 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.2: Vaccines exports and imports (volumes, tonnes)



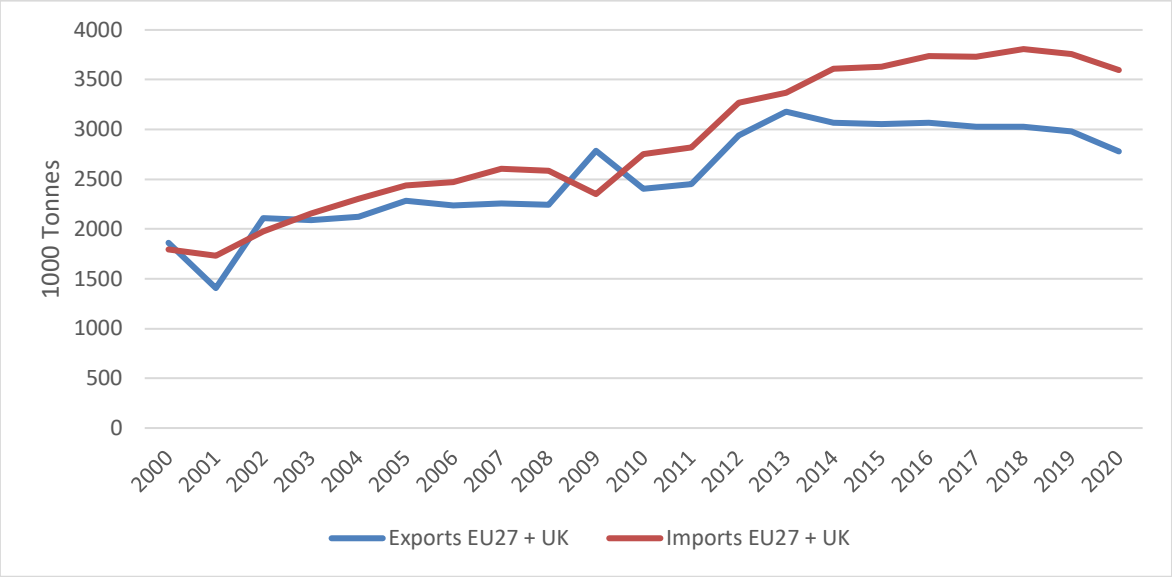
Source: Eurostat. EU28 (EU27 and UK) vaccines exports (imports) to (from) all countries of the world. Vaccines correspond to code 300220 as described in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.3: FPPs exports and imports (volumes, tonnes)



Source: Eurostat. EU28 (EU27 and UK) FPPs exports (imports) to (from) all countries of the world. FPPs correspond to the 13 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.4: API exports and imports (volumes, tonnes)

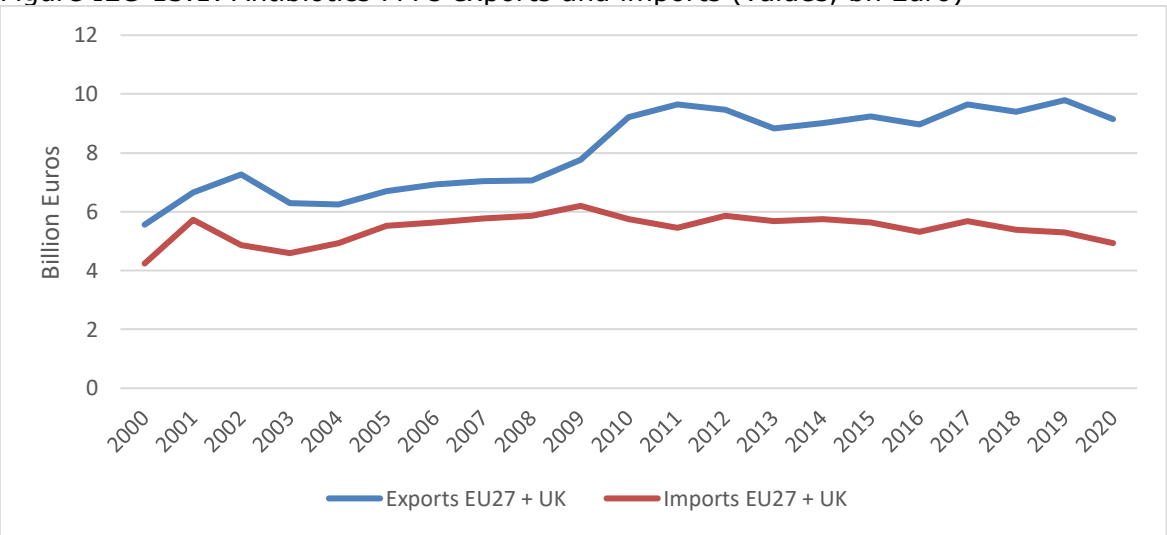


Source: Eurostat. EU28 (EU27 and UK) APIs exports (imports) to (from) all countries of the world. Active Pharmaceutical Ingredients include the 101 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

IEC-13: Values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

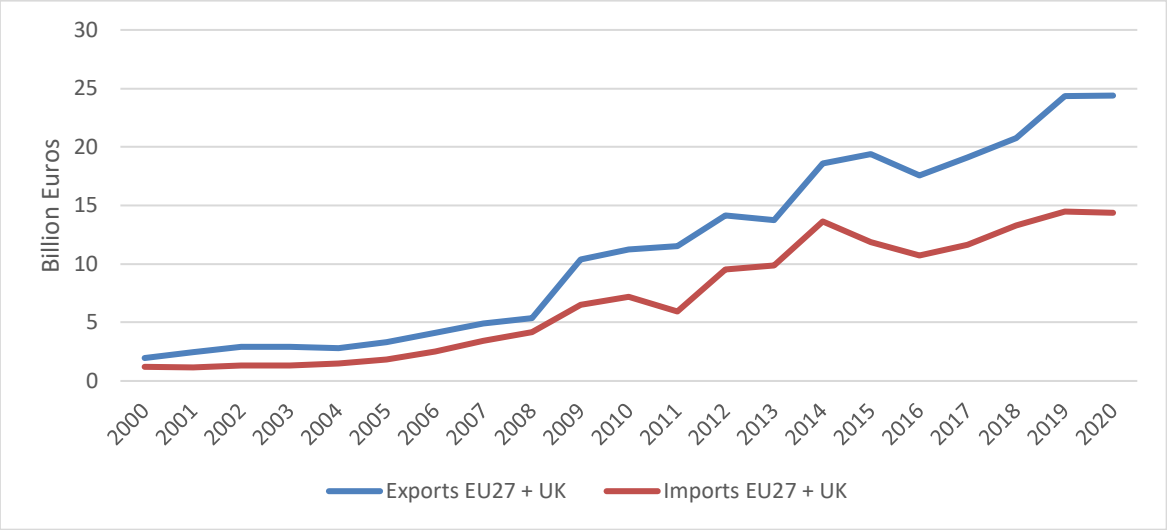
In terms of value, EU28 **antibiotics** finished pharmaceutical products (FPPs) exports have shown an important growth from 2008 until 2011 when they seem to have stalled just as with the graph representing volumes. On the other hand, EU28 imports values for antibiotics FPPs reached their highest point in 2008 just as with the graph representing volumes (Figure IEC-13.1).
EU28 **vaccines** imports and exports values display high growth rates, in particular since 2008 (Figure IEC-13.2), while import and export values for overall FPPs and APIs have also displayed more consistent growth rates between 2000-2020 (Figures IEC-13.3 and IEC-13.4).

Figure IEC-13.1: Antibiotics FPPs exports and imports (values, bn Euro)



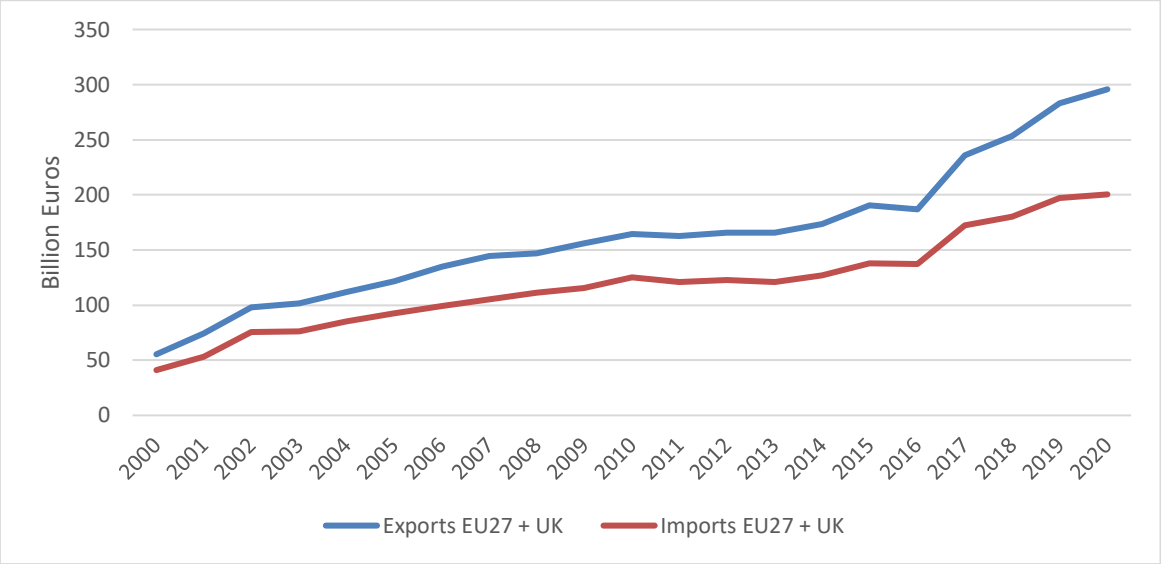
Source: Eurostat. EU28 (EU27 and UK) Antibiotics FPPs exports (imports) to (from) all countries of the world. Antibiotics FPPs include the 2 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

Figure IEC-13.2: Vaccines exports and imports (values, bn Euro)



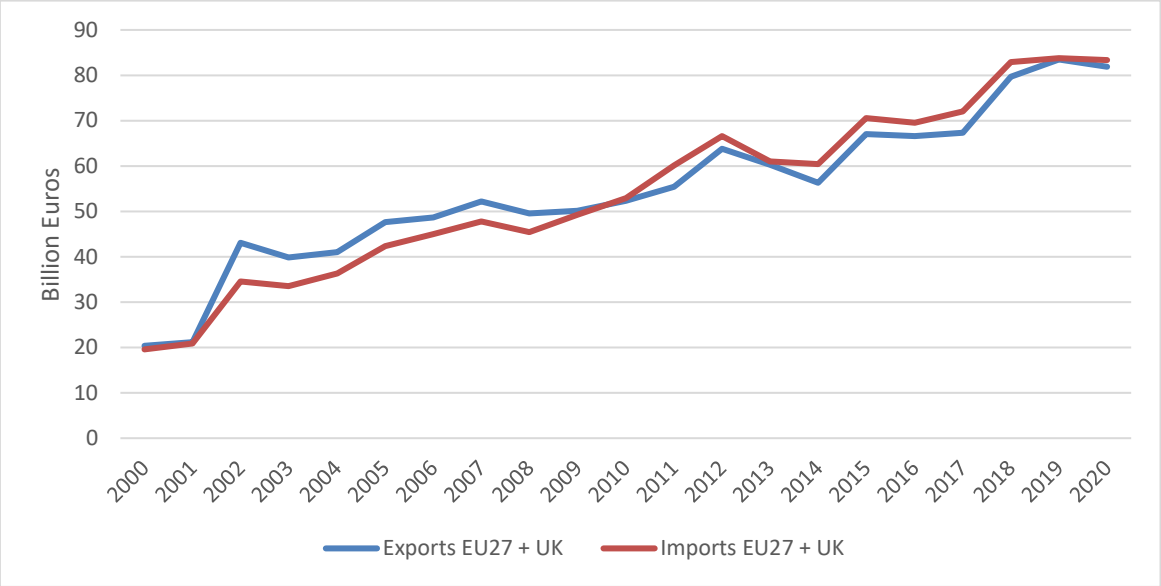
Source: Eurostat. EU28 (EU27 and UK) vaccines exports (imports) to (from) all countries of the world. Vaccines correspond to code 300220 as described in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. Figures are not adjusted for inflation.

Figure IEC-13.3: FPPs exports and imports (values, bn Euro)



Source: Eurostat. EU28 (EU27 and UK) FPPs exports (imports) to (from) all countries of the world. Finished Pharmaceutical Products include the 13 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

Figure IEC-13.4: API exports and imports (values, bn Euro)



Source: Eurostat. EU28 (EU27 and UK) APIs exports (imports) to (from) all countries of the world. Active Pharmaceutical Ingredients include the 101 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

1.2 RESEARCH & INNOVATION INDICATORS

The pharmaceutical industry is highly research intensive, with firms active across all phases of the R&D lifecycle, making the largest contribution to translating and applying knowledge to develop products. The industry invests particularly heavily in the clinical trials required to generate data to obtain marketing authorisation. There was an assumption that the 2004 revisions of the EU general pharmaceutical legislation would enhance the global attractiveness to catalyse increased R&D activities to develop innovative products and ultimately leading to the authorisation of new medicines in Europe. The following indicators were developed to provide quantitative evidence supporting the evaluation of the 2004 revision of the general pharmaceutical legislation.

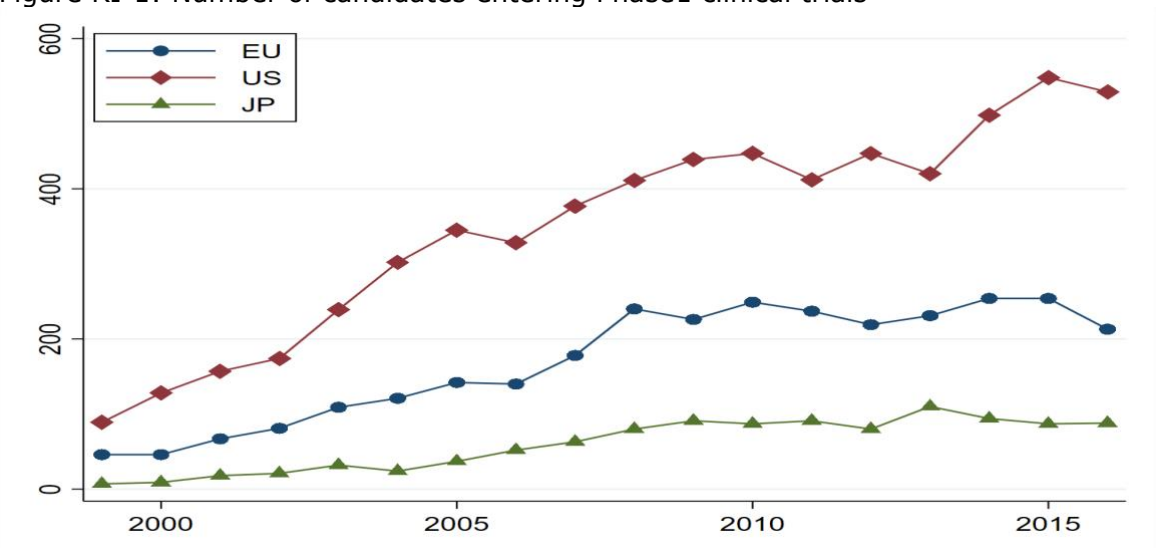
Indicator name	Indicator description
	Conversion rates:
RI-1	Number of candidates entering Phase 1 clinical trials
RI-2	Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials
RI-3	Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials
RI-4	Transition success rate (%) of candidates from Phase 3 to approval
RI-6	Overall Likelihood of Approval (LOA) from Phase 1
	Public research funding:
RI-7	Number of grants and value of grant funding by country and/or funding body
	Private R&D investment:
RI-8	Amount of private R&D investment in the sector
	Innovative products:
RI-9	Number of innovative medicines

Note that RI-5 involved the transition from application to approval, but it was possible to measure this due to the lack of systematic data published on applications for marketing authorisation. Therefore, the step from Phase 3 to approval (RI-4) cannot be broken down to examine the transition from application to approval.

RI-1: Number of candidates entering Phase1 clinical trials

RI-1 counts the number of candidate medicinal products entering Phase 1 clinical testing in the EU, the USA, and Japan, respectively. Since data availability is scarce until the late 1990s and in the most recent years, we limit the analysis to the 1999-2016 period. The figure below illustrates that the number of candidates has increased over time. In the period after 2004, between 300 and 600 Phase 1 candidates are tested annually in the USA, between 150 and 250 in the EU, and between 40 and 110 in Japan.

Figure RI-1: Number of candidates entering Phase1 clinical trials



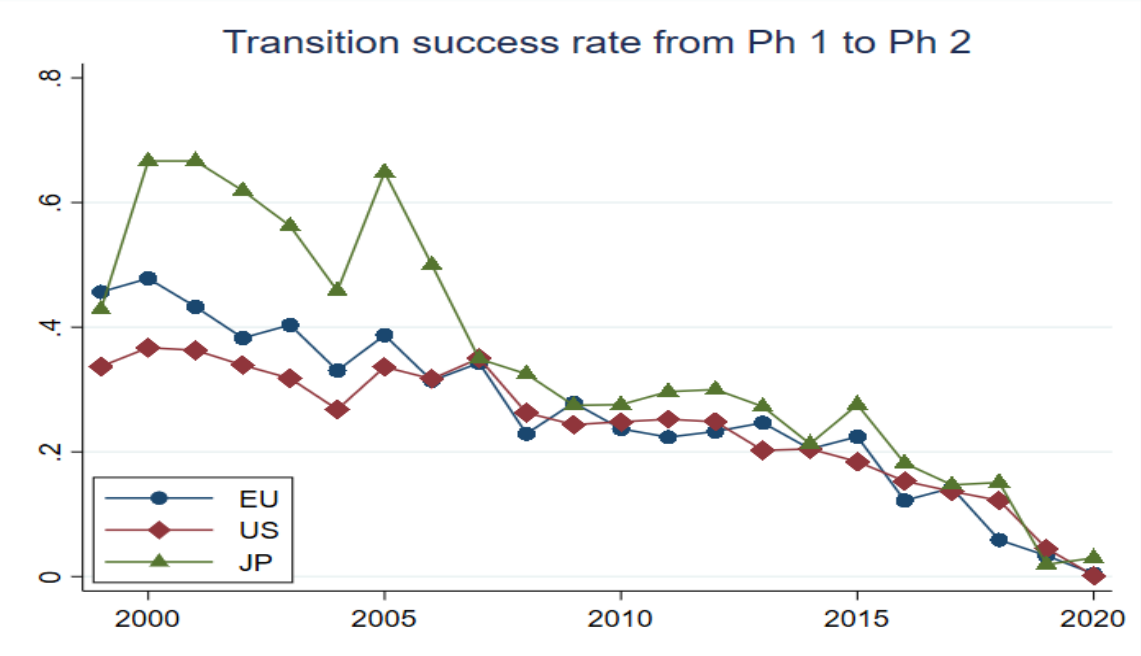
Source: Trialtrove and Pharmaprojects. We consider that a Phase 1 trial in time t-1 was completed successfully if a candidate medicinal product is observed in a Phase 2 trial in time t. The third and final phase is considered as completed successfully if the medicinal product is observed as being approved for sale in time t+1. The final dataset contains a total of 13,849 Phase 1 trials, 16,484 Phase 2 trials, and 8,168 Phase 3 trials.

RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

RI-2 indicates the share of Phase 1 candidate drugs that successfully transition to Phase 2 clinical trials. Again, we differentiate by geographic region and limit the analysis to the 1999-2016 period. Still, the time series for Japan remains rather volatile, particularly in early periods.

We count a Phase 1 trial as completed successfully if we observe a subsequent Phase 2 trial for the same candidate medicinal product in the same indication. Thus, the likelihood of success is expected to decrease towards the end of the sample period, because it is less likely that we observe subsequent trials in the dataset. Yet, we observe a decrease in the Phase 1 success rate over the entire sample period, dropping from about 40% before 2005 to about 20% in the period after, which is indicative of the decrease in research productivity for the pharmaceutical industry in the last two decades (an alternative explanation would be an increased willingness on the part of pharmaceutical companies to terminate drugs early in the development process before too many resources are expended). Noticeably, the probability of a successful Phase 1 clinical trial is higher for Japanese trials than in the other two regions.

Figure RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials



Source: Trialtrove and Pharmaprojects.

Next, we conduct a regression analysis of successful Phase 1 trials, following a difference-in-differences setup: comparing the EU to the USA and Japan before and after the implementation of the 2004 revision of the general pharmaceutical regulations gives us an estimate of the change in the likelihood of trial success in the EU vis-à-vis the other regions and the pre-2005 period. In all regressions, it is important to account for year fixed-effects (and potentially other confounders), to account for the decrease in the likelihood of success over time.

The table below contains the results for three different regression setups. In column (1), we control for year fixed-effects, as well as for the composition of trial sponsors. Trials can be conducted by academic units, government researchers, or pharmaceutical firms – which we further divide into large (top 20) and small (the rest). Controlling for sponsors is akin to keeping the composition of sponsors constant across jurisdictions. In column (2), we add fixed-effects for therapy areas, accounting for the fact that the different regions might be focused on research in different areas. Finally, column (3) contains the same control variables as column (2), but dissects the average treatment effect (ATE) on a yearly basis. Thus, instead of reporting an overall impact for the post-2004 period, column (3) estimates a different coefficient for each year in the post period.

Table RI-2: transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

	(1)		(2)		(3)	
ATE	-0.042*	(-1.92)	-0.050**	(-2.31)		
2005					-0.015	(-0.35)
2006					-0.052	(-1.18)
2007					-0.036	(-0.90)
2008					-0.085**	(-2.32)
2009					-0.024	(-0.65)
2010					-0.054	(-1.49)
2011					-0.068*	(-1.85)
2012					-0.055	(-1.48)
2013					-0.004	(-0.12)
2014					-0.038	(-1.07)

2015			-0.022	(-0.62)
2016			-0.069*	(-1.88)
2017			-0.050	(-1.38)
2018			-0.124***	(-3.30)
2019			-0.042	(-1.04)
2020			-0.025	(-0.69)
N	13847	13847	13847	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post period. * p < 0.1, ** p < 0.05, *** p < 0.01

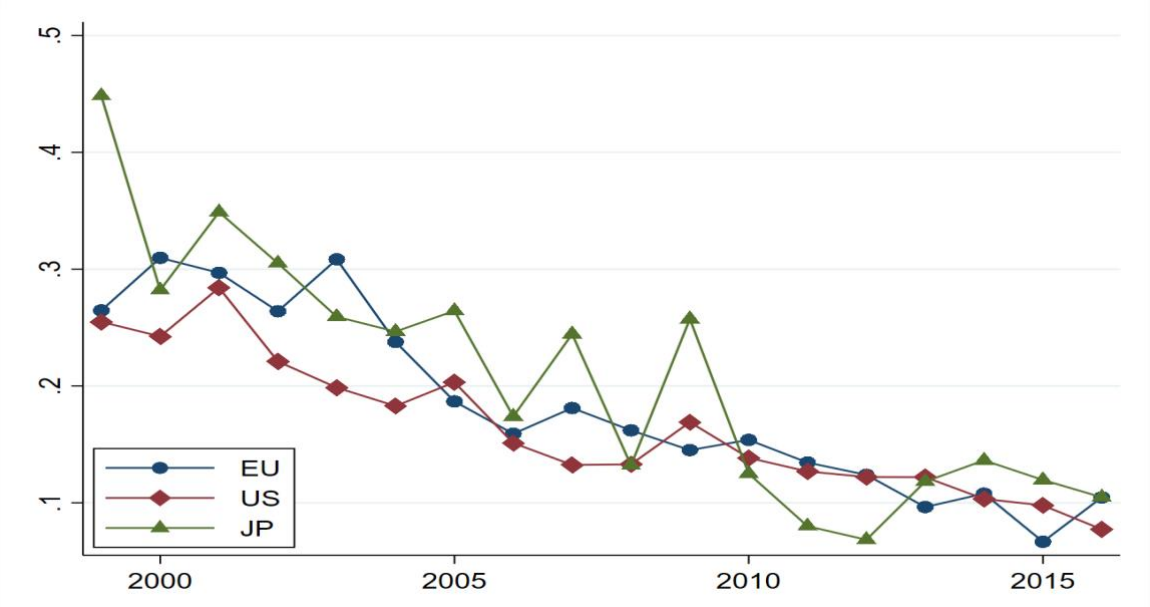
The results show that the probability of successful Phase 1 trials (as captured by the coefficient ATE) decreased in the EU, relative to the USA and Japan, and relative to the pre-2005 period. In column (1), the effect is only weakly significant and indicates a decrease of 4 percentage points. In column (2), the effect size increases to 5 percentage points, as does the significance. Finally, column (3) shows that the effect is not constant across time periods. While the estimates are negative for all individual years from 2005 onwards, only few coefficients are statistically significant. The largest effect is observed in 2018, when the likelihood of success of Phase 1 trials drops by 12.4 percentage points in the EU.

Thus, in terms of successfully completed Phase 1 trials, the EU seems to have underperformed relative to the US and Japan.

RI-3: Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

RI-3, similarly, indicates the share of successfully completed Phase 2 trials, which we infer from the observation of subsequent Phase 3 trials. The same caveats apply as for RI-2. Again, we see the probability of success decline over time. While the average success rate before 2005 oscillates between 20% and 30%, it drops to around 10% after. As before, Japanese trials seem to exhibit a higher success rate than the USA or the EU.

Figure RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials



The regression analysis of successful Phase 2 trials follows the same approach as the analysis of Phase 1 trials above; results are collected in the table below. Again, we

observe a decrease in the likelihood of success in the EU vis-à-vis the other regions. Columns (1) and (2) indicate a decrease of around 4 percentage points, significant at the 1% level. Column (3) shows that the decrease is up to 7 or 8 percentage points in specific periods (2009 and 2013, but also 2015 and 2017), while being insignificant and close to zero in others (2007, 2008, 2011, and 2018).

Table RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

	(1)		(2)		(3)	
ATE	-0.043***	(-3.25)	-0.041***	(-3.14)		
2005					-0.056**	(-2.02)
2006					-0.040	(-1.45)
2007					-0.009	(-0.32)
2008					-0.009	(-0.34)
2009					-0.081***	(-3.15)
2010					-0.024	(-0.90)
2011					-0.017	(-0.62)
2012					-0.027	(-0.95)
2013					-0.071**	(-2.56)
2014					-0.036	(-1.29)
2015					-0.068**	(-2.37)
2016					-0.029	(-1.07)
2017					-0.067**	(-2.39)
2018					-0.016	(-0.55)
2019					-0.052*	(-1.76)
2020					-0.032	(-1.29)
N	16484		16484		16484	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

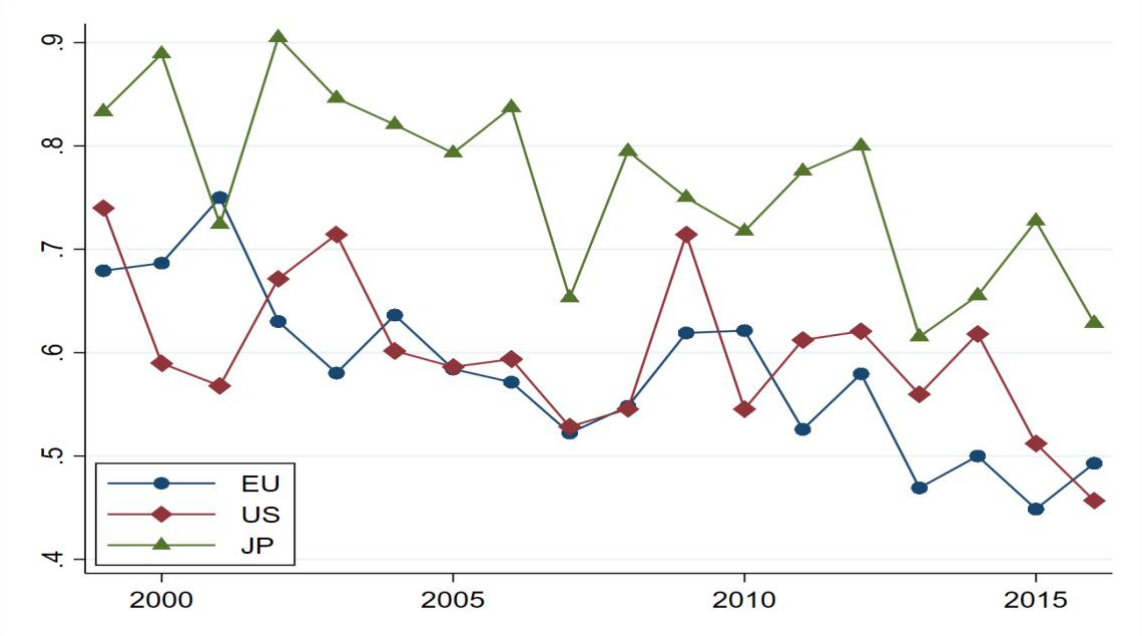
Thus, in terms of successfully completed Phase 2 trials, the EU seems to have underperformed relative to the US and Japan.

RI-4: Transition success rate (%) of candidates from Phase 3 to approval

RI-4 represents the share of candidate medicinal products entering Phase 3 trials that later end up being approved for marketing. The approval year of a drug is merged from the Informa Pharma Pharmaprojects database. We thus calculate the share of medicines in Phase 3 trials that end up being approved for marketing later, and differentiate the three regions of interest: the EU, the USA, and Japan. Note that the approval date is not available for combinatorial drug treatments. Thus, in the following, we focus on single-drug trials.

Once more, we observe that the probability of success declines over time, but to a much smaller extent compared to Phase 1 and Phase 2 trials. The likelihood of success is around 65% before 2005 (and more than 80% in Japan), and declines to around 50% (67% in Japan) after. The likelihood of success is higher for Japanese trials in almost all individual time periods, as can be seen in the figure below.

Figure RI-4: transition success rate (%) of candidates from Phase 3 to approval



Turning to the regression analysis of successful Phase 3 trials, we again follow the setup described above and report the findings in the table below. While the ATEs estimated in columns (1) and (2) are negative, neither of the two is significantly different from zero. Thus, the probability of successfully completing a Phase 3 trial did not decrease in the EU, relative to the other regions and the pre-2005 period.

In column (3), we see that the effect is also insignificant for the individual years between 2005 and 2019. The negative impact in 2020 is likely due to a significant increase in approval of Japanese drugs in 2020 and not due to any effects in the EU.

Table RI-4: transition success rate (%) of candidates from Phase 3 to approval

	(1)		(2)		(3)	
ATE	-0.037	(-1.23)	-0.036	(-1.21)		
2005					0.007	(0.11)
2006					-0.058	(-0.95)
2007					0.020	(0.29)
2008					-0.013	(-0.21)
2009					-0.057	(-0.84)
2010					0.070	(1.08)
2011					-0.082	(-1.24)
2012					-0.022	(-0.32)
2013					-0.082	(-1.19)
2014					-0.100	(-1.42)
2015					-0.075	(-1.08)
2016					0.028	(0.38)
2017					-0.057	(-0.74)
2018					0.040	(0.51)
2019					-0.031	(-0.40)
2020					-0.141**	(-2.13)
N	5117		5117		5117	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus, in terms of successfully completed Phase 3 trials, the EU seems to have performed at a comparable level to the US and Japan.

RI-6: Overall likelihood of approval from Phase 1

RI-6 is similar to RI-4 in that it records success as the approval for a candidate medicinal product to be marketed. It differs from RI-4 insofar that it not only records successful Phase 3 trials, but instead looks at the overall success rate for any candidate in our data (irrespective of the trial phase) to be eventually approved. It is thus correctly interpreted as the share of drugs starting clinical trials in a given year, which later end up being approved for marketing.

The figure below illustrates the overall likelihood of approval in the three regions over time. The likelihood of approval declines until 2005 and remains relatively stable (or declines slightly due to end-of-sample data restrictions) after. Once more, Japanese trials appear to be more successful across the whole sample period.

Figure RI-6: Overall likelihood of approval from Phase 1

The regression results reported in the table below show that the overall likelihood of approval in the EU did not significantly change, relative to the other regions. The coefficients in columns (1) and (2) are small and insignificant. In column (3), we see that the probability of success was lower in the EU in some periods (2013 and 2020), but the coefficients change sign across periods, indicating that no systematic relationship emerges.

Table RI-6: overall likelihood of approval from Phase 1

	(1)		(2)		(3)	
ATE	-0.018	(-1.20)	-0.017	(-1.19)		
2005					-0.001	(-0.03)
2006					0.019	(0.67)
2007					-0.006	(-0.20)
2008					-0.004	(-0.14)
2009					0.010	(0.35)
2010					0.028	(0.98)
2011					-0.027	(-0.96)
2012					0.005	(0.16)
2013					-0.056*	(-1.90)
2014					-0.024	(-0.83)
2015					-0.044	(-1.56)
2016					-0.037	(-1.31)
2017					-0.028	(-1.01)
2018					-0.027	(-0.93)

2019			-0.022	(-0.76)
2020			-0.055**	(-2.20)
N	17431	17431	17431	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, in terms of the overall likelihood of drug approval for all Phase 1 candidates, the EU seems to have performed at a comparable level to the US and Japan.

Analysis of heterogeneous effects

In the previous section, we reported ATEs that indicated the average effect of the 2004 revision of the general pharmaceutical legislation in the post-2004 period, as well as effects for each year in that period. In this section, we extend our analysis in three dimensions: first, we look at the probabilities for trial success in different therapy areas; second, we examine whether the identity of the trial sponsor plays a role in the success of trials; and third, we distinguish drugs by their modality.

Therapy areas

In the Trialtrove data, we observe which therapy area and disease a medicine is being tested for. While an analysis at the disease level would be too disaggregate, as there are hundreds of diseases in the data, we report ATEs for individual therapy areas in the table below.

There are nine broad therapy areas in the data. Drugs are being developed in the areas of i) oncology, ii) metabolic/endocrinology, iii) cardiovascular, iv) CNS, v) autoimmune/inflammation, vi) genitourinary, vii) infectious diseases, viii) ophthalmology, and ix) vaccines.

Table RI-6.1: Phase transitions and LoA by therapeutic area

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Oncology	-0.068***	-0.017	0.067	0.023
	(-2.78)	(-1.06)	(1.30)	(1.21)
Metabolic	-0.056*	-0.016	-0.020	-0.033
	(-1.73)	(-0.66)	(-0.41)	(-1.52)
Cardiovascular	-0.030	-0.049*	-0.048	-0.023
	(-0.83)	(-1.93)	(-0.97)	(-0.93)
CNS	-0.076**	-0.057***	-0.045	-0.025
	(-2.51)	(-2.99)	(-1.03)	(-1.26)
Autoimmune	-0.036	-0.058***	-0.079*	-0.036*
	(-1.23)	(-3.02)	(-1.88)	(-1.89)
Genitourinary	-0.028	-0.059	-0.030	-0.063*
	(-0.46)	(-1.55)	(-0.42)	(-1.77)
Infectious Disease	-0.044	-0.062***	-0.084*	-0.019
	(-1.51)	(-2.97)	(-1.83)	(-0.89)
Ophthalmology	-0.066	-0.012	-0.065	-0.047
	(-0.97)	(-0.27)	(-0.76)	(-1.20)
Vaccines	0.006	-0.069*	0.124	0.041
	(0.17)	(-1.94)	(1.58)	(1.28)
N	13847	16484	5117	17431

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

It can be observed that the ATEs differ quite substantially across therapy areas, and, in particular, that the negative impact on the success of Phase 1 and Phase 2 trials in the EU – described above – can be attributed to specific areas, while others are not significantly affected.

In particular, the decrease in successful Phase 1 trials in the EU – which was estimated to be around 4-5 percentage points – most strongly and significantly manifests in the areas of oncology and CNS, as well as – to a lesser extent – metabolic diseases (column (1)). While the coefficients for other therapy areas are mostly negative, they are not statistically significant.

From column (2) it becomes apparent that the decreased probability of Phase 2 trial success in the EU can be explained through decreased success in the areas of CNS, autoimmune diseases, and infectious diseases, as well as – at a lower statistical significance – cardiovascular diseases and vaccines. Thus, while the decreased success of Phase 1 trials can be traced back to only 3 therapy areas, Phase 2 trial success decreases for 5 areas.

The impact on the success of Phase 3 trials – for which no significant overall effect was found above – is mixed and mostly insignificant across therapy areas. Only in two areas (autoimmune and infectious diseases) do we observe reductions at a marginal level of statistical significance.

The change in the overall likelihood of drug approval – for which we also found no significant ATE – is insignificant in most therapy areas, but marginally decreases for autoimmune drug trials and genitourinary drug trials.

Thus, when evaluating successful phase transitions and the overall likelihood of approval for individual therapeutic areas, the below become apparent.

i) In Phase 1 transitions, the EU seems to have underperformed relative to the US and Japan in three therapy areas.
ii) In Phase 2 transitions, the EU seems to have underperformed relative to the US and Japan in five therapy areas.
iii) In Phase 3 transitions, the EU seems to have performed at a comparable level to the US and Japan.
iv) In the overall likelihood of approval, the EU seems to have performed at a comparable level to the US and Japan.

Trial sponsors

The Trialtrove data also contain a field with the identity of the trial sponsor(s) and a classification of trial sponsors into four groups. We distinguish trials sponsored by academic research, by government research, and by the research of pharmaceutical companies; in the latter case, we distinguish trials run by the top 20 pharmaceutical companies (according to Informa Pharma's Scrip database) and other pharmaceutical companies. Note that these categories are non-exclusive: the same trial might be run by academic researchers jointly with pharmaceutical companies. Yet, the overlap across sponsor types is limited, as the average trial is run by only 1.2 sponsors. The table below reports regression results for the individual trial phases and for the overall likelihood of approval.

Table RI-6.2 Phase transitions and LoA by trial sponsor

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Academic	-0.012	-0.002	-0.071**	0.009
	(-0.67)	(-0.14)	(-2.21)	(0.64)
Top 20 pharma	-0.057***	-0.071***	0.058*	-0.039***
	(-2.94)	(-4.65)	(1.65)	(-2.65)
Government	-0.012	0.015	0.164***	0.083***
	(-0.50)	(0.85)	(3.07)	(4.29)
Other pharma	-0.031*	-0.036***	-0.023	-0.001
	(-1.67)	(-2.66)	(-0.74)	(-0.04)
N	13847	16484	5117	17431

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

The analysis of sponsor types reveals some interesting heterogeneities. The EU's relative decline in the success of Phase 1 and Phase 2 trials reported above is due to less trial success by pharmaceutical companies. The top 20 firms are particularly affected (with a decrease of almost 6 percentage points in Phase 1 and 7 percentage points in Phase 2 trials), while other pharma firms are somewhat affected (a decrease of 3-4 percentage points). Conversely, the success rates for academic and government run trials did not decline.

In column (3), we see that academic run Phase 3 trials in the EU are almost 7 percentage points less likely to succeed after 2004, relative to the USA and Japan. Surprisingly, we see a large increase of 16 percentage points in the likelihood of success of government run trials. At a baseline success rate of 32% for European Phase 3 trials, this corresponds to a 50% increase.

Finally, column (4) reports the findings for the overall likelihood of approval. Again, we see a large increase in the success rate of government trials, while the success rate of top 20 pharmaceutical companies diminishes modestly. No significant effect is found for academic trials or other pharmaceutical companies.

The increased success in Phase 3 and marketing authorization for government-backed trials in the post period can, to some degree, be explained by changes in the sample composition before and after 2004. Before 2004, more than 30% of trials involving government funding were focused in the indication of oncology. Oncology is, on average, the therapeutic area with the lowest trial success rate, across all regions and periods (29% success vs 34% for all other therapeutic areas). After 2004, the share of government-backed oncology trials in the EU drops to less than 22%. Instead, more focus is being put on therapeutic areas with a higher average success rate (the share of trials for cardiovascular drugs, which enjoy a success rate of more than 42%, has increased from 6% to 9%).

Thus, the increased success of trials involving governmental researchers in the EU after 2004 can partially be explained by a shift away from research in therapeutic areas where success is unlikely, towards those with higher success rates.

The composition of trial sponsors has also changed over time (we observe more trials by other pharma firms; less trials by the government and top 20 pharma firms; and roughly equally many trials involving academic sponsors in the EU after 2004). However, we would not expect this to affect the results: firstly, the outcome is the ratio of successful over total trials and should therefore be robust to size effects. Secondly, the matching analysis below accounts for such difference in composition and yields consistent findings.

Thus, when evaluating successful phase transitions and the overall likelihood of approval by sponsor type, the below become apparent.

i) The relative decline of successful Phase 1 and 2 transitions in the EU can be explained by a decline in the success of trials run by pharmaceutical companies (both large and small).
ii) Government-backed drug trials in the EU are much more likely to successfully complete Phase 3/be approved for marketing after 2004 than their US and Japan counterparts.

Drug modality

As a final dimension of heterogeneity, the data allow us to distinguish drug modalities. We observe seven different modalities in the data: i) small molecule, ii) antibody, iii) cellular therapy, iv) gene therapy, v) RNA, vi) peptide, and vii) fusion protein. While these categories are non-exclusive (such as in the case of antibody fusion proteins), 86% of drugs in the data fall in exactly one category, while 7% fall in none. Thus, only 7% of drugs have more than one modality.

Another important point is the unequal distribution of drugs across modalities. While almost 76% of drugs in the data fall into the small molecule category and almost 13% into the antibody category, only 5% of drugs are cell therapy or gene therapy related. The remaining categories (RNA, peptide, fusion protein) account for around 1% of drugs each. Thus, estimates for those drugs will have a high degree of statistical uncertainty and should be interpreted with caution.

In the table below, we report the ATEs on the probabilities of phase transitions and LoA, disaggregated by drug modality.

Table RI-6.3. Phase transitions and LoA by drug modality

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Small molecule	-0.040***	-0.022*	-0.087***	-0.029**
	(-2.61)	(-1.94)	(-3.23)	(-2.44)
Antibody	0.026	-0.011	0.048	-0.024
	(1.17)	(-0.70)	(0.84)	(-1.17)
Cell therapy	-0.004	0.035	-0.311**	-0.121***
	(-0.13)	(1.04)	(-2.52)	(-4.23)
Gene therapy	-0.047	-0.080**	-0.101	0.001
	(-1.31)	(-2.52)	(-1.02)	(0.04)
RNA	-0.095	0.018	-0.408**	-0.103*
	(-1.49)	(0.24)	(-2.13)	(-1.77)
Peptide	-0.129*	-0.075	0.138	-0.029
	(-1.72)	(-1.03)	(0.66)	(-0.44)
Fusion protein	0.062	-0.027	-0.093	-0.056
	(1.20)	(-0.57)	(-0.69)	(-1.14)
N	13847	16484	5117	17431

t statistics in parentheses. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$, all regressions contain fixed-effects for years, indications, and sponsors.

We see a consistent and negative impact on small molecule drugs: the probabilities for successful phase transitions and for LoA are lower in the EU after 2004, compared to Japan and the US. The size of the effect is 2-4 percentage points in Phase 1, Phase 2, and LoA, and almost 9 percentage points in Phase 3.

For cell therapies and RNA drugs, we observe lower success rates for Phase 3 and LoA. Gene therapies have a lower Phase 2 transition probability and peptide drugs a lower Phase 1 transition probability. As the estimated coefficients are based on very few observations (except for those on small molecule drugs), the size of the coefficients should be regarded as indicative at best. For example, the estimate that the Phase 3 transition probability of RNA based drugs has decreased by 40.8 percentage points is based on only 6 RNA based drugs developed in the EU after 2004. For antibody drugs, peptide drugs, and fusion proteins, we see no significant effects.

Thus, we find that the success of small molecule drugs in the EU has declined through all phases of clinical testing after 2004, relative to the US and Japan.

Analysis using propensity score matching

In the analysis so far, we have relied on using all available data on clinical trials in the EU, the US, and Japan. While this approach yields the most general results as all available data are used, there might also be drawbacks: if the composition of clinical trials differs across geographies, differences found between geographies might actually be due to differences in sample composition. To be specific, assume that the EU and the US are identical when it comes to regulatory and research conditions. If clinical trials in the EU systematically focus on therapeutic areas where progress is harder to achieve (relative to the trials conducted in the US), we would expect to see a lower rate of phase progressions in the EU. However, this lower rate would not be due to policy or regulation, but simply due to the fact that more challenging projects are attempted.

In this section, we will control for the composition of clinical trials across geographies through propensity score matching. Intuitively, we will i) estimate if clinical trials in the EU are statistically different from those in other regions based on their observable characteristics; ii) select for each EU trial a US or Japanese trial that is as similar as possible; and iii) repeat the above analysis in the resulting matched sample. By pairing EU and non-EU trials that are individually as similar as possible, we should obtain a sample that is on aggregate not too different across regions, based on the observable characteristics of drug trials.

The first step in this procedure is to estimate a selection model, in which the probability of a trial being conducted in the EU is estimated as a function of observable characteristics. Since the dependent variable is binary (EU 0/1), we estimate a probit model. The independent variables available refer to trial sponsors, an indicator for whether a trial is run for a combinatorial drug treatment, therapeutic area indications, and the phase of the trial. Estimation results are reported in the table below.

Table RI-6.4. Selection model: characteristics of European trials

Other pharma	-0.145***	(0.021)
Government	-0.410***	(0.019)
Top 20 pharma	-0.078***	(0.021)
Academic	-0.055***	(0.018)
Combinatorial drug	0.070***	(0.016)
Metabolic	0.209***	(0.026)
Cardiovascular	0.239***	(0.028)
CNS	0.184***	(0.022)
Autoimmune	0.349***	(0.022)
Genitourinary	0.334***	(0.043)
Infectious disease	0.299***	(0.023)
Ophthalmology	-0.027	(0.051)
Vaccines	0.638***	(0.035)
Phase 2	0.103***	(0.016)
Phase 3	0.297***	(0.019)
Observations	38501	
Pseudo R^2	0.030	

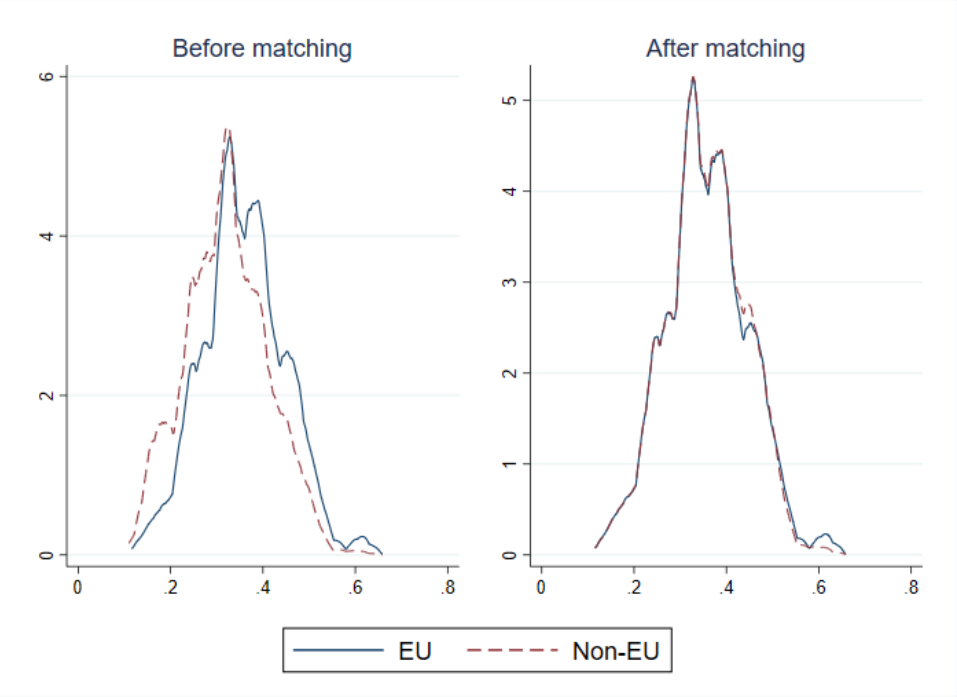
Standard errors in parentheses, * p < 0.1, ** p < 0.05, *** p < 0.01

The estimation results show that, on the one hand, European trials differ from US and Japanese trials in almost all observable characteristics, but – on the other hand – the amount of heterogeneity that can be explained through the observables is limited, as the explanatory power (the pseudo R^2) of the model is quite low.

European trials have, on average, fewer sponsors than those in other regions: the involvement of Top 20 pharma firms, other pharma firms, and academic participants is lower, and particularly government involvement is much lower than in the other regions. Combinatorial drugs are more likely to be tested in the EU. The probability of trials occurring in a specific therapeutic area are measured relative to the first therapeutic area in the data (oncology). The mostly positive and significant coefficients therefore suggest that the EU conducts relatively less trials in oncology compared to the US and Japan, but relatively more in most other therapy areas. Finally, we observe more Phase 2 and Phase 3 trials in the EU (compared to Phase 1 trials).

Thus, EU and non-EU trials are somewhat different with regard to their composition. To account for this, we implement a propensity score matching procedure as follows: first, we use the selection model calibrated above to obtain the predicted values. Thus, for every trial, we estimate the likelihood that this trial was conducted in the EU, based on the model coefficients. Next, for each European trial, we find a non-European trial (conducted in the same year) that is as similar as possible in its probability of being run

in Europe (i.e., with a very similar predicted value). By pairing EU and non-EU trials that are as similar as possible, we obtain a sample of (the same amount of) EU and non-EU trials with similar characteristics. Additional non-EU trials are discarded. The figure below plots the kernel densities of the propensity scores (i.e., the ex-ante likelihoods of being an EU trial) for EU and non-EU trials before (left) and after (right) the matching procedure. While the distribution of propensity scores across the two groups looks quite dissimilar in the left panel, the matching procedure results in almost identical kernel densities across the two groups. This shows that the samples have been made more comparable.



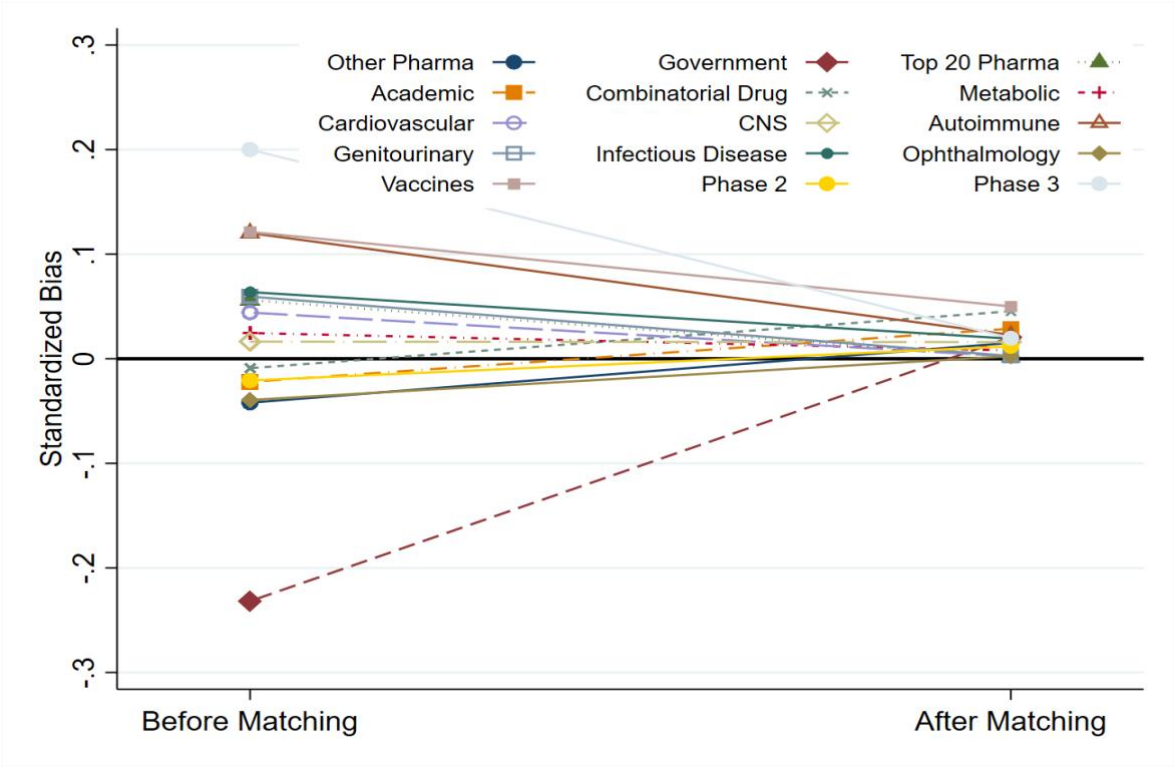
This can also be illustrated based on the trials' observable characteristics. The table below reports sample averages for all trial characteristics used in the matching procedure (sponsors, combinatorial drugs, therapeutic areas, and trial phases), distinguishing EU and non-EU trials and calculating the statistical significance of the difference between the two ("p"). Before the matching procedure (columns 1-3), almost all the means are significantly different between the two groups (as indicated by p-values smaller than 0.1 in column 3). Conversely, after the matching procedure, (columns 4-6), the means have become more similar and most differences now lack statistical significance, although some differences remain.

Table RI-6.5. Trial characteristics before and after matching

	Before matching			After matching		
	Mean EU	Mean non-EU	p	Mean EU	Mean non-EU	p
Other pharma	0.303	0.322	0.00	0.303	0.310	0.22
Government	0.127	0.213	0.00	0.127	0.120	0.10
Top 20 pharma	0.277	0.252	0.00	0.277	0.276	0.91
Academic	0.419	0.430	0.04	0.419	0.405	0.02
Combinatorial Drug	0.434	0.438	0.41	0.434	0.411	0.00
Metabolic	0.095	0.088	0.02	0.095	0.097	0.52
Cardiovascular	0.080	0.068	0.00	0.080	0.079	0.85
CNS	0.147	0.141	0.13	0.147	0.152	0.20
Autoimmune	0.154	0.113	0.00	0.154	0.163	0.07
Genitourinary	0.032	0.022	0.00	0.032	0.032	0.83
Infectious disease	0.134	0.113	0.00	0.134	0.127	0.12

Ophthalmology	0.016	0.021	0.00	0.016	0.016	0.84
Vaccines	0.055	0.030	0.00	0.055	0.044	0.00
Phase 2	0.421	0.432	0.06	0.421	0.427	0.34
Phase 3	0.268	0.184	0.00	0.268	0.259	0.12

Finally, the matching procedure can also be illustrated by comparing the standardized biases. The standardized bias (the difference in means of treatment and control group divided by the standard deviation in the treatment group) is the bias one incurs by comparing EU to non-EU trials. The figure below illustrates how standardized biases with regard to the individual matching variables change from before matching (left) to after matching (right). Most standardized biases are substantially reduced through matching; in particular, some heavily biased characteristics such as Phase 3 trials and government sponsors are much improved.



In the following, we repeat the regression analyses for indicators RI-2, RI-3, RI-4, and RI-6 in the propensity-score matched sample.

RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

The table below compares the success rate of Phase 1 trials in the EU in the period including and after 2005 to the success rate before 2005, as well as to success rates in the US and Japan. Conducting the same analysis in the full sample, we found that success rates in the EU declined by 4-5%, significant at the 5-10% level. Estimating yearly ATEs, we found that all coefficients were negative, but only some were significant.

Repeating the analysis in the matched sample, we find no significant difference between Phase 1 success in the EU and the other regions after 2004. The coefficient estimates of the ATE are close to zero and not statistically significant, both including year fixed-effects (column (1)) and including year and indication fixed-effects (column (2)). When looking at yearly ATEs in column (3), we see that the coefficients are never significantly different from zero.

Table RI-2: transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials in matched sample

	(1)		(2)		(3)	
ATE	0.014	(0.51)	0.010	(0.39)		
2005					0.035	(0.65)
2006					0.016	(0.29)
2007					0.002	(0.03)
2008					-0.036	(-0.82)
2009					0.004	(0.08)
2010					0.027	(0.62)
2011					0.012	(0.26)
2012					0.050	(1.11)
2013					0.000	(0.01)
2014					0.017	(0.40)
2015					0.019	(0.43)
2016					-0.017	(-0.37)
2017					0.025	(0.57)
2018					-0.067	(-1.47)
2019					0.030	(0.61)
2020					0.030	(0.68)
N	8019		8019		8019	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus we conclude that once we control for differences in the observable characteristics of clinical trials across regions, there are no significant differences in successful Phase 1 trials in the EU vis-à-vis the other regions after 2004.

RI-3: Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

Next, we analyse the impact on RI-3 in the matched sample. Recall that above we found successful Phase 2 trials had become about 4% less likely in the EU after 2004.

The table below reports the findings from the matched sample. While the two estimates of the ATE in columns (1) and (2) remain negative, they lose their statistical significance. The year-specific ATEs (column (3)) reveal that the effect is significant only in one period, 2009. While some indications of a negative impact on Phase 2 trial success remain, the treatment effects are mostly insignificant in the matched sample.

Table RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials in matched sample

	(1)		(2)		(3)	
ATE	-0.011	(-0.69)	-0.013	(-0.83)		
2005					-0.038	(-1.18)
2006					0.003	(0.08)
2007					0.015	(0.47)
2008					0.023	(0.70)
2009					-0.079***	(-2.64)
2010					0.004	(0.13)
2011					-0.008	(-0.23)
2012					0.002	(0.07)
2013					-0.033	(-1.00)
2014					0.007	(0.21)
2015					-0.029	(-0.84)
2016					-0.020	(-0.61)
2017					-0.020	(-0.59)
2018					0.012	(0.33)
2019					-0.015	(-0.42)
2020					-0.011	(-0.36)

N	10870		10870		10870	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, there are only minor differences in successful Phase 2 trials in the EU vis-à-vis the other regions after 2004.

RI-4: transition success rate (%) of candidates from Phase 3 to approval

The next indicator we re-evaluate in the matched sample is the rate of successfully completed Phase 3 trials (Phase 3 to approval). In the full sample above, we found that although the ATE coefficients were negative, EU Phase 3 trials were not significantly less successful than those in other regions.

This finding is replicated for the matched sample in the table below. The ATE coefficients are very similar to those obtained in the full sample and not statistically significant. The estimated yearly effects are also insignificant, except for two periods, where marginal significance is attained.

Table RI-4: transition success rate (%) of candidates from Phase 3 to approval in matched sample

	(1)		(2)		(3)	
ATE	-0.035	(-1.10)	-0.034	(-1.09)		
2005					0.041	(0.60)
2006					-0.079	(-1.21)
2007					0.065	(0.91)
2008					0.003	(0.04)
2009					-0.062	(-0.88)
2010					0.036	(0.52)
2011					-0.117*	(-1.68)
2012					-0.039	(-0.53)
2013					-0.080	(-1.05)
2014					-0.062	(-0.80)
2015					-0.030	(-0.38)
2016					0.092	(1.10)
2017					-0.064	(-0.76)
2018					-0.042	(-0.47)
2019					-0.074	(-0.87)
2020					-0.152**	(-2.08)
N	4151		4151		4151	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, the success rate of Phase 3 trials in the EU after 2004 did not differ substantially from that in the other regions.

RI-6: Overall likelihood of approval from Phase 1

Next, we turn to the overall likelihood of approval for drugs. In the full sample, we found i) no significant overall impact in the EU after 2004 and ii) positive as well as negative effects in some specific years.

In the matched sample we find – as reported in the table below – no significant differences between the EU and the other regions, neither in the overall ATEs, nor in the disaggregated yearly coefficients.

Table RI-6.1: overall likelihood of approval from Phase 1 in matched sample

	(1)		(2)		(3)	
ATE	0.012	(0.69)	0.010	(0.59)		
2005					0.014	(0.40)
2006					0.004	(0.12)
2007					0.018	(0.50)
2008					0.008	(0.24)
2009					0.019	(0.57)
2010					0.041	(1.23)
2011					-0.033	(-1.00)
2012					0.015	(0.42)
2013					-0.010	(-0.30)
2014					0.016	(0.46)
2015					0.012	(0.34)
2016					0.048	(1.41)
2017					0.005	(0.16)
2018					-0.007	(-0.19)
2019					-0.001	(-0.03)
2020					-0.017	(-0.54)
N	12407		12407		12407	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus, the overall likelihood of drug approval did not change in the EU after 2004.

Heterogeneous effects in the PSM sample

For completeness and to corroborate the previous findings, we also repeat the analyses of heterogeneous effects (specifically, the impact of therapeutic area, of trial sponsor, and of drug modality on the indicators) in the propensity score matched sample.

Therapy areas

In the full sample it was found that in some therapeutic areas (CNS, autoimmune, infectious disease) the EU seems to be at a disadvantage, particularly in earlier trial phases.

On the one hand, these findings of a negative effect are largely replicated in the matched-sample analysis below. Specifically, we see that Phase 2 success is lower for autoimmune and infectious disease drug trials, and Phase 3 success is lower for autoimmune disease drug trials.

On the other hand, we also find positive effects on trial success in the matched sample. The Phase 3 and LoA success of oncology drugs has increased by 11 and 9 percentage points respectively, and the Phase 1 and LoA success for vaccines trials in the EU has increased by 8 percentage points. For the other therapeutic areas, no significant effects are found.

Table RI-6.2 Phase transitions and LoA by therapeutic area in matched sample

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Oncology	-0.030	0.029	0.113**	0.086***
	(-0.99)	(1.56)	(2.01)	(3.80)
Metabolic	-0.002	0.005	-0.021	-0.018
	(-0.06)	(0.20)	(-0.42)	(-0.72)
Cardiovascular	0.025	-0.043	-0.076	-0.022

	(0.58)	(-1.47)	(-1.46)	(-0.78)
CNS	-0.003	-0.031	-0.075	-0.020
	(-0.09)	(-1.42)	(-1.63)	(-0.88)
Autoimmune	0.030	-0.038*	-0.073*	-0.008
	(0.89)	(-1.77)	(-1.66)	(-0.35)
Genitourinary	0.071	-0.038	-0.015	-0.053
	(1.04)	(-0.89)	(-0.20)	(-1.33)
Infectious disease	0.042	-0.047**	-0.078	0.001
	(1.19)	(-1.97)	(-1.63)	(0.03)
Ophthalmology	-0.039	0.034	0.025	0.047
	(-0.48)	(0.62)	(0.26)	(0.99)
Vaccines	0.076*	-0.040	0.130	0.081**
	(1.87)	(-1.05)	(1.62)	(2.26)
N	8019	10870	4151	12407

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that some (Phase 2 and 3) success rates have decreased in the EU is corroborated in the matched sample. Yet, we additionally find that the overall likelihood of approval rate has increased for oncological drugs and vaccines.

Trial sponsors

Second, we estimate heterogeneous effects for trial sponsor types (top 20 pharma, other pharma, government, and academic) in the matched sample. In the full sample, it was found for the EU that academic-backed trials have a lower Phase 3 success rate; that top 20 pharma firm trials have a higher Phase 3 success rate, but lower Phase 1, Phase 2, and LoA success rates; that government-backed trials are highly successful in Phase 3 and LoA; and that other pharma firms are at a disadvantage in Phase 1 and Phase 2 trials.

Most of these findings are corroborated in the table below. While the negative impact on top 20 pharma firms' LoA and the effects on other pharma firms have vanished, the coefficients for academic- and government-backed trials are very similar to above.

Table RI-6.3 Phase transitions and LoA by trial sponsor in matched sample

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Academic	-0.005	0.004	-0.081**	-0.008
	(-0.21)	(0.33)	(-2.42)	(-0.47)
Top 20 pharma	-0.023	-0.060***	0.070*	-0.016
	(-0.99)	(-3.40)	(1.89)	(-0.90)
Government	0.006	0.006	0.115**	0.099***
	(0.21)	(0.29)	(1.97)	(4.22)
Other pharma	-0.009	-0.021	-0.035	0.016
	(-0.41)	(-1.36)	(-1.04)	(1.03)
N	8019	10870	4151	12407

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that after 2005 in the EU government-backed trials were particularly successful in the later stages of testing is reinforced.

Drug modality

Finally, we estimate heterogeneous effects for drug modalities. In the full sample, it was found that small molecule drugs in the EU have lower chances of being successfully tested in all phases of testing, including LoA. While negative effects were also found in some other modality groups, those were estimated based on few observations and have to be interpreted with caution.

The results in the matched sample, by and large, mirror those found in the full sample. While the negative effects of small molecule drugs are insignificant in Phases 1 and 2 in the matched sample, the negative effects on Phase 3 and LoA retain statistical significance.

Table RI-6.4 Phase transitions and LoA by drug modality

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Small molecule	-0.022	-0.003	-0.092***	-0.023*
	(-1.32)	(-0.27)	(-3.30)	(-1.73)
Antibody	0.043*	0.009	0.048	-0.005
	(1.82)	(0.54)	(0.83)	(-0.22)
Cell therapy	0.002	0.047	-0.317**	-0.120***
	(0.06)	(1.33)	(-2.57)	(-3.93)
Gene therapy	-0.041	-0.072**	-0.100	0.011
	(-1.13)	(-2.19)	(-1.02)	(0.33)
RNA	-0.091	0.040	-0.390**	-0.090
	(-1.39)	(0.50)	(-2.05)	(-1.46)
Peptide	-0.120	-0.067	0.160	-0.028
	(-1.56)	(-0.89)	(0.76)	(-0.41)
Fusion protein	0.069	-0.018	-0.092	-0.064
	(1.30)	(-0.36)	(-0.68)	(-1.19)
N	8019	10870	4151	12407

t statistics in parentheses. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that after 2005 in the EU small molecule trials were less successful in the later stages of testing is reinforced.

Summary

The analyses of clinical trial data, and, specifically, the probabilities of successfully completing Phase 1, Phase 2, and Phase 3 trials, as well as successfully reaching marketing approval, have yielded mixed results. No clear-cut and robust divergence of success in clinical testing between the EU and the US/Japan has been found in the 2005-2020 period. This is not too surprising, as the "treatment" being evaluated in the analysis (the change of pharmaceutical regulations in the EU that came into force in 2005) did not occur randomly or in isolation. Also, rather than comparing a specific policy in one region to regions without that policy, we are evaluating the impact of a large set of regulations relative to a moving benchmark. This makes it difficult to identify any causal effect of such a treatment, particularly over such a long period of observation. The tendencies uncovered in the above analysis should therefore be regarded as the result of the entire research environment in the EU, including pharmaceutical regulations, but also other factors such as the availability of research funding and technological opportunities.

Methodologically, we analysed both the full dataset available and a propensity-score

matched sample, where for each EU trial we chose a non-EU trial that is as similar as possible in terms of observable characteristics. While the former approach covers the whole data range available, the latter approach controls for differences in, e.g., the composition of trials in the different regions. Thus, for the purposes of informing policy, the PSM approach is preferable and should be given more weight, as it makes sure that "apples are compared to apples".

While in the full sample, the likelihood of Phase 1 and Phase 2 success diminishes slightly in the EU vis-à-vis the other regions, these findings cannot be replicated in the matched sample. For successful Phase 3 trials and the overall likelihood of approval, findings are inconclusive in both evaluated samples. These results are summarized in the table below.

Table RI-6.5. Summary of findings on EU performance relative to US/Japan performance on main indicators

Indicator	Full sample	Matched sample
RI-2		
RI-3		
RI-4		
RI-6		

We do, on the other hand, find some interesting and robust patterns when looking at heterogeneous effects.

When differentiating trial success by therapeutic area, we find that the likelihood of successful Phase 2 trials has diminished in the EU for trials in five areas, two of which (autoimmune and infectious diseases) are corroborated by the matching analysis. For autoimmune diseases, Phase 3 trials are also less likely to be successful.

Looking at trial success by sponsor type, we find in the full sample analysis and corroborate in the matched sample analysis that Phase 2 trials by large pharmaceutical companies and Phase 3 trials by academic sponsors have become less likely to succeed in the EU in the period after 2004. Conversely, Phase 3 trials sponsored by large pharmaceutical companies, as well as Phase 3 trials and the likelihood of approval of drugs trialled in government-backed research have become more successful.

Finally, the analysis of heterogeneities by drug modalities has shown that Phase 3 trials have become less successful in the EU in the areas of small molecule drugs, cell therapies, and RNA drugs, and that the overall likelihood of approval has diminished for the former two.

RI-7: Number of grants and value of grant funding by country

Indicator definition and relevance with respect to the evaluation

Public R&D investment is an important indicator of the status of fundamental scientific research, as it is the ultimate source of much innovation in the pharmaceutical industry.

While no data are available for the analysis period prior to the introduction of the general pharmaceutical legislation, RI-7 assesses the relative investment in fundamental scientific research by certain member states of the EU between 2015 and 2020, where the most complete data are available.

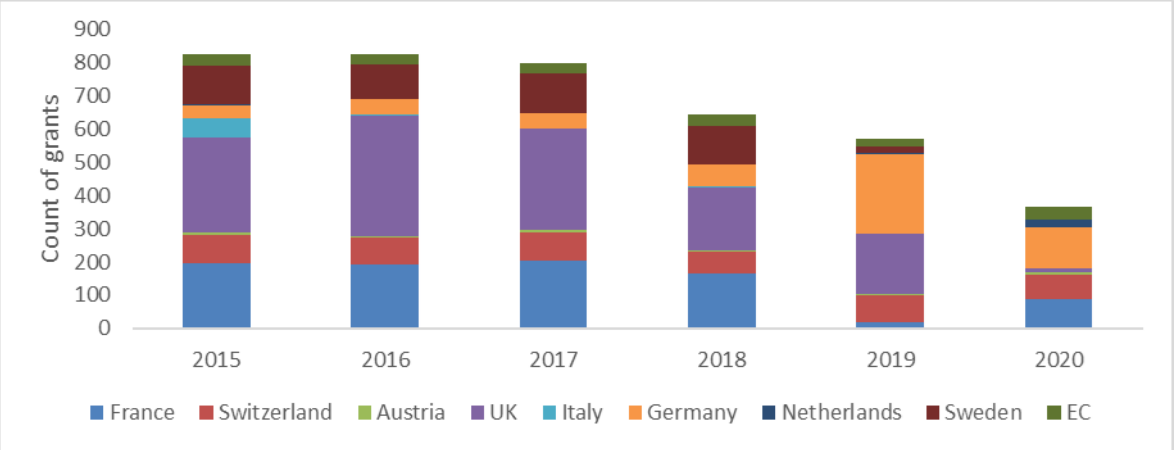
Methodology

The scientific grants analysis dataset for indicator RI-7 consists of approximately 6,500 grant records that have been collected and curated by Informa Pharma Custom Intelligence. When grants were extracted from a country or funding body database, they were screened to select only grants that might potentially lead to the development of a medicinal product, in order to prevent any analysis of the grants data from being confounded by grants not relevant to pharmaceutical innovation. Data were gathered from more than 20 grant agencies across 9 countries in the EU, plus the EC's H2020 and FP7 programmes, and Switzerland. The data available in each funding body database are not consistent, so temporal data for Spain are unavailable, and total or average grant values are not available for the Netherlands or Germany, so these data are not presented.

Description of trends and interpretation of possible causes for changes in RI-7

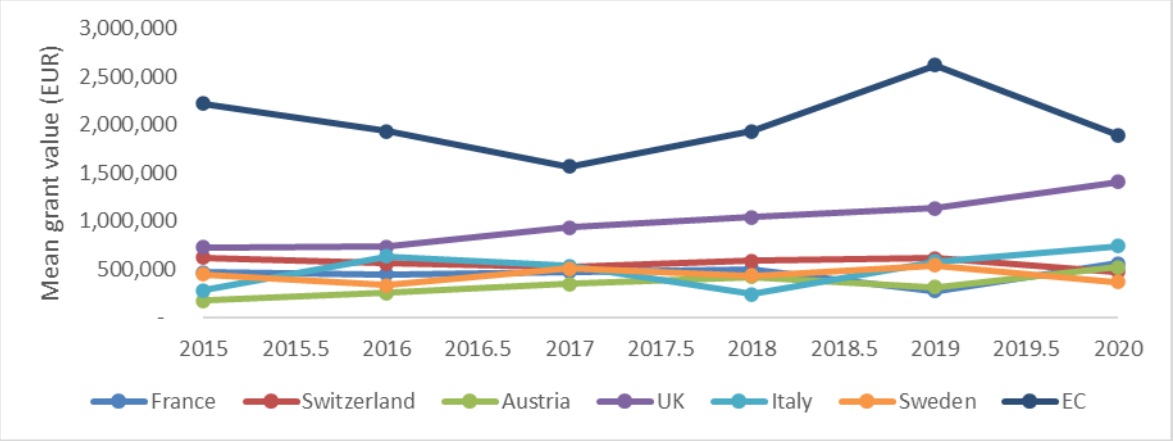
While no data for the period prior to the implementation of the general pharmaceutical legislation were available, the number of grants and the average value of grants over time are shown in Figure RI-7.1 and Figure RI-7.2, respectively. Only 6 years of complete data for 8 member states were available, plus data for the EC, but these data show that, in general, the overall number of grants is decreasing, while the average grant value stays relatively constant. This is in line with a known trend in the funding of fundamental scientific research, where in recent years decisions taken by funding bodies are often to award larger sums to fewer academic or research institutions or consortia of academic or research institutions with a lead institution (with or without industrial partnerships) that is responsible for allocating funding to smaller partners or projects in the consortium. This is generally seen as more efficient, as the main funding body has fewer applications to consider each year.

Figure RI-7.1 Total number of grants starting each year (2015-2020).



Source: Informa grants database (2015-2020).

Figure RI-7.2 Average value of grants starting each year (2015-2020).

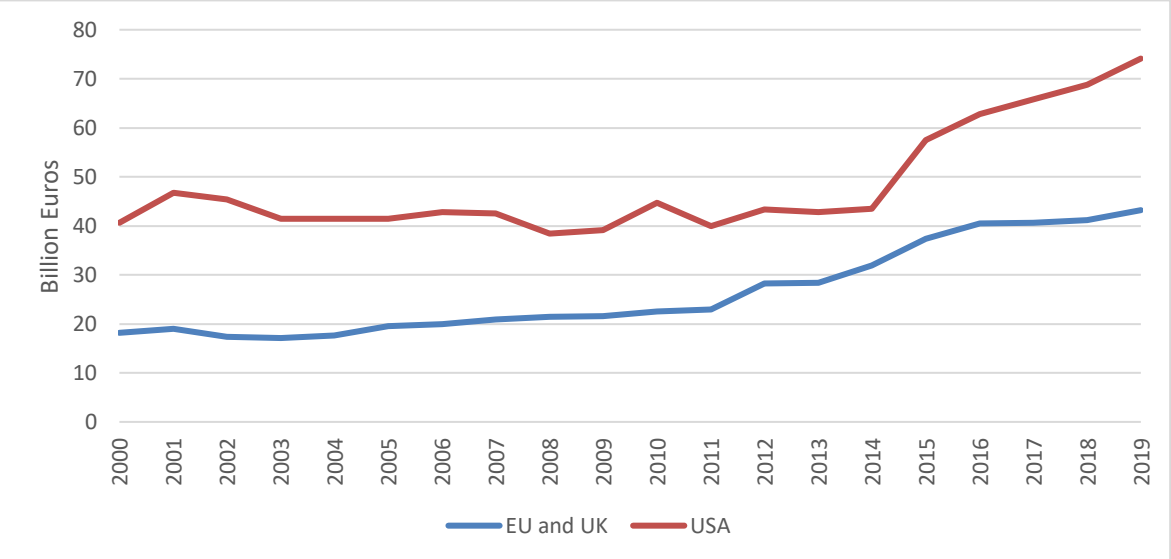


Source: Informa grants database (2015-2020).

RI-8: Amount of private R&D investment in the sector

There has been an increase in total R&D expenditure, as captured by the EU R&D Scoreboard, doubling from around €20bn in 2000 to more than €40bn in 2019, albeit there is no significant change in investment evident in data in the 3-5 year period around the implementation of the legislation. Indeed, the data show two distinct phases, with the first 10 years largely flat, with investment struggling to keep pace with inflation, and with a second phase, where investment levels have increased strongly. The highest and most persistent growth in R&D investment in EU companies that operate in pharmaceuticals and biotechnology took place in 2011-2016. This is in line with global trends, whereby the OECD review of research and development in the pharmaceutical sector (2019) concluded that expenditure on R&D in the pharmaceutical industry across the OECD grew by 14% in real terms, between 2010 and 2016. On the other hand, in the US, R&D investment remained almost stationary from 2003 until 2011 (close to €40bn) and experienced significant growth in the period between 2014 and 2019.

Figure RI-8: Private R&D investment in pharmaceuticals and biotechnology in the EU and UK relative to the US



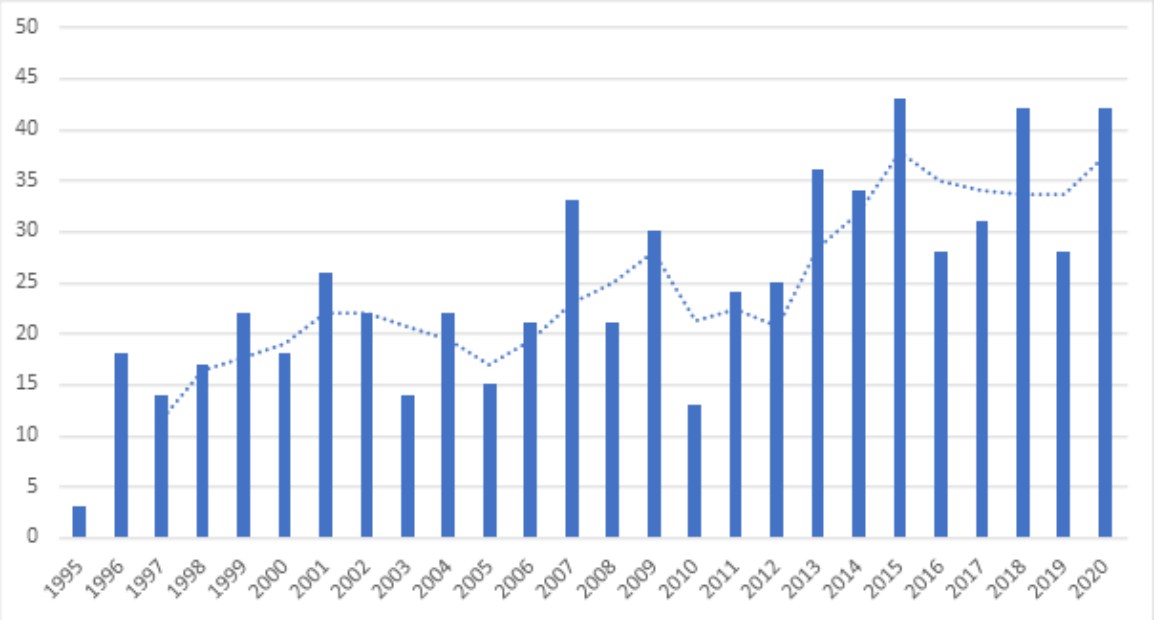
Source: EU Industrial R&D Investment Scoreboard (2000-2019). The figure shows annual R&D investment of the top EU+UK companies operating in the pharmaceuticals and biotechnology sector. Data for 2000-2003 is based on TOP500 companies; data for 2004 is based on TOP700 companies. From 2005 onwards, data is based on TOP1000 companies. Data for the US comes from Congressional Budget Office's April 2021 report Research and Development in the Pharmaceutical Industry.

RI-9: Number of innovative medicines

To provide insight in the yearly number of innovative medicines authorised by EMA we developed two definitions of 'innovative medicines'.

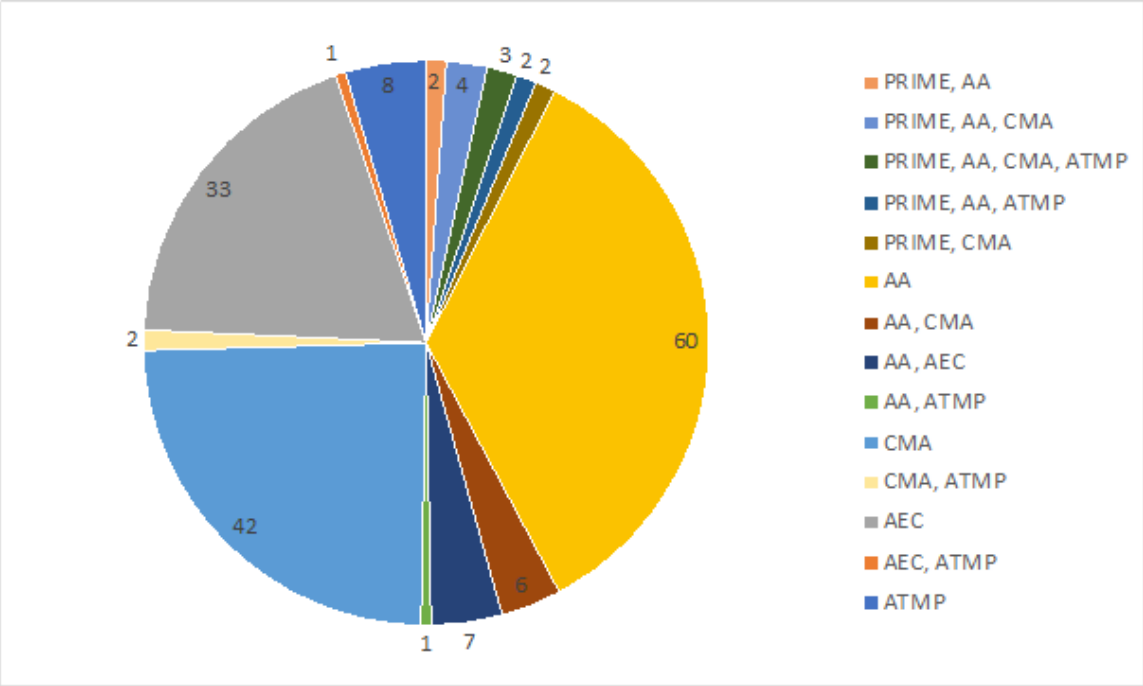
1. New active substances centrally (NAS) authorised by EMA. As medicinal products are only qualified as new active substances by the CHMP since 2011 we use this NAS qualification after 2011 and apply a similar methodology to classify medicines as NAS before 2011. Moreover, in case of multiple applications for the same substance including applications as combination medicines we remove duplicates and use the first date the active substance was authorised. A comparison of NASs with NMEs approved at FDA is provided in ACC-1.
2. All medicines that address unmet medical needs and/or are innovative from a technological point of view. This definition includes all medicines designated a PRIority MEdicine (PRIME), all medicines authorised under exceptional circumstances (AEC) or via the conditional marketing authorisation (CMA) pathway, all medicines for which Accelerated Assessment (AA) was granted by the CHMP and all authorised Advanced Therapy Medicinal Products (ATMP). We show absolute numbers (Figure RI-9.2 and RI-9.3) as well as the proportion of innovative medicines relative to the total number of full applications (Figure RI-9.4). The data covers medicines regulated under Regulation 726/2004 (since 2006) given that most pathways used for this definition did not exist before implementation of Regulation 726/2004.

Figure RI-9.1: Number of new active substances authorised by EMA (yearly, 1995-2020) (definition 1)



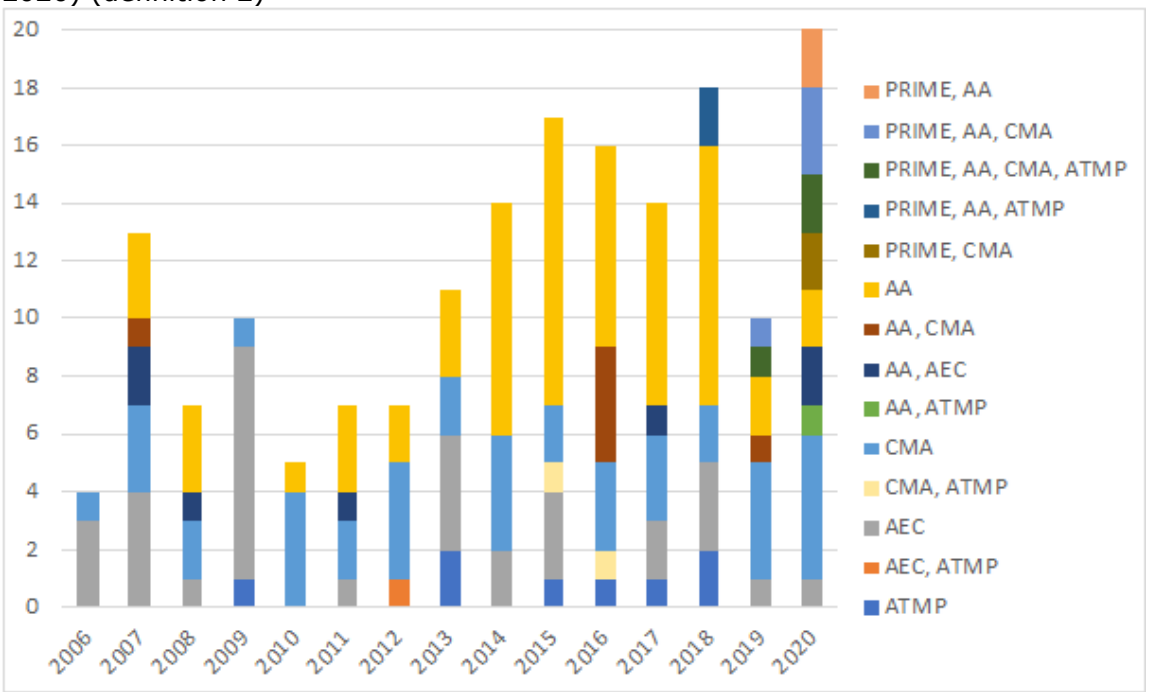
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.2: Number of innovative medicines authorisations by EMA (overall, 2006-2020) (definition 2)



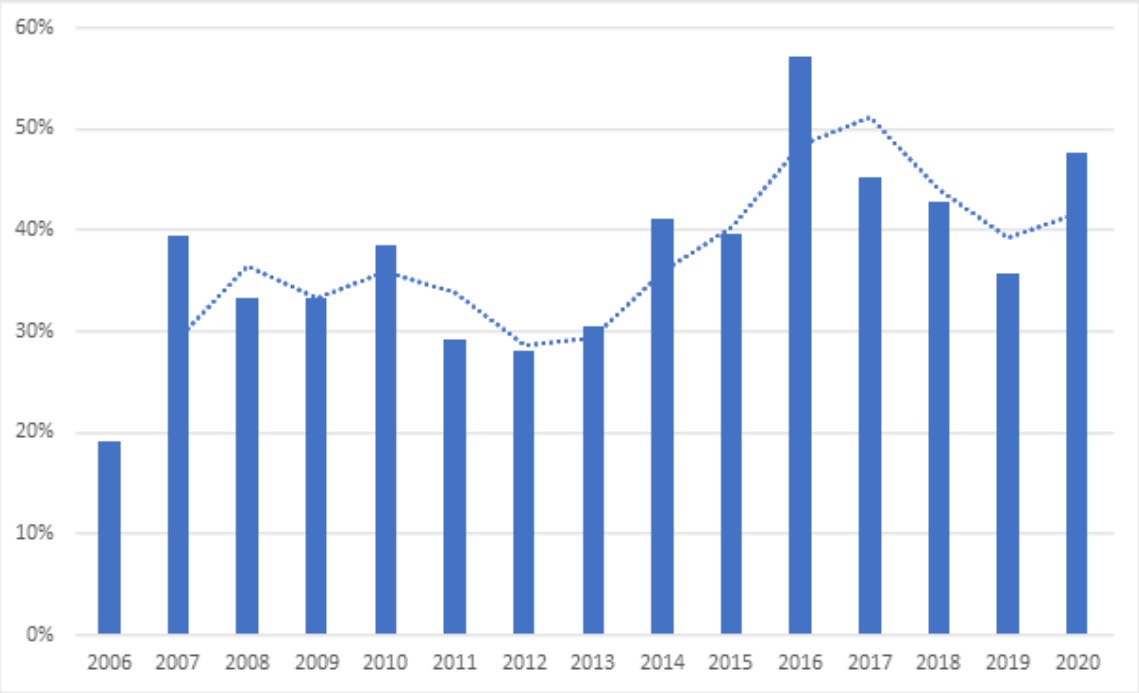
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.3: Number of innovative medicines authorisations by EMA (yearly, 2006-2020) (definition 2)



ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Autorisation; PRIME = Priority Medicine; AA = Accelerated Assessment granted; AEC = Authorisation under exceptional circumstances. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.4: Proportion of innovative medicines authorisations (definition 2) relative to the total number of new active substances (definition 1), (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

The number of innovative drugs gradually increases over time, particularly from 2012 onwards and when looking at products that address unmet medical needs and/or are innovative from a technological point of view.

The increase is also visible when looking at drugs that address an unmet medical need as a proportion of the total number of new active substances.

Over time, there is also an increase in the combined use of pathways – especially those including PRIME (in 2020).

1.3 ACCESS INDICATORS

Indicator name	Indicator description
	Access to approved medicines:
ACC-1	Number of medicines authorised
ACC-2	Speed of approval for authorised medicines
ACC-3	Number of approved medicines with zero sales volume in EU countries*
	Time to coverage:
ACC-4	Time from authorisation to non-zero sales volume reported for authorised medicines in individual EU countries*
ACC-5	Share of EU population with access to medicines sold on the market*
ACC-6	Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)
ACC-7	Number of indication extensions after first authorisation*
ACC-8	Number of market withdrawals
ACC-9	Time from market authorisation to market withdrawal
ACC-10	Number of Type I and Type II variations

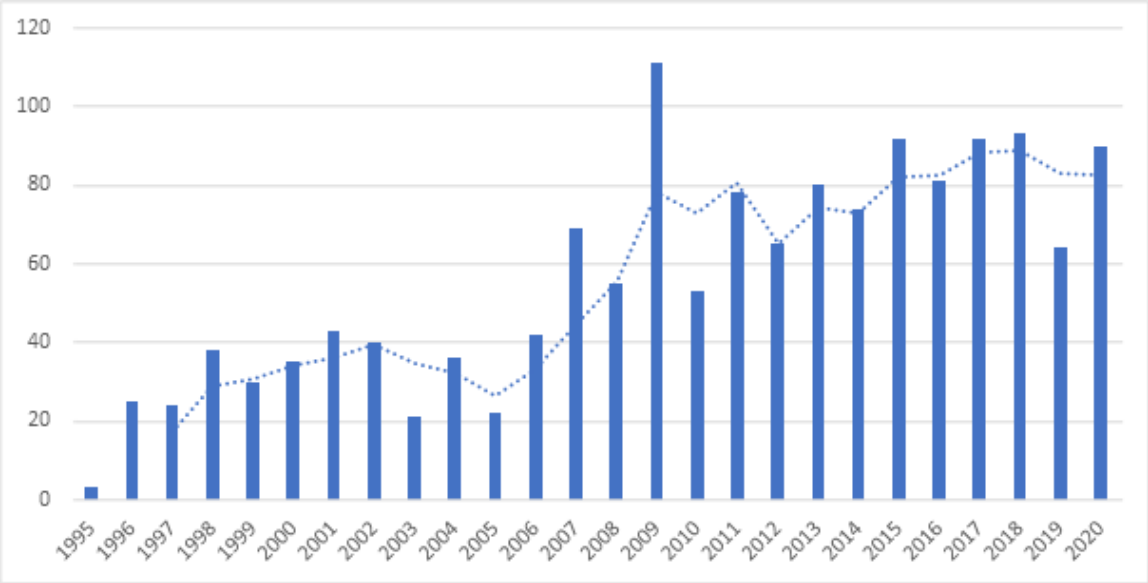
* Note that these indicators were not calculated

ACC-1: Number of medicines authorised

Figure ACC-1.1 provides an overview of the total number of medicinal products that were granted a market authorisation under the centralised authorisation by EMA per year (1995-2020). This includes all centrally authorised medicinal products authorised under Regulation 2309/93 (n = 317) and under Regulation 726/2004 (n = 1,139), irrespective of their legal basis (see indicator EFF-2 for a stratification by legal basis).
Figure ACC-1.2. focuses specifically on new active substances (NASs) centrally authorised by EMA and compares the yearly number of authorisations with the approval of New Molecular Entities (NMEs) by the FDA. As medicinal products are only qualified as NASs by the CHMP since 2011, the database uses a similar definition to classify medicinal products as NAS before 2011. Moreover, in case of multiple applications for the same substance including applications as combination medicines we remove duplicates and use the first date on which the substance was authorised.

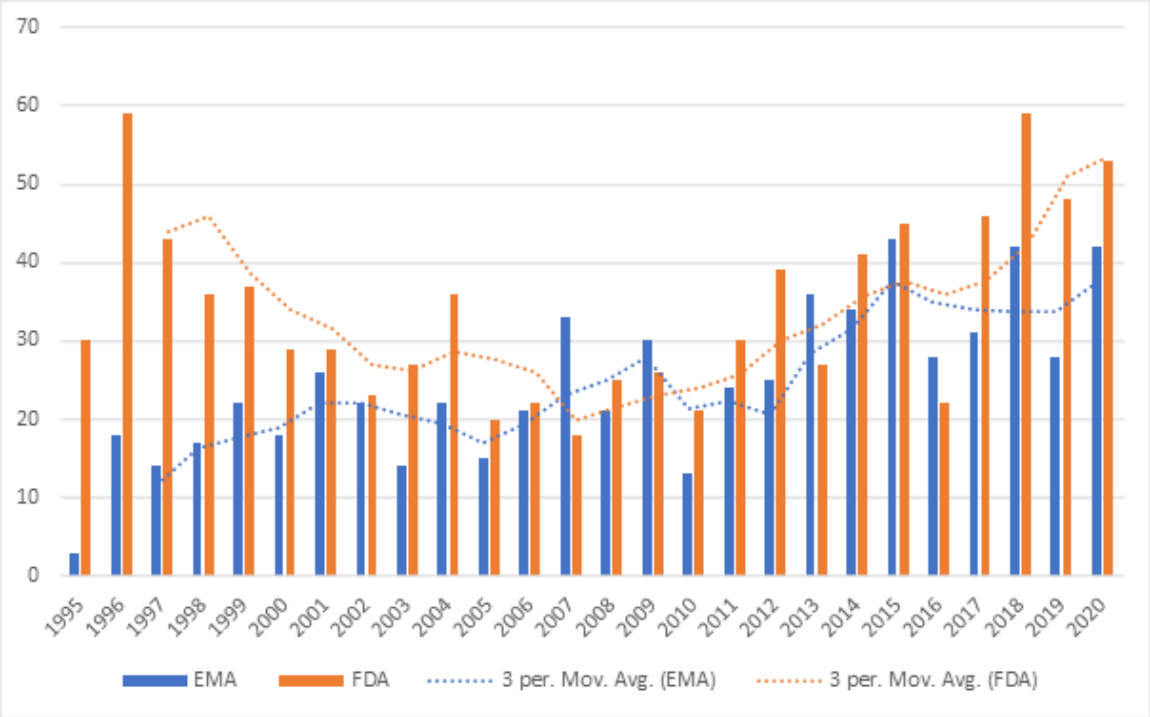
Figure ACC-1.3 and ACC-1.4 provides one-to-one comparisons between NASs/NMEs authorised by EMA/FDA to provide insight into whether the same NAS/NME is authorised earlier by EMA or FDA. When an active substance qualified as NAS/NME was authorised by EMA and FDA up to 31st December 2020 they were matched based on the following matching criteria: same brand name OR same applicant OR - if not same brand name or same applicant - same substance authorised within two years (earlier/later) of each other. Figure ACC-1.3 shows the time difference from the perspective of NASs authorised by EMA, i.e. the time difference in approval date with FDA of all NASs authorised by EMA. Figure ACC-1.4 the time difference in approval date of all new active substances/new molecular entities authorised by EMA and/or FDA (five-year periods, 1995-2020)

Figure ACC-1.1: Total number of centrally authorised medicinal products by EMA (yearly, 1995-2020)



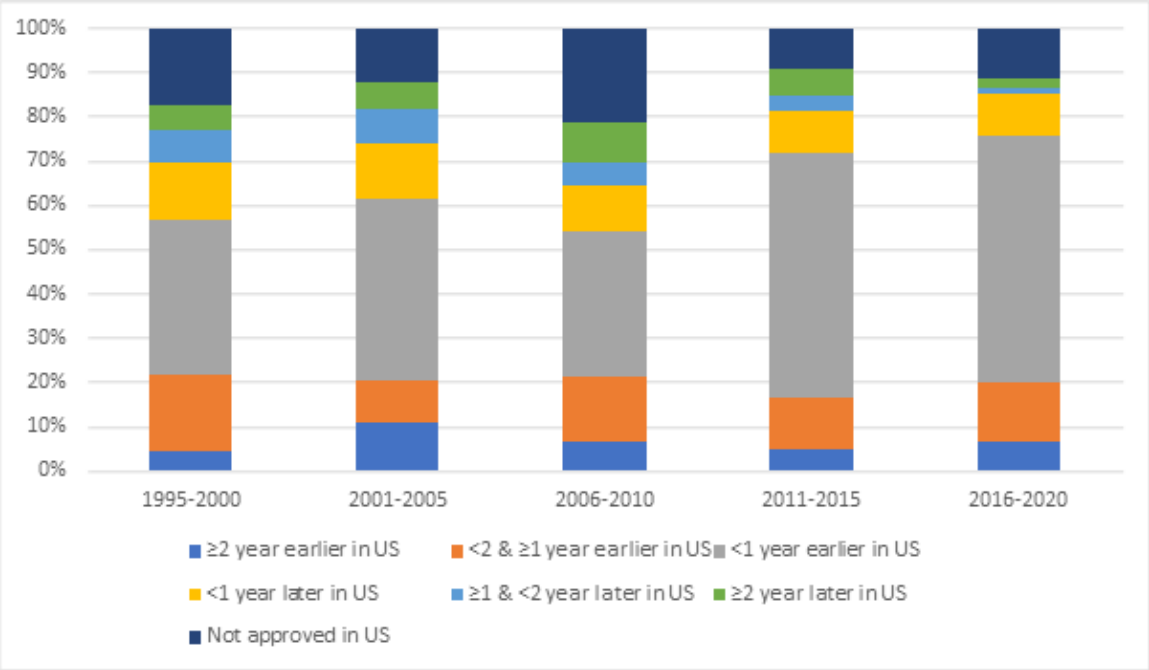
Note: trend-line indicates three-year moving average. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.2: Total number of new active substances/new molecular entities authorised by EMA and FDA (yearly, 1995-2020)



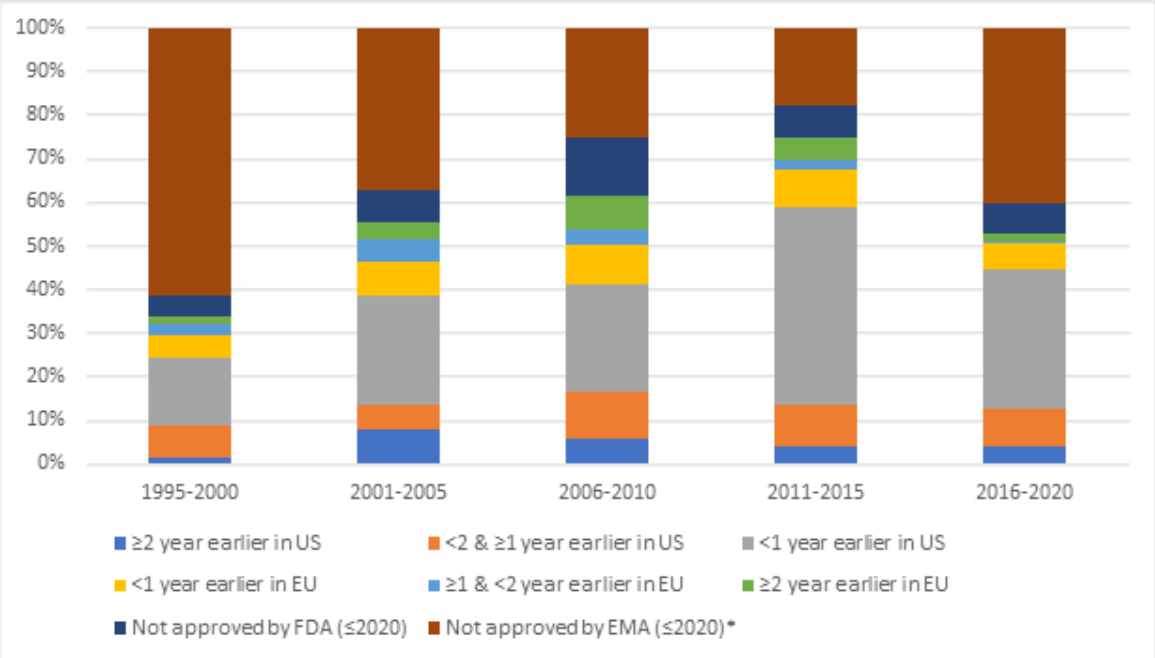
Note: trend-line indicates three-year moving average. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.3: Time difference in approval date with FDA of new active substances authorised by EMA (five-year periods, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.4: Time difference in approval date of all new active substances/new molecular entities authorised by EMA and/or FDA (five-year periods, 1995-2020)



* Some of the new molecular entities in this category might be authorised through the decentralised or mutual recognition procedure or authorised after 2020. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It was found that:

- Figure ACC-1.1 shows an increase in the number of medicinal products authorised through EMA's centralised procedure over time, stabilising somewhat around the mid-2010s
- A steep increase in the three-year moving average is particularly visible in the period 2005-2009 possibly following from the widening of the mandatory scope

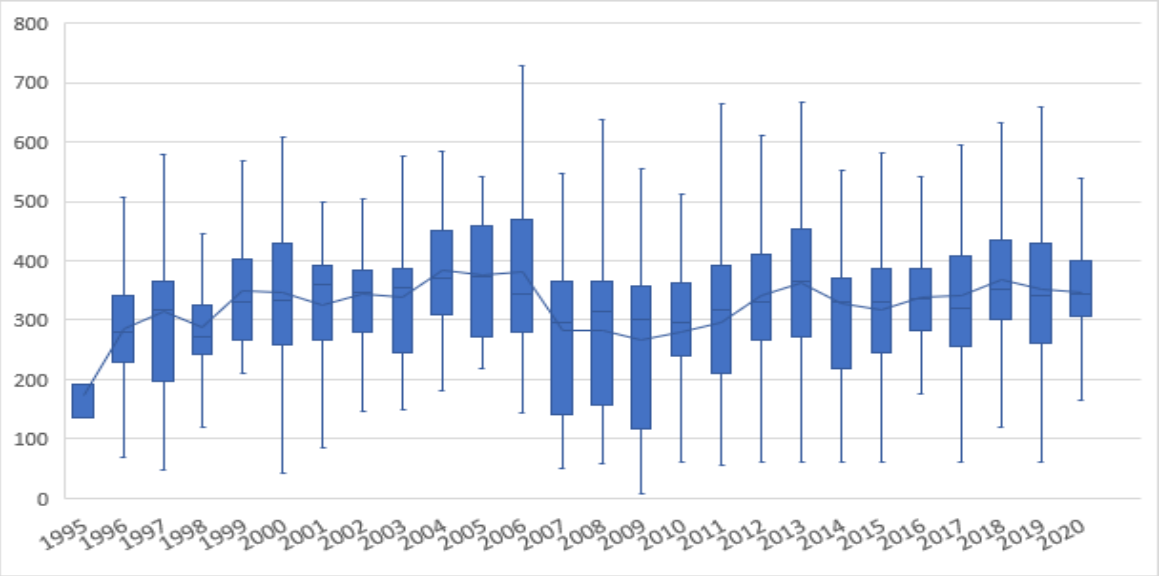
of the centralised procedure in Regulation (EC) No 726/2004, see also Figure EFF-2-1 for a stratification by legal basis
- Figure ACC-1.2 shows a gradual increase in the number of new active substances authorised through EMA's centralised procedure over time
- The 3-year moving average of the number of FDA authorised new molecular entities decreases up to 2007 and gradually starts to increase afterwards
- The number of FDA authorised new molecular entities is higher than the number of EMA authorised new active substances in almost every year in the period 1995-2020. In 2016-2020 we observe 171 new active substances authorised by EMA and 228 new molecular entities by the FDA.
- Figure ACC-1.3 and ACC-1.4 show that the majority of new active substances is authorised earlier by the FDA over the entire period
- Over time, the proportion of substances authorised <1 year earlier by the FDA than EMA is increasing. This group comprise the majority of substances (~55%) in the period 2011-2020.
- Over time, the proportion of FDA authorised substances not authorised by EMA decreases, with the exception of the latest period (2016-2020) which is probably due to censoring issues.

ACC-2: Speed of approval for authorised medicines

Figure ACC-2.1 shows the median and mean (line) total assessment time (in days) of all centrally authorised medicinal products per year. Total assessment time in days comprises a combination of active assessment time by EMA and clock-stop time by the applicant. Assessment times exclude the time for the European Commission to authorise the CHMP opinion (maximum 67 additional days).

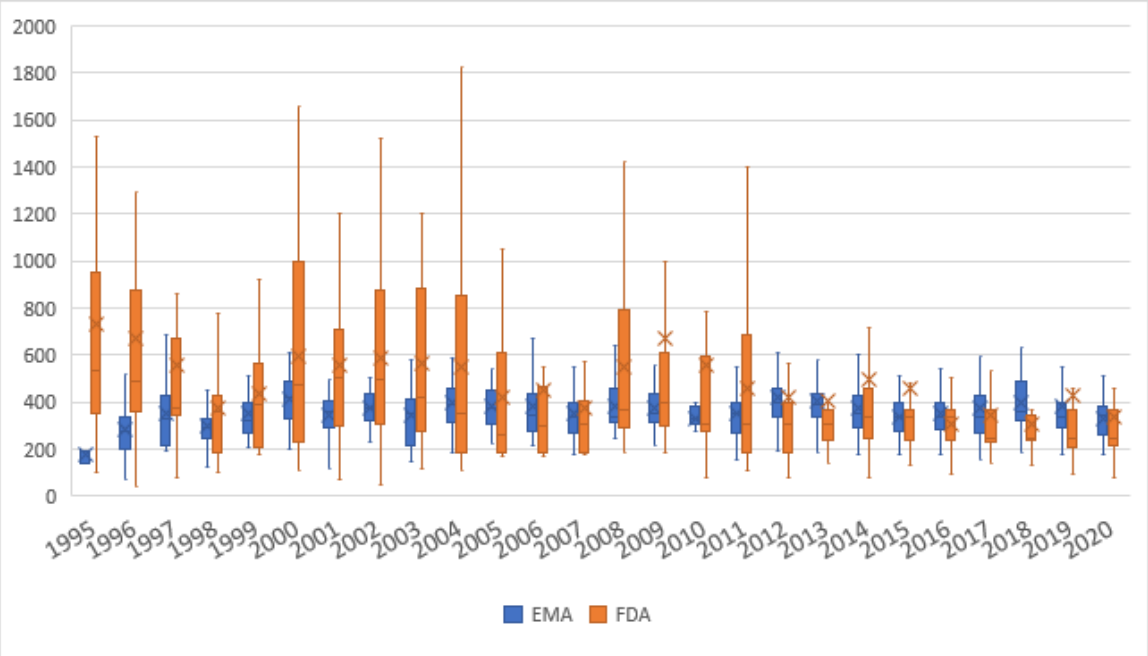
In Figure ACC-2.2 mean and median assessment times are visualized for NASs centrally authorised by EMA and compared to assessment times for NMEs by the FDA. Assessment times by FDA are calculated as the date the first and complete marketing application was received by FDA until the data the FDA authorised the original application. When comparing assessment times between jurisdictions it thus needs to be taken into account that the FDA assessment times can include a longer period were applicants work on addressing issues brought up in a complete response letter send by the FDA based on a decision that the original application could not (yet) be approved in its present form. In contrast, at EMA this would result in a refusal after the maximum active assessment time was reached. A new marketing authorisation application would then have a restart of the assessment clock.

Figure ACC-2.1: Total assessment times for centrally authorised medicinal products by EMA in days (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-2.2: Total assessment times of new active substances/new molecular entities authorised by EMA and FDA in days (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-2.1 shows that the total assessment time of EMA centrally authorised products is relatively stable in the period 1995-2020, with no clearly discernible trend in mean and median total assessment times

When comparing EMA assessment times of new active substances with assessment times of new molecular entities authorised by FDA in Figure ACC-2.2 the following trends can be noticed:

- Mean and median assessment times at FDA are longer in the period up to 2010, and the variation in assessment times is larger by FDA compared to EMA, particularly up to 2012. These differences are influenced by the different ways in which the datasets account for refusals. At FDA

assessment times are calculated based on the data from first application to authorisation. At EMA assessment times are calculated as the date of the application that resulted in the authorisation up to the moment of authorisation. Thus, in case an application is refused one or multiple times these assessment times are not included.

- Mean and median assessment times at FDA gradually decrease over time.
- Median review times at FDA are shorter in the period 2016-2020 compared to EMA (median of 244 days at FDA and 343.5 days at EMA)

ACC-6: Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)

Table ACC-6.1 indicates the total number of Rapporteur and Co-Rapporteur roles for initial market authorisations through the centralised procedure per country in the period 1995-2020.

Table ACC-6.1: Number of EMA Rapporteur and Co-Rapporteur roles per country (yearly 1995-2020)

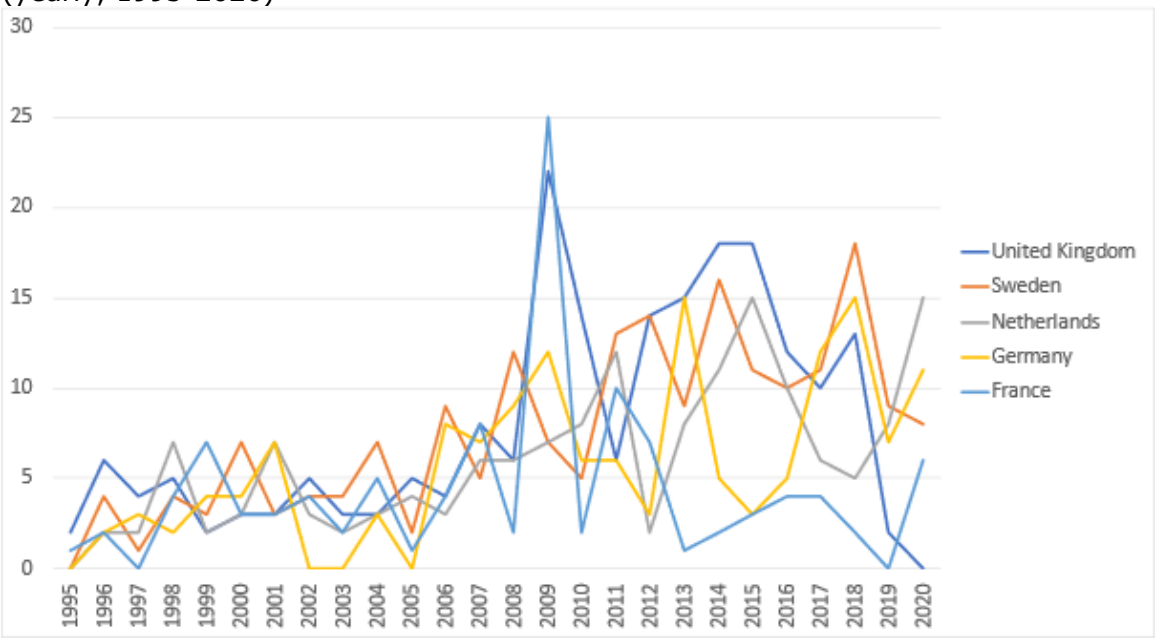
Rapporteur	N	Co-Rapporteur	N
United Kingdom	203	No Co-rap	256
Sweden	196	Germany	117
Netherlands	157	Sweden	100
Germany	149	United Kingdom	97
France	112	France	96
Spain	105	Netherlands	86
Denmark	91	Ireland	79
Ireland	69	Italy	75
Belgium	60	Spain	69
Austria	55	Belgium	68
Portugal	36	Norway	52
Finland	33	Denmark	50
Italy	30	Portugal	46
Malta	26	Austria	46
Czech Republic	23	Finland	44
Estonia	21	Hungary	40
Norway	17	Poland	29
Iceland	14	Estonia	27
Hungary	10	unknown	17
Poland	9	Czech Republic	14
Latvia	7	Greece	12
unknown	7	Luxembourg	10
Slovenia	7	Lithuania	9
Lithuania	6	Latvia	7
Greece	6	Iceland	4
Croatia	4	Romania	3
Slovakia	2	Malta	2
Romania	1	Croatia	1

Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

In addition, for the top 5 (Co-)Rapporteurs overall, a yearly number of (Co-Rapporteur roles is shown in Figures ACC-6.2 and ACC-6.3. The category "No Co-rap" comprises procedures for which no Co-Rapporteur was required (e.g., authorisation of generics) and the category "unknown" comprises procedures for which no Rapporteur has been reported.

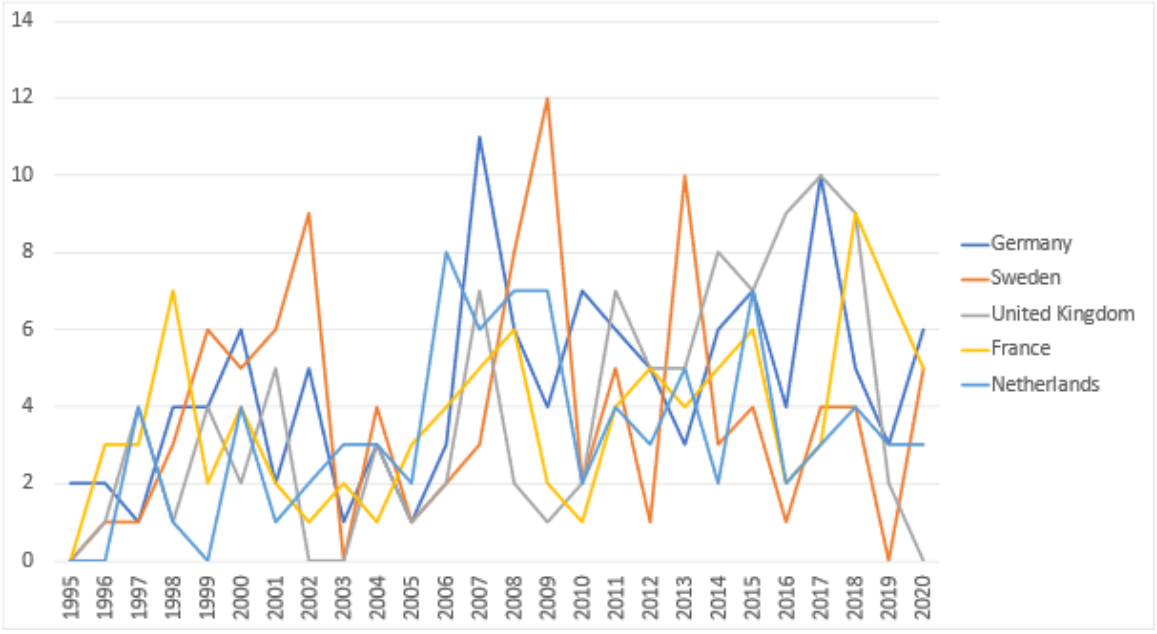
The five countries with the highest number of (co)-rapporteurs for initial marketing authorisations are the United Kingdom, Sweden, the Netherlands, Germany and France.

Figure ACC-6.2: Number of EMA Rapporteur roles for the top 5 Rapporteur countries (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-6.3: Number of EMA Co-Rapporteur roles for the top 5 Co-Rapporteur countries over time (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

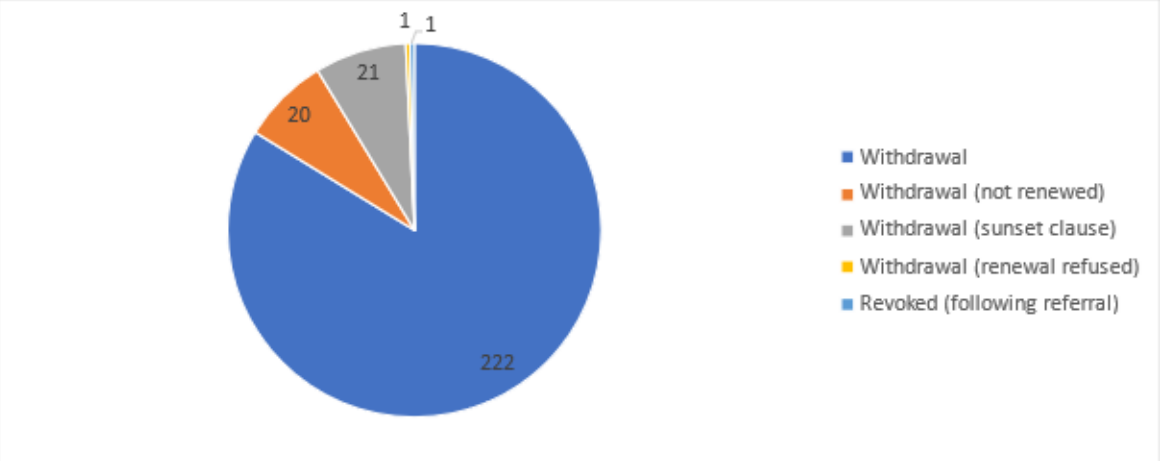
ACC-8: Number of market withdrawals

Figure ACC-8.1 indicates the total number of withdrawn medicinal products initially authorised through the centralised procedure in the period 1995-2020. Withdrawals are recorded in the Union Register of Medicinal Products under 5 different withdrawal types that are mentioned in Figure ACC-8.1. Withdrawals due to non-renewals or the sunset clause are 'passive' withdrawals for which no formal decision-making procedure was initiated.[1]

Figures ACC-8.2 indicates the yearly number of withdrawals by withdrawal type, while Figure ACC 8.3. indicates the number and legal basis of withdrawals. The latter provides insight into withdrawals of products that were approved based on a full application (i.e. article 8(3) of Directive No 2001/83/ec). Figure ACC-8.4 provides an overview of the proportion of medicinal products that were withdrawn as of December 31st 2020 per year of market authorisation.

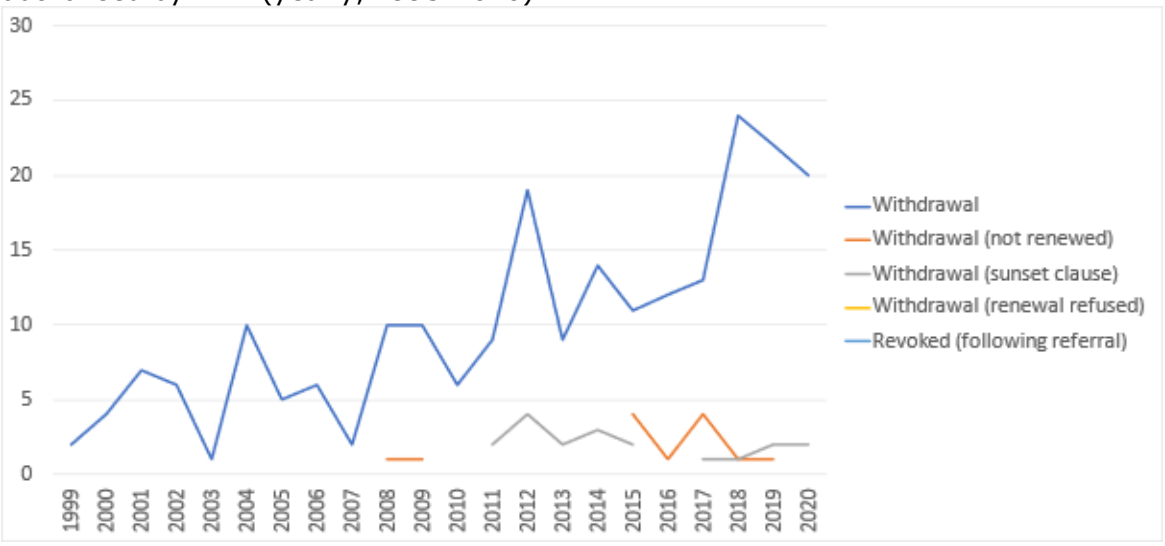
For the matched new active substances that are authorised by both EMA and FDA it was determined whether they were withdrawn in any or both jurisdictions. An overview is provided in Figure ACC-8.5. For FDA withdrawals we rely on the marketing status of new molecular entities in Drugs@FDA[2] and consider a product withdrawn in case the status of a product is discontinued. Publicly available data does not allow us to provide more insight in the reasons for these withdrawals.

Figure ACC-8.1: Total number and type of market withdrawals of medicinal products authorised by EMA (1995-2020)



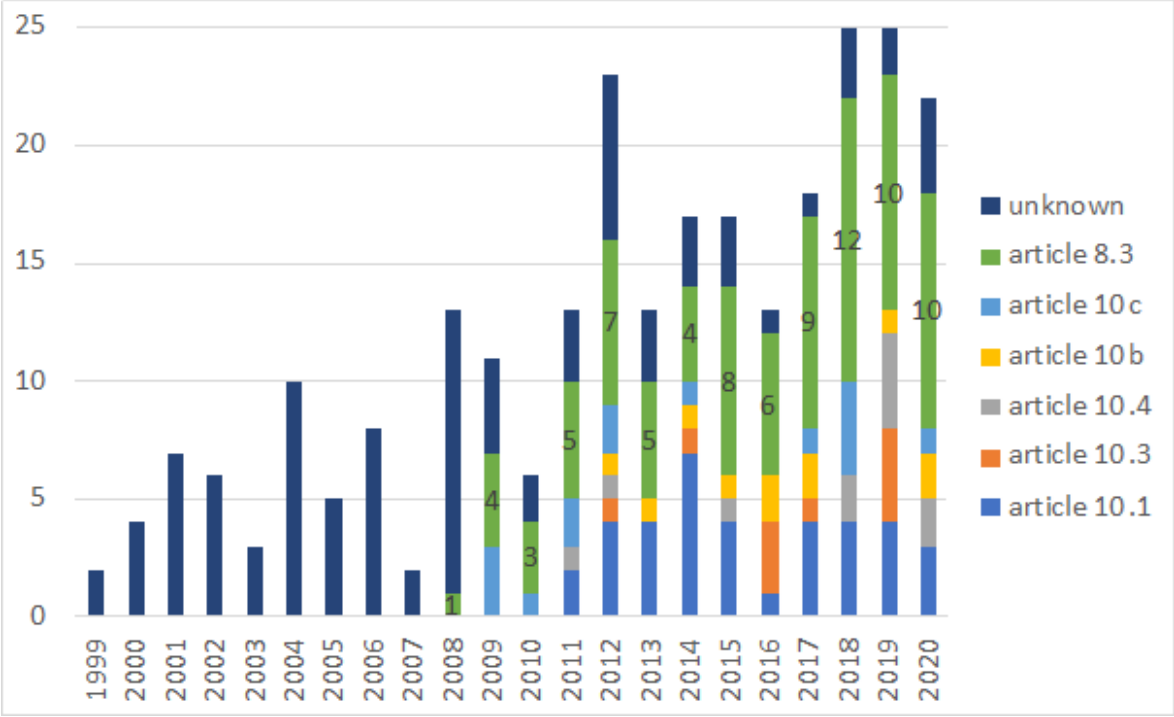
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.2: Number and type of market withdrawals of medicinal products authorised by EMA (yearly, 1995-2020)



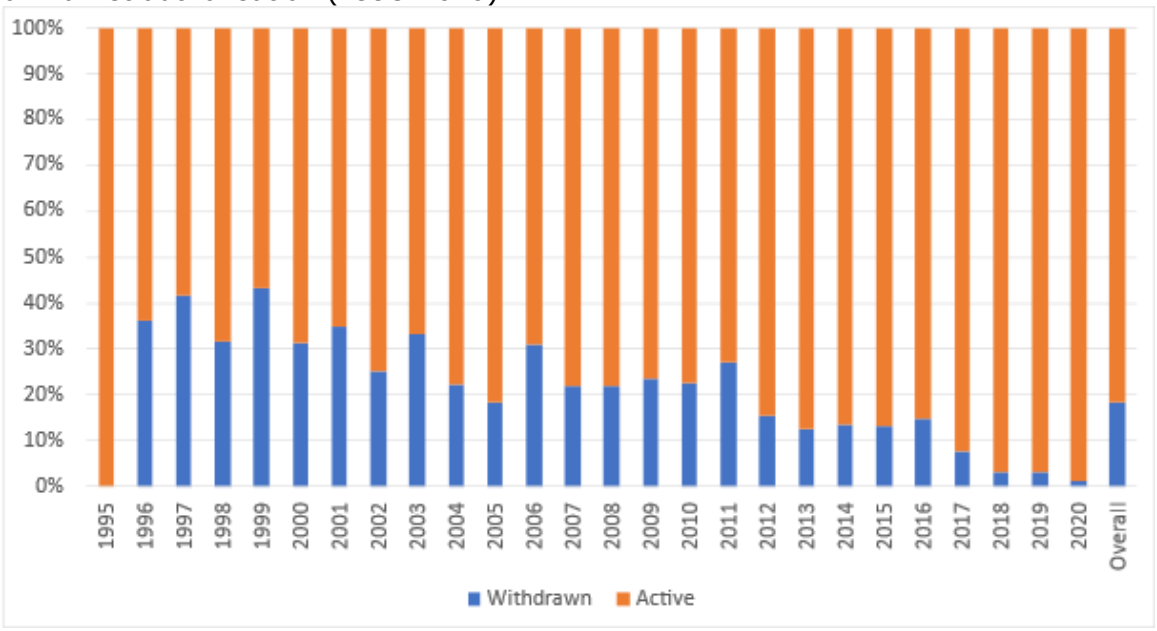
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.3: Number and legal basis of market withdrawals of medicinal products authorised by EMA (yearly, 1995-2020)



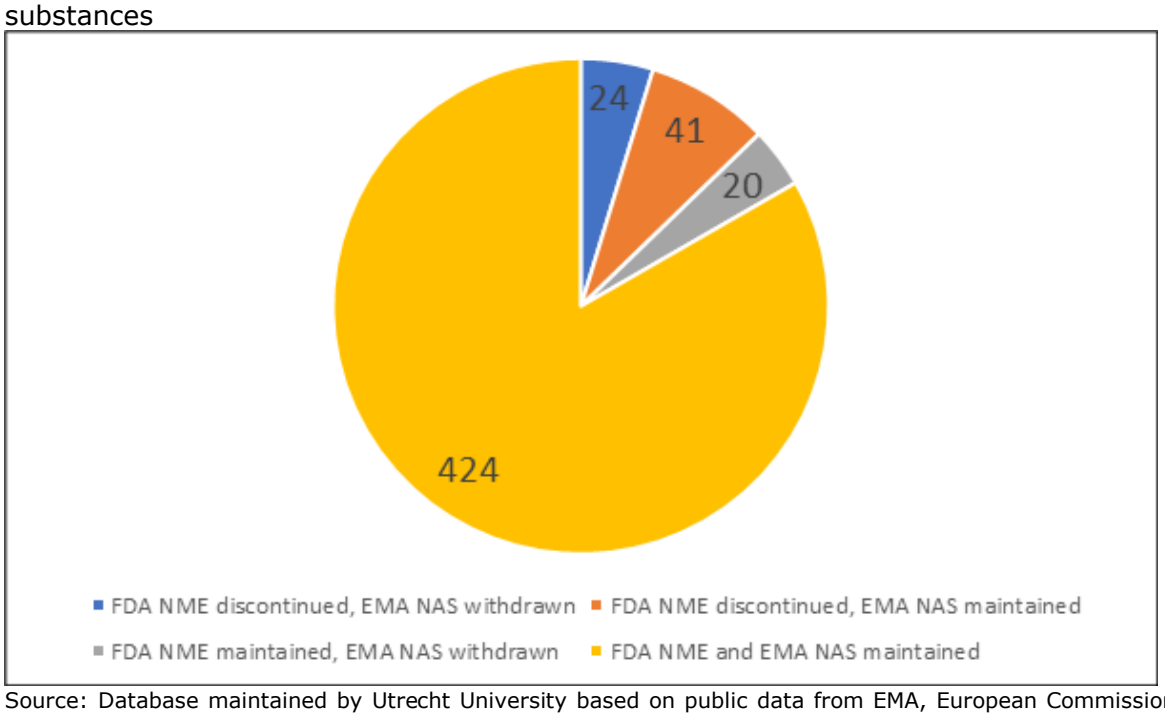
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.4: Proportion of withdrawn medicinal products authorised by EMA per year of market authorisation (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.5: Number of withdrawals by EMA and FDA for matched new active substances



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Of all 1,456 EMA centrally authorised products, 265 have been subsequently withdrawn (18.2%). While the number of withdrawals increases over time, the proportion of withdrawals per year of authorisation decreases over time, probably due to an increase in the number of authorised products, yet with shorter follow-up (see below).

Of all 509 centrally authorised new active substances matched with FDA new molecular entities[2], 24 have been withdrawn in both EU and the US. In addition, 20 NASs have only been withdrawn in the EU and 41 NMEs only in the US.

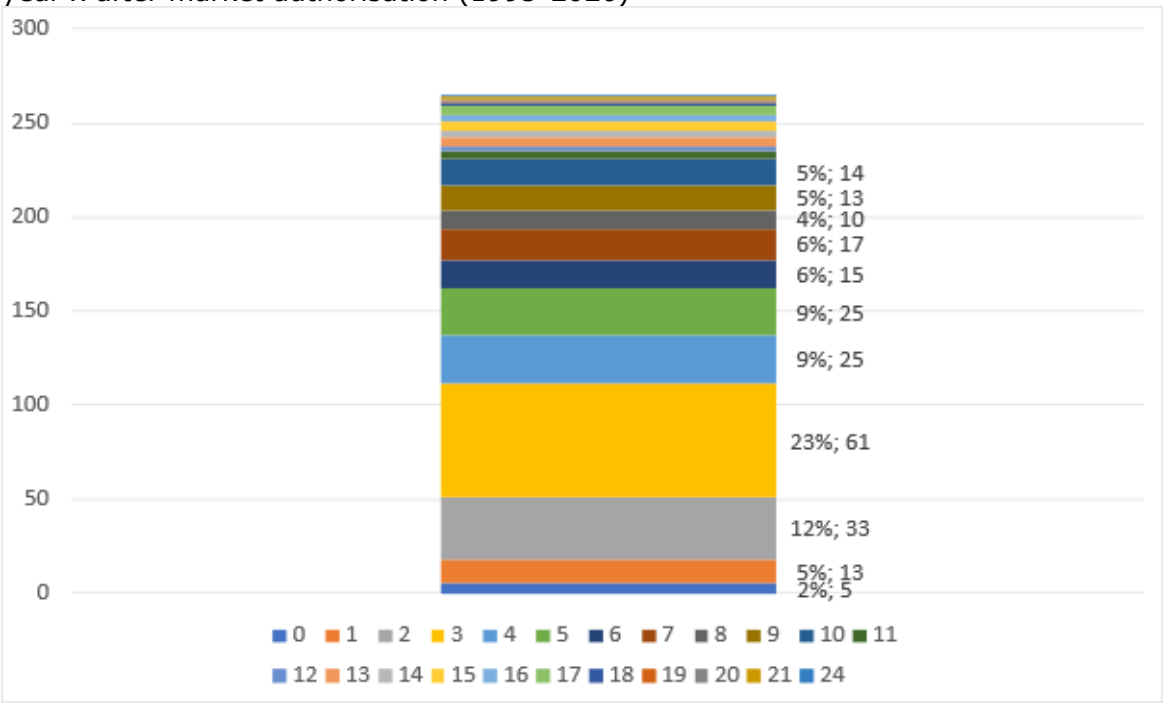
Note that two withdrawal procedures of products are excluded from these figures: one that was renewed anyway one month after withdrawal (NovoNorm) and one that only concerned certain presentations of a product but not the whole authorisation (Daquiran). Two other authorisations that are no longer active concern products that are now integrated as separate presentations of a third authorisation (Humalog-Humaject and Humalog-Pen, integrated in the Humalog authorisation). Since these are not formal withdrawals, these have also not been included in the figures.

ACC-9: Time from marketing authorisation to withdrawal from the market

Figure ACC-9.1 indicates the year after market authorisation in which market withdrawals of medicinal products authorised through the centralised procedure took place. Absolute numbers and percentages are shown for year 0-10 after market authorisation.

Figure ACC-9.2 shows the same data stratified by groups of medicinal products that were authorised in the same year. The absolute number and percentage of withdrawals that took place in the 3rd year after market authorisation are presented as this is the largest category of withdrawals.

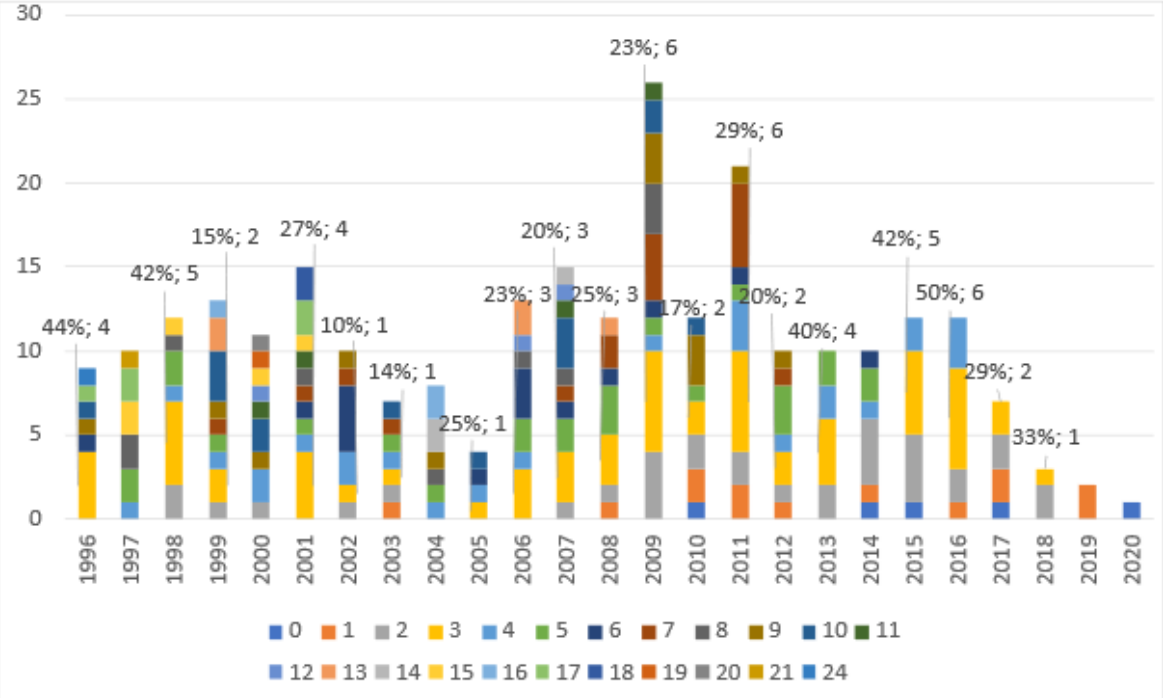
Figure ACC-9.1: Number of medicinal products authorised by EMA and withdrawn in year x after market authorisation (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

[2] https://www.accessdata.fda.gov/scripts/cder/daf/

Figure ACC-9.2: Number of medicinal products authorised by EMA and withdrawn in year x after market authorisation (yearly, 1995-2020)



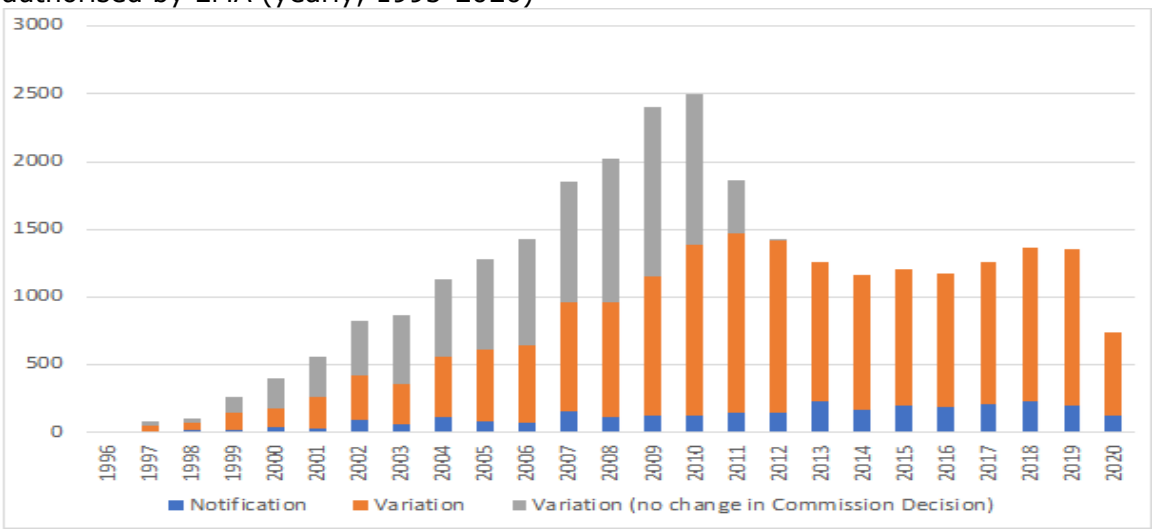
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Of 265 market withdrawals, 137 (52%) took place in the first four years after market authorisation – mostly in year 3 (61, 23%). There is no discernible trend over time with respect to early withdrawals in the first four years after marketing authorisation.

ACC-10: Number of Type I and Type II variations

Figure ACC-10.1 indicates the number of notifications and variations in the period 1995-2020. Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Variations without change in Commission Decisions are those that did not affect the terms of the marketing authorisation (e.g., summary of product characteristics, annex II, labelling, package leaflet). Both groups of variations comprise Type IA, Type IB and Type II variations.

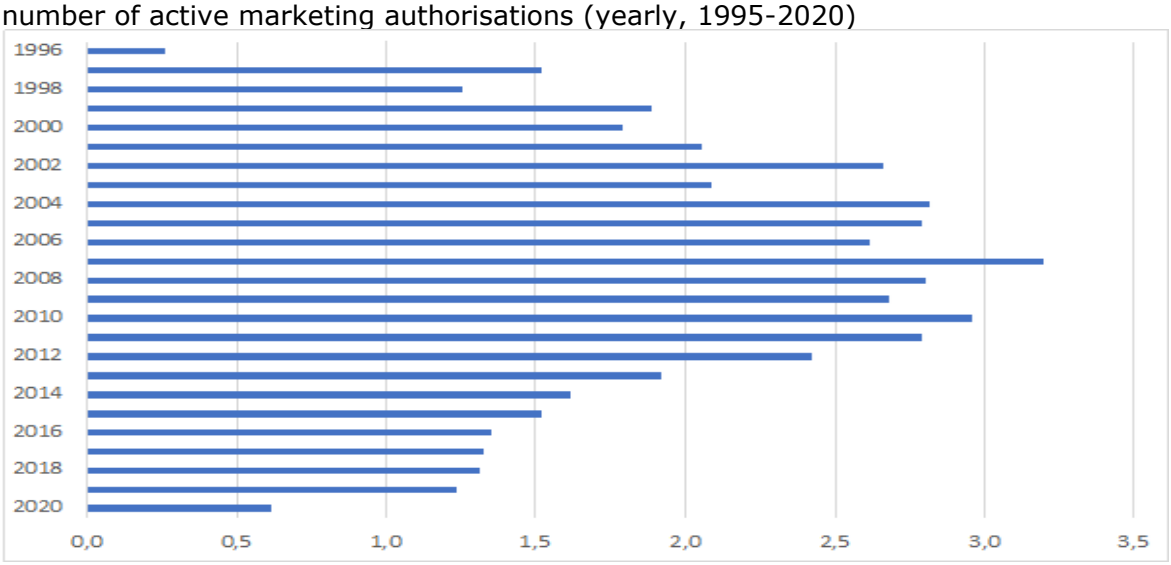
Figure ACC-10.1: Number of Notifications and Variations for medicinal products authorised by EMA (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-10.2 indicates the yearly ratio of the number of Notifications and Variations relative to the number of active marketing authorisations. Variations without change in Commission Decision are excluded from this figure and the yearly number of active marketing authorisations is calculated based on the total number of medicines authorised up to and including each year, minus the number of withdrawn medicines up to and including that year.

Figure ACC-10.2: Ratio of the number of Notifications and Variations relative to the number of active marketing authorisations (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It is found that in total, 2,939 Notifications, 17,223 Variations and 8,327 Variations without change in Commission Decision occurred between 1995 and 2020.

The yearly ratio of the number of Notifications and Variations and the number of active marketing authorisations increased to 3.2 in 2007 and then steadily decreased to a ratio around 1.2-1.4 in 2016-2019.

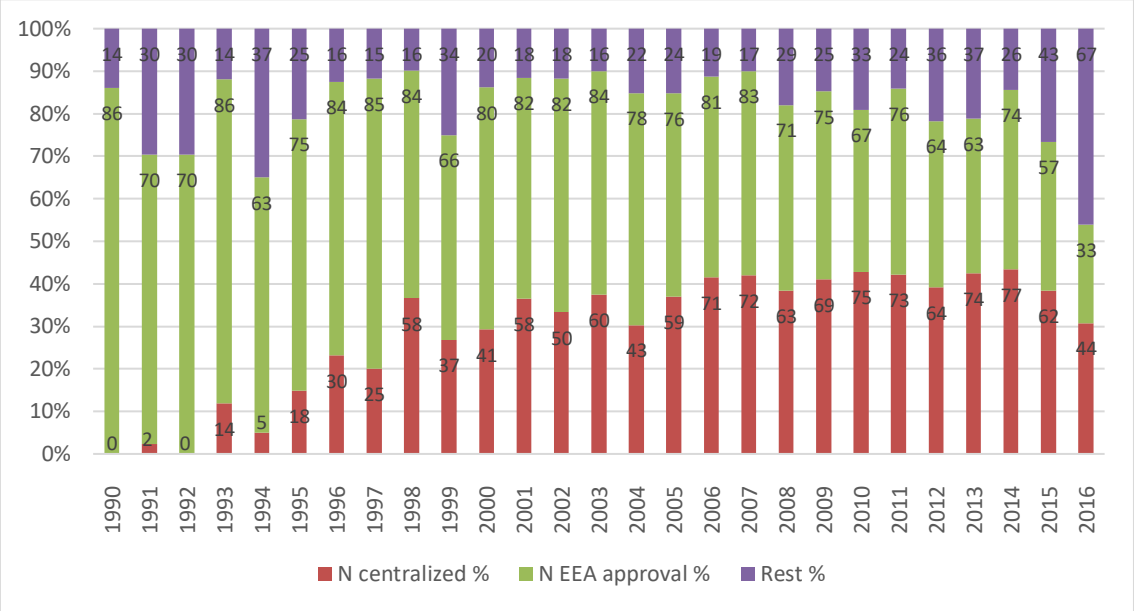
In 2020, a notable drop in both the absolute number of Notifications and Variations and the ratio relative to the number of active marketing authorisations can be observed. This might be a consequence of the COVID pandemic.

Other access indicators from the literature:

Kyle (2019) reports the approval outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016.[3] The next two figures show the outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016.

Figure ACC-1.1 shows the share of NCEs that used the EMA's centralized procedure and the share that were launched somewhere in the EEA (N EEA approval), both relative to the number of NCEs first launched in each year. It is worth noting that since 2005 consistently a higher share of NCEs that were launched in the EEA used the centralized procedure relative to the previous years.

Figure ACC-1.1: New chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



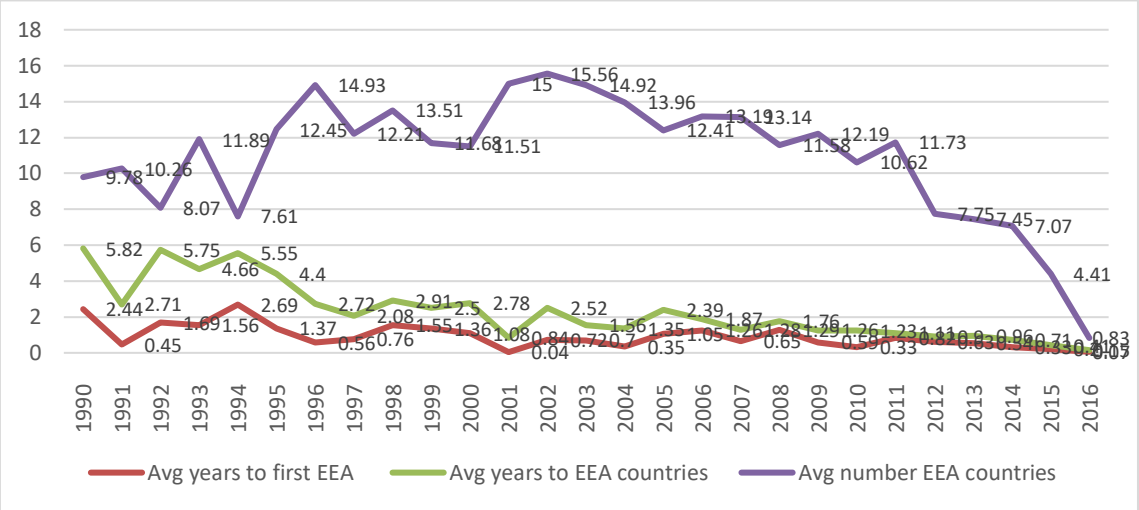
Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

Figure ACC-1.2 shows the average lag between the first global launch and the first EEA launch (Average years to first EEA), the average lag between the first global launch and all EEA countries in which the drug was eventually introduced (Avg years to EEA countries), and the number of countries where these drugs are launched (Avg number EEA countries).

Figure ACC-1.2 shows that over the years, the average time to approval across the EEA (conditional on launch) has fallen, and the average number of EEA countries in which a product is launched has decreased in the last years. However, there is no clear 'jump' in 2005 (apart from a slightly lower number of NCEs launched using the centralized procedure in 2004, relative to 8 years before and after) that could indicate an impact of the 2004 revision of the general pharmaceutical legislation in any of the outcomes.

[3] Kyle, M. The Single Market in Pharmaceuticals. Review of Industrial Organization. 2019. Vol. 55, no. 1, p. 111–135.

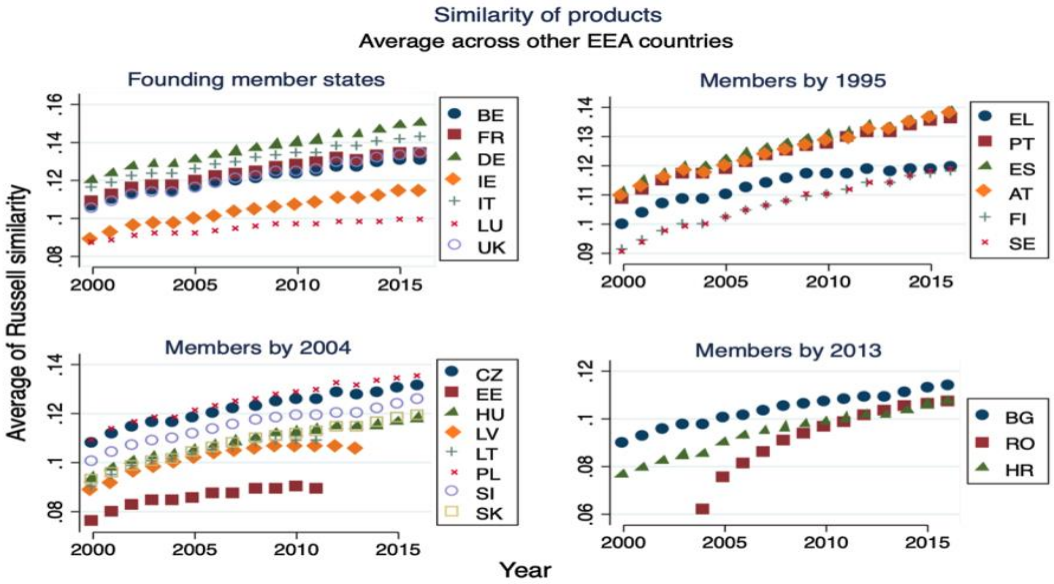
Figure ACC-1.2: Outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

Kyle (2019) also investigates whether pharmaceutical product markets in the EU had increased in similarity over time (Figure ACC-1.3). To assess this, she calculates the Russell–Rao binary similarity coefficient for all possible country pairs[4]. As shown in the next figure, from 2000 to 2016, the average similarity between a country and other member states has grown over time, yet there is no change in the trends that can be attributed to the 2004 revision of the general pharmaceutical legislation.

Figure ACC-1.3: Average product similarity between a country and other MS



Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

[4] This coefficient measures the proportion of pharmaceutical products that are available in both countries out of all products available somewhere in the sample of countries.

1.4 AFFORDABILITY AND SINGLE MARKET INDICATORS

Indicator name	Indicator description
AFF-1	Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries
AFF-2	Ratio of net price of medicines to GDP per capita in individual countries
AFF-3	Expenditure on medicines in total healthcare spending in individual countries
AFF-4	Rate of generics/biosimilars entry and uptake
AFF-5	Time to entry after IP protection expires*
AFF-6	Average price discount (%) of generics/biosimilars over originator*

* Note that these indicators were not calculated

For the analysis of indicators AFF-1, AFF-2 and AFF-4 we employed the IQVIA MIDAS dataset containing information on disaggregated drug sales in different countries. The data were provided in two distinct datasets: while the 'historical' dataset covers the 2002 – 2009 period, the 'current' dataset contains data from the last quarter of 2009 until the end of 2020. Thus, the joint dataset covers the 19 years period from 2002 to 2020 at a quarterly time resolution.

We observe a total of 221,877 individual drugs being sold in up to 38 different countries (data are available for the following countries: Australia, Austria, Belarus, Belgium, Bosnia, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Kazakhstan, Korea, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK and USA), resulting in a total of 384,078 time-series' of drug sales at the country level. The final dataset contains around 19.5m observations.

For these drugs, we observe the quantity and revenue sold in a country and quarter, allowing us to calculate approximate (see caveats below) prices. Further, we can distinguish biological and non-biological drugs, generics and branded products, as well as observe a drugs' active molecule. This allows us to link branded products to their subsequent generic versions to investigate price discounts and time to entry.

In most analyses EU countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK) are compared to either i) all other available countries (see list above) or ii) to a selection of relevant comparators, specifically Australia, Canada, Japan, Korea, Switzerland and the US.

Caveats

Price data without discounts: The revenues and prices reported in the IQVIA MIDAS data do not account for any price discounts from vendors or manufacturers. They also do not account for the fact that a large share of drug expenses is borne by social security systems in most of the countries surveyed.

Joining of current and historical datasets: to extend the analysis to the period before 2010, two separate and non-coherent dataset had to be joined. This results in two main issues. First, only around 1/3 of the time series of drug sales could be matched across the two datasets, the remaining drugs exist independently in the 'historical' and 'current' datasets. This can result in a 'jump' at the point where the two datasets are joined. Secondly, the recording of sales and quantities are not coherent in the historical data and the first period of the current dataset. This results in a 'kink' in the third quarter of 2009, which has been largely eliminated through interpolation from the previous and subsequent period, but is still visible in some of the graphs.

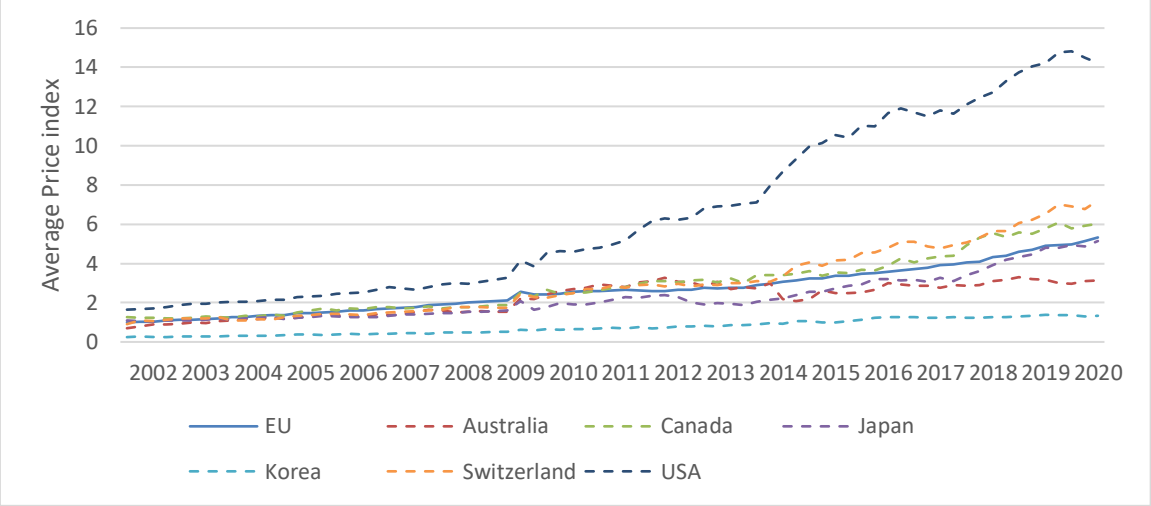
Data aggregation: For the purposes of the analysis, data were aggregated to the drug/country level. Particularly, sales of the same drug across different ATC classes were added up.

Backward interpolation of drug attributes: Some drug attributes (e.g. whether a compound is generic or branded) are not available in the historical data. For the subset of drugs where current and historical data could be linked, these attributes were 'backwards interpolated' from the current to the historical data.

AFF-1: Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries

The goal of this indicator is to track the evolution of drug prices over time and compare the situation in the EU with that of comparator regions. Specifically, the average price of drugs over time in the EU will be compared to prices in Australia, Canada, Japan, Korea, Switzerland and the US. Figure AFF-1.1 calculates average prices for all EU countries and compares them to the other regions. For the average prices, all available drugs (i.e., more than 200,000 different products) are employed and the price per standardized unit is normalized to "1" in the EU in the first quarter of 2002.

Figure AFF-1.1: Average price of all drugs



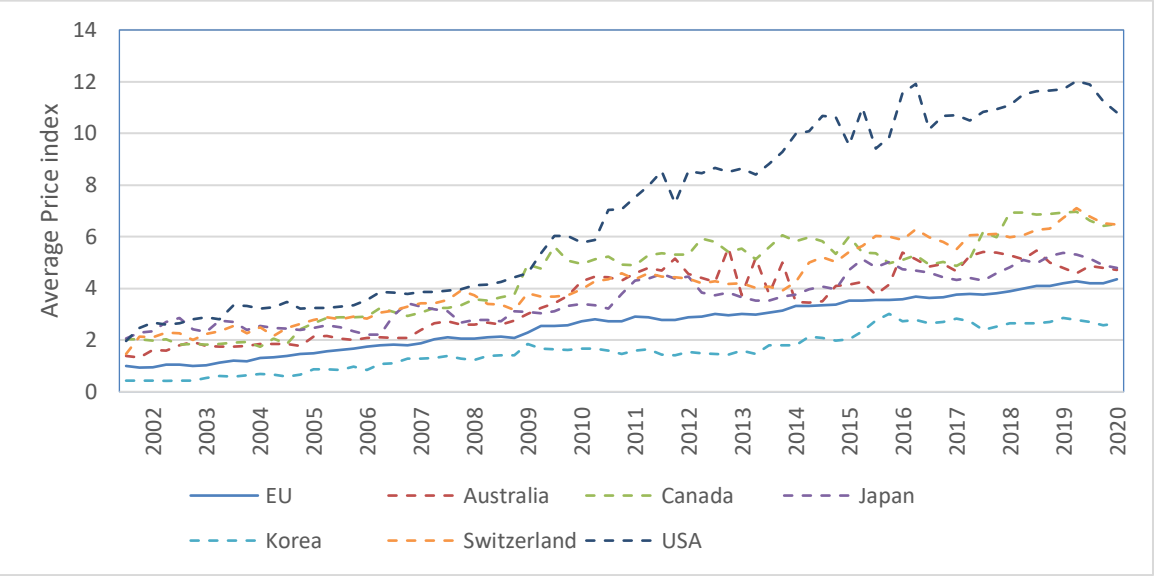
Source: IQVIA-MIDAS

Figure AFF-1.1 shows that the initial level of prices in the EU is intermediate: while lower than in the US and Canada, it is higher compared to Australia and Korea and similar to Japan and Switzerland. The dynamics of the graph show two extreme cases of price evolution. In Korea, prices remain constantly low and increase only moderately over the whole sample period. On the other hand, in the US, price increase rapidly, particularly after 2009, and increase almost tenfold over the sample period. The evolution in Europe is intermediate. Prices increase steadily, reaching about five times their 2002-level in

2020 (the small spike in 2009 is due to the joining of the datasets and should be disregarded, see "Caveats"). The increase in prices seems to slightly increase after 2017 and rather similar developments can be observed for Switzerland, Canada and Japan.

Figure AFF-1.2 follows the same logic, but restricts the price averages to key drugs, the total sales of which exceed a revenue of 10m €. Only 193 drugs fall in this category. Thus, the graph focuses on the commercially top-selling drugs across all countries. While the resulting picture is similar to the one before, the price growth of drugs in the EU is now visibly below that of other comparators, except for Korea. Thus, while the price increases in the EU are similar to most comparator regions (except the US and Korea) when looking at all drugs, price increases in the EU are relatively lower when focussing on the most commercially successful drugs.

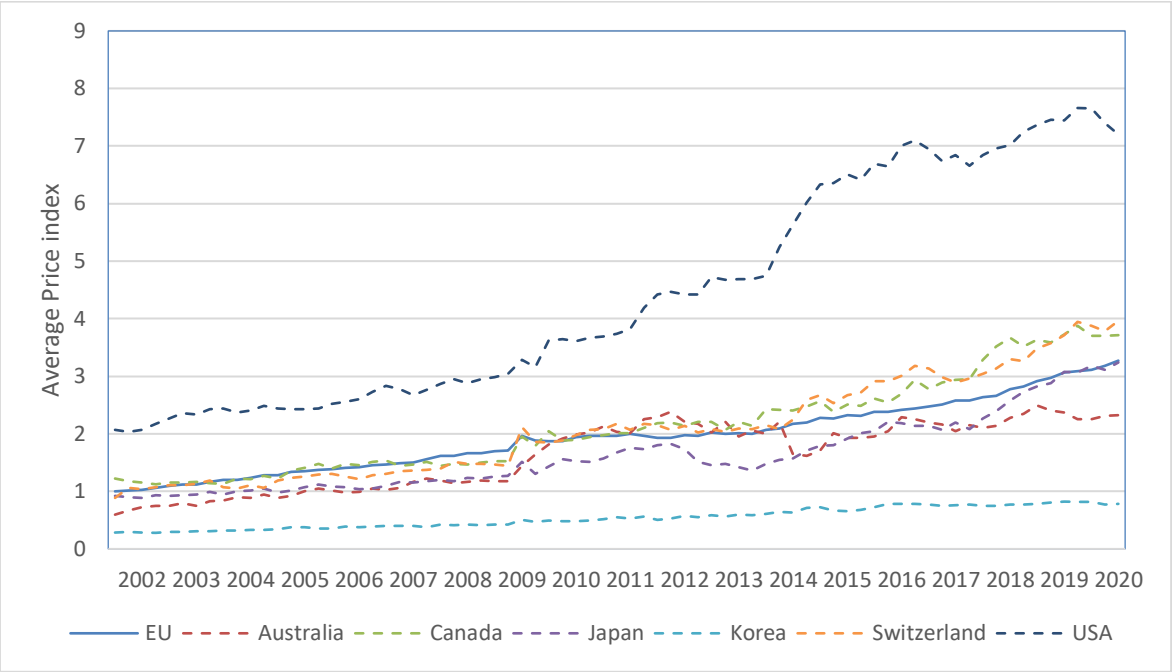
Figure AFF-1.2: Average price of key drugs



Source: IQVIA-MIDAS

Figure AFF-1.3 focuses on the price evolution of relatively expensive drugs. These correspond to the highest price-quartile in each country. Thus, for each country, we calculated the average price of each drug and selected the most expensive quarter of the data. The resulting graph is very similar to the first graph, containing the average prices of all drugs. This suggests that the overall price evolution is driven by the relatively expensive drugs.

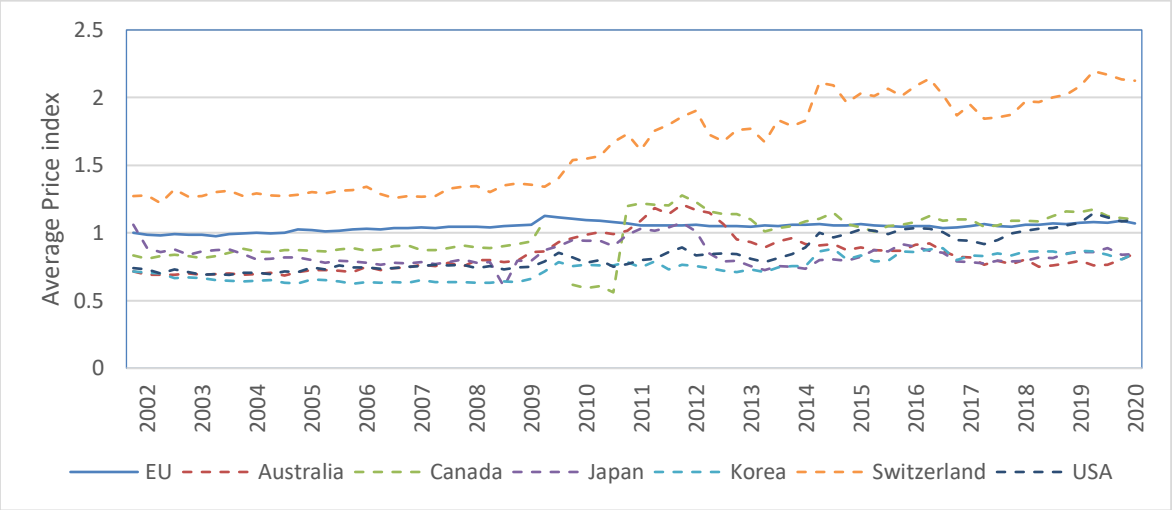
Figure AFF-1.3: Average price of high-price drugs



Source: IQVIA-MIDAS

This intuition is corroborated by Figure AFF-1.4, which illustrates the price evolution of relatively cheap drugs, corresponding to the first quartile of the distribution of average drug prices. While the resulting time series is somewhat noisy for some comparators, it is almost completely flat for the EU, suggesting that the prices of these drugs have risen by only about 10% on average over the sample period.

Figure AFF-1.4: Average price of low-price drugs



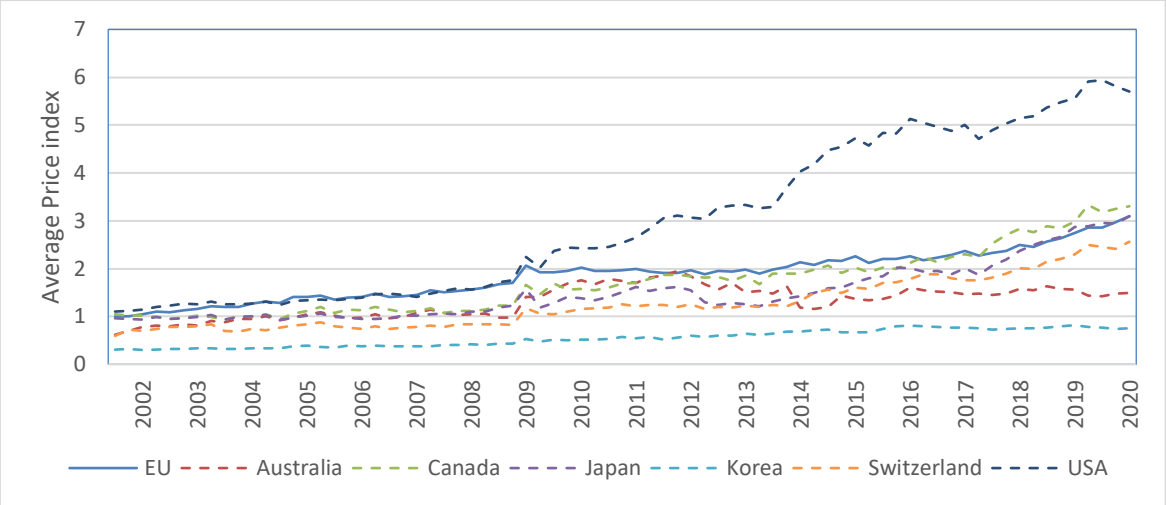
Source: IQVIA-MIDAS

AFF-2: Ratio of net price of medicines to GDP per capita in individual countries

AFF-2 is similar to AFF-1 in that it plots the average prices in different regions over time. It differs insofar, as price are normalized by the GDP per capita in the respective regions. Thus, instead of calculating changes in nominal prices, the evolution of prices is calculated accounting for differences in wealth across the regions compared. Data on GDP per capita is obtained from the World Bank.

As before, we compare four different baskets of drugs: all drugs available, the top-grossing (>10m €) drugs, as well as the most expensive and the most affordable quarter of drugs. The evolution of all drug prices relative to GDP per capita is similar to the non-GDP-adjusted graph shown earlier, but also contains some interesting differences. First, the overall increase in drug prices is more moderate in real terms than in nominal terms. While the increase in nominal prices in the EU was about five-fold, real prices have increased by a factor of approximately two and a half. The situation is similar for the comparators. Thus, while the increase is lower in real terms, it is still substantial. Second, while the EU was in the middle field of price increases in nominal terms, it now ranks only behind the US and Canada. Thus, in real terms, price increases were larger in the EU than in Switzerland.

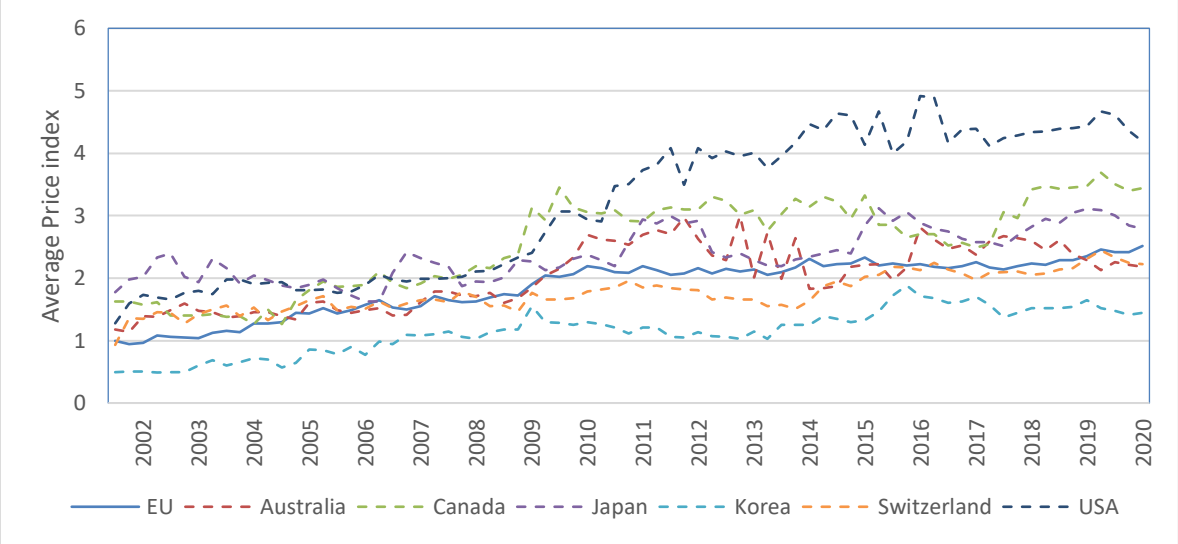
Figure AFF-2.1: Average price of all drugs relative to DGP per capita



Source: IQVIA-MIDAS

When looking at the most commercially successful drugs in the next graph, the situation is quite similar to before. Again, the EU's price growth is relatively higher compared to the nominal scenario, but it remains in the middle field of comparator regions.

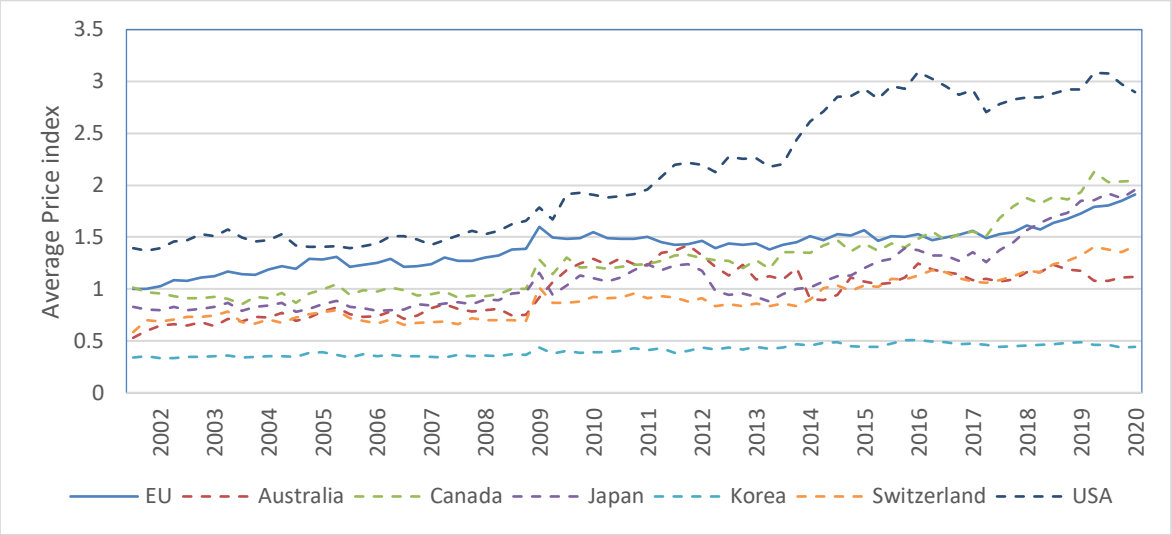
Figure AFF-2.2: Average price of key drugs relative to GDP per capita



Source: IQVIA-MIDAS

Focussing on high-price drugs yields a picture that is comparable to the nominal case, with price increases scaled down. The average, real price of high-price drugs has approximately doubled in the EU over the sample period.

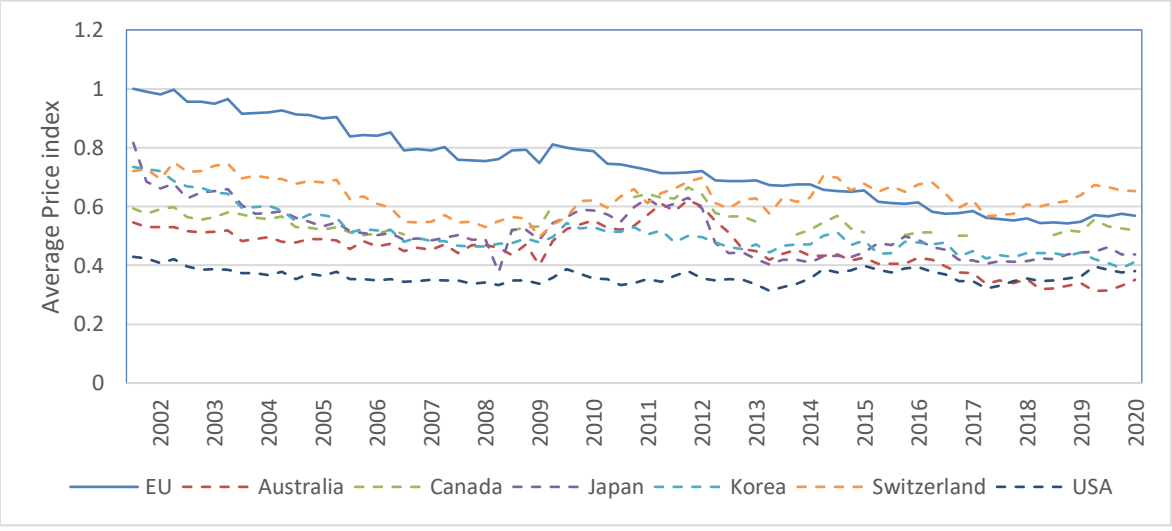
Figure AFF-2.3: Average price of high-price drugs relative to DGP per capita



Source: IQVIA-MIDAS

Interestingly, the price increases of low-price drugs seem to be below GDP growth on average, such that their real prices decline. The average, real prices of these drugs are decreasing over the sample period in the EU and all comparator regions, except for the US. In the US, these drugs start at a price level substantially below that in the EU and other regions and remain mostly constant. In all other regions, price decline, with the decline being most accentuated in the EU. Here, the real prices of these low-cost drugs have declined by more than a third over the sample period.

Figure AFF-2.4: Average price of low-price drugs relative to DGP per capita



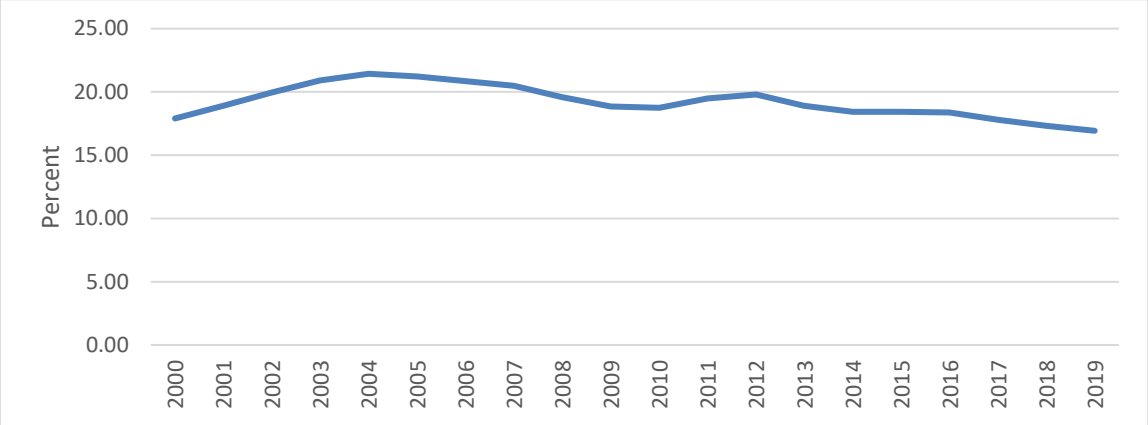
Source: IQVIA-MIDAS

AFF-3: Expenditure on medicines in total healthcare spending

We find that in the EU, average drug spending as a percentage of health spending stood between 17–21% during the last 20 years. While this share was higher in 2003- 2007 it decreased slightly in the last 12 years. The figure is in line with the findings of a recent

report by the IQVIA institute that highlights that drug spending has been growing more slowly than health spending in recent periods in most countries.[5]

Figure AFF-3: Average share of pharmaceutical expenditures in total health spending in EU27 and UK



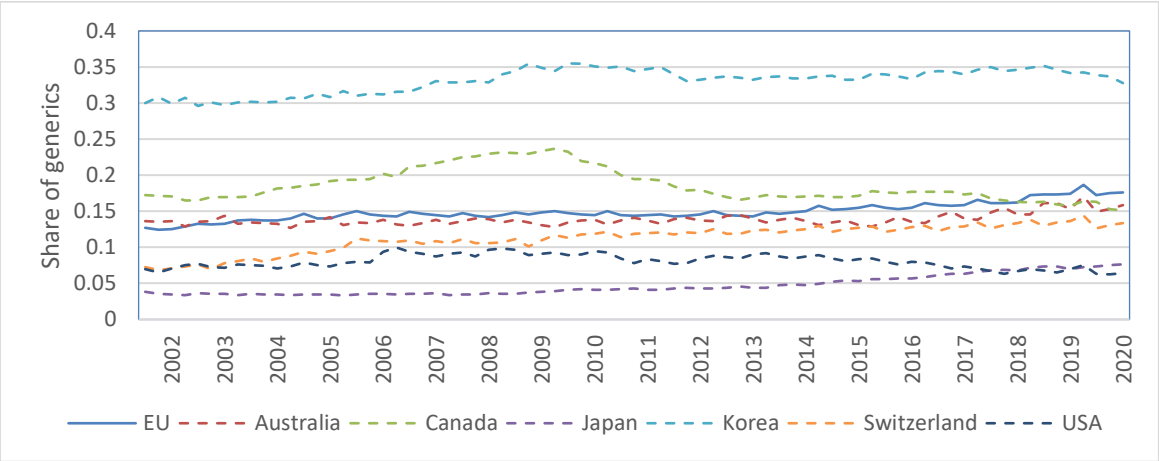
Source: OECD Health Statistics. Average across countries is not a weighted average. Pharmaceutical spending covers expenditure on prescription medicines and self-medication, often referred to as over-the-counter products. In some countries, other medical non-durable goods are also included. Pharmaceuticals consumed in hospitals and other health care settings are excluded. Final expenditure on pharmaceuticals includes wholesale and retail margins and value-added tax. This indicator is measured as a share of total health spending.

AFF-4: Rate of generics/biosimilars entry and uptake

This indicator aims to assess the importance of generics in the EU and comparator regions. Unfortunately, the information of whether a product is branded or generic is only available for the current dataset, but not for the historical one (up to 2009). This has been addressed by matching current and historical drug products via their name and extrapolating their branded/generic status from the current to the historical dataset. This approach successfully links about one third of drugs across datasets.
Figure AFF-4.1 shows that the share of generics in total drugs sales is increasing in the EU and most comparator regions. The share of generics has been rising in the EU over the whole sample period, but with a rather modest rate of growth.

[5] In Aitken., et al. (2021), drug spending as a percentage of health spending is inclusive of all products and locations where they can be delivered (retail, hospitals) and are reported after discounts and rebates received by payers.

Figure AFF-4.1: Share of generics in total drug sales

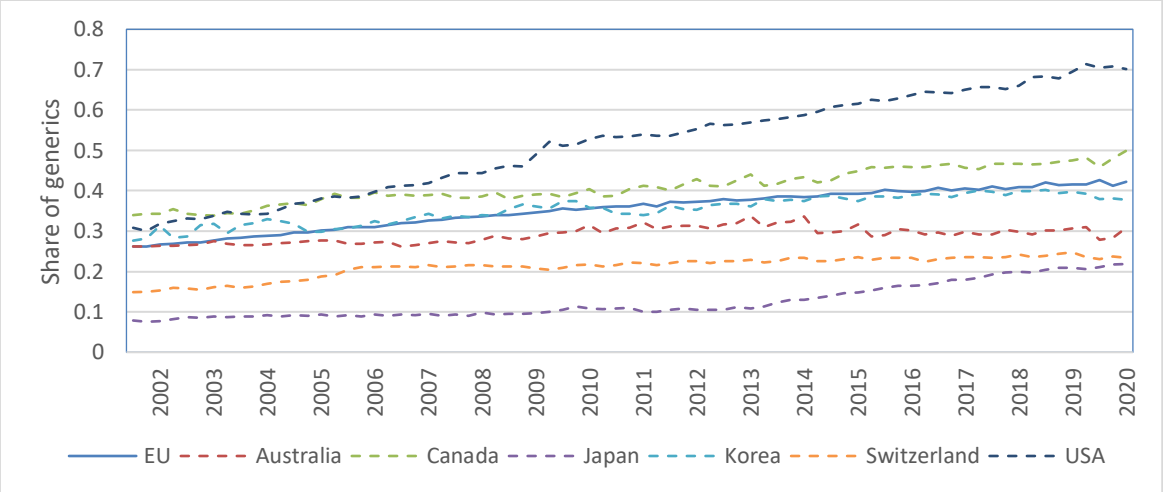


Source: IQVIA-MIDAS

As the prices of generic drugs are usually much lower than those of branded drugs, it might be misleading to only look at sales data when assessing the degree of generics adoption. In the MIDAS dataset, the imputed price of generics per unit is, on average, four times lower than that of branded products. Thus, in order to avoid understating the relevance of generics due to their low price, we repeat the analysis above using the share of generics in total consumption rather than their share in total sales.

Figure AFF-4.2 shows that generics consumption as a share of total consumption is highest in the US, reaching almost 80% of total consumption at the end of the sample period. The rise of generics consumption in the US is almost continuous, rising from around 30% in 2002 to around 70% in 2020. The EU and most other comparators also experience a rise in the share of generics, but at a lower growth rate. The share of generics in total consumption in the EU reaches around 50% at the end of the sample period, up from approximately a quarter at the beginning. The trajectory is quite similar to those of Canada and Korea. Australia, Japan and Switzerland consume generics to a lesser degree.

Figure AFF-4.2: Share of generics in total consumption



Source: IQVIA-MIDAS

1.5 SINGLE MARKET INDICATORS

Indicator name	Indicator description
	Shortage-related indicators:
SM-1:	Trend of shortage duration for medicines in shortage
SM-2:	Trend of volume drop for medicines in shortage (critical, severe, moderate)
SM-3:	Change of root cause reported for medicines
SM-4:	Proportion of generic products in shortage
	Therapeutic area competition:
SM-5:	Number of authorised medicines per class, therapeutic area
SM-6:	Number of pipeline products per class, therapeutic area

SM-1: Trend of shortage duration for medicines in shortage

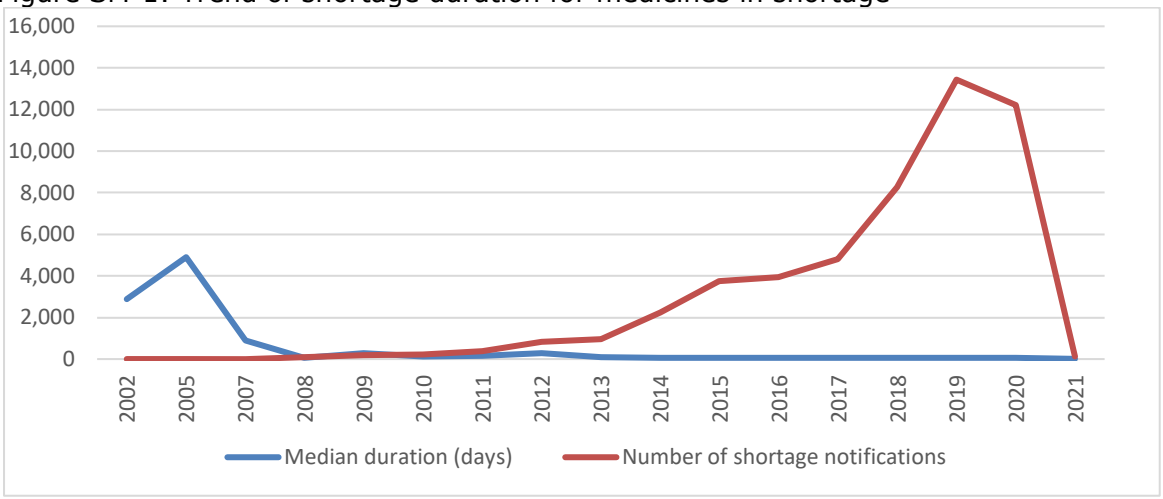
Medicine shortages occur when the quantity demanded is greater than the quantity supplied at the market price. There are two main causes of shortages—increase in demand or decrease in supply. It is useful to distinguish between short and more sustained medicine shortages as they may differ in their root causes. Longer shortages may be more likely to be caused by manufacturing and quality issues, as these sorts of issues can take weeks or even months to be resolved. By contrast, shortages that are caused by, for instance, supply quotas or incorrect forecasting may be resolved more quickly as they reflect problems with local availability rather than with overall supply. To understand the typical duration of drug shortages in the EU, we use data from the study "Future-proofing pharmaceutical legislation: study on medicine shortages".[6]

Figure SM-1 shows that while the number of shortage notifications has increased substantially and persistently since 2013, reaching its peak in 2019 with close to 14,000 notifications, the median duration of shortages remains close to 102 days on average during the period 2008-2021. However, these trends should be interpreted with caution since most countries only reported data on shortages notifications from 2018 onwards. On the other hand, the apparent reduction in the median shortages duration since 2007 is explained by the fact that very few shortages were reported before 2007 and those are unusually long-lasting ones.

Table SM-1 shows the median shortage duration for medicines by ATC1 code during the period 2007-2021 (with the majority being reported during 2017-2020). Medicines for the cardiovascular system as well as dermatologicals report the highest median shortage durations (246 and 238 days, respectively).

[6] https://data.europa.eu/doi/10.2875/211485

Figure SM-1: Trend of shortage duration for medicines in shortage



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. The average number of countries reporting data on notifications during 2002-2010 is 2; from 2011-2013 is 7; and, from 2014-2021 is 15. The average number of countries reporting data on shortages duration for 2002-2010 is 2; from 2011-2013 is 4; and, from 2014-2021 is 11.

Table SM-1: Median shortage duration for medicines by ATC1 code

ATC1	ATC code description	Median duration (days)	Min. duration (days)	Max duration (days)
A	Alimentary tract and metabolism	183	1	5388
B	Blood and blood forming organs	168	1	5145
C	Cardiovascular system	246	1	5793
D	Dermatologicals	238	1	3723
G	Genito-urinary system and sex hormones	213	1	5969
H	Systemic hormonal preparations (excluding sex hormones)	114	3	5586
J	General anti-infectives systemic	184	1	5983
K	Hospital solutions	129	7	4998
L	Antineoplastic and immunomodulating agents	151	1	5587
M	Musculo-skeletal system	184	1	4828
N	Nervous system	198	1	5930
P	Parasitology	92	2	2045
R	Respiratory system	119.5	1	4974
S	Sensory organs	148	2	5353
T	Diagnostic agents	226	7	5083
V	Various	138	7	3982
Total		**187**	**1**	**5983**

Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs.

SM-2: Trend of volume drop for medicines in shortage (critical, severe, moderate)

Most countries define a shortage simply as any situation whereby supply does not meet demand, but do not define how wide the gap between the two must be before a notification must be made. To better understand the extent of product shortages and their impact on overall product availability we use the analysis presented in the study

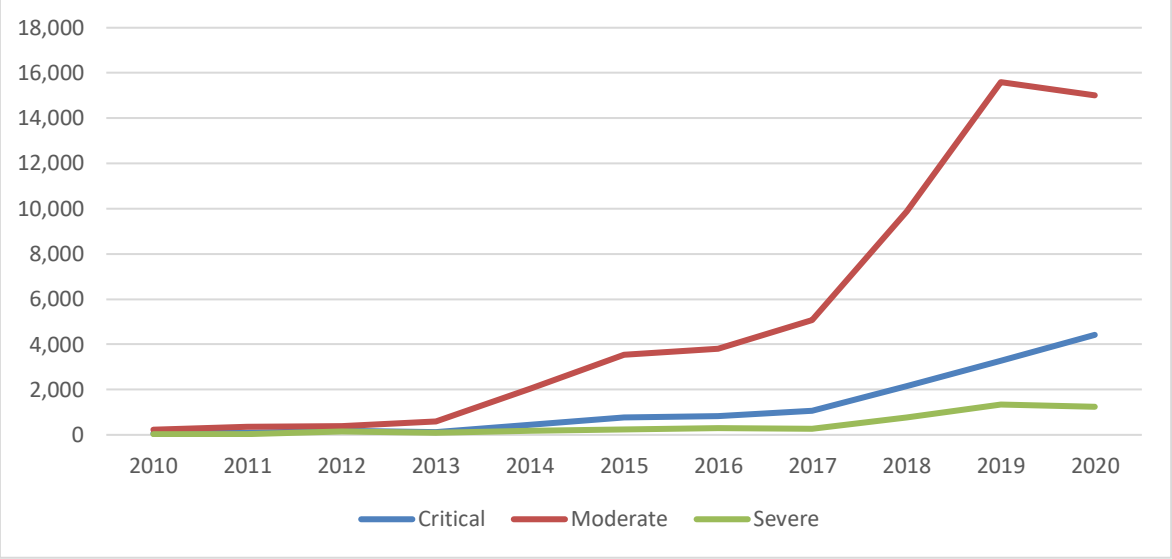
"Future-proofing pharmaceutical legislation: study on medicine shortages".[7] This analysis compares total remaining sales volume during a reported shortage to the sales volume for that same product a year earlier (reference period). This approach is based on several assumptions:

- The recorded sales in the year where the shortage was reported represent all remaining supply (i.e. all product sold is made available in the market and not held in stock, no safety stocks were used to mitigate the shortage)
- Demand can be approximated by the recorded sales exactly one year before the shortage was first reported (reference period).

We classify shortages according to their intensity. Severe shortages are those where volume dropped to 20% or less of the volume on the previous year, critical shortages are those where volume dropped to 21%-79% of the volume on year prior, and moderate when volume drops to 80% or more of the volume of the previous year. Figure SM-2 shows the evolution of the three types of shortages (i.e., critical, severe, moderate). The rise in the total number of shortages is driven by a significant growth in moderate shortages, however, since 2018 critical and severe shortages have been also on the rise.

Table SM-2 shows the proportion of products for which the volume decreased to 20% or less of the volume on the previous year. Such severe shortages were most commonly recorded in Romania (14% of all reported shortages) and Austria (13% of all reported shortages) during the period 2007-2021 (with the majority of data being recorded during 2017-2020).

Figure SM-2: Trend of volume drop for medicines in shortage (critical, severe, moderate)



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs.

[7] https://data.europa.eu/doi/10.2875/211485

Table SM-2: Summary statistics on change in sales volumes for medicines in shortage, per country

Country	# Products	Median volume change (%)	Shortages with volume change to ≤ 20% (%)
Austria	144	-8%	13%
Croatia	88	-6%	8%
France	1,256	-3%	8%
Sweden	734	-2%	11%
Ireland	653	-2%	10%
Slovenia	674	-2%	9%
Estonia	566	-2%	8%
Italy	1,009	-2%	7%
Netherlands	1,417	-1%	8%
Spain	2,056	-1%	7%
Romania	7	1%	14%
Belgium	1,646	1%	9%
Norway	705	1%	8%
Portugal	2,823	1%	7%

Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. Volume change calculated as the percentage change in between volume sold in first quarter of a shortage and volume 1 year prior

SM-3: Change of root cause reported for medicines

To better understand the circumstances that contribute to product shortages in their countries, National competent authorities (NCAs) may ask Marketing Authorisation Holder (MAHs) and wholesalers to submit information about the causes of the shortages along with the notification, and to indicate what steps are being taken to solve the issues. We use data from the study "Future-proofing pharmaceutical legislation : study on medicine shortages".8 Out of the 14 countries for which NCA representatives completed the study survey, eight indicate recording root causes in their reporting system (six according to their own definitions of root causes and two in line with SPOC definitions).9 In the data at our disposal, 15 out the 22 countries who reported shortage data have begun systematically collecting information on the causes of specific shortages.10 Some request this information using predefined categories of root causes. However, this has at times posed challenges when these categories are not sufficiently granular. For instance, in Sweden it was reported that, in a previous iteration of the reporting system, nearly all respondents selected 'other' as the root cause. Consequently, it was decided to expand the list of options, remove the 'other' category, and offer the possibility to add information in free form. Even when root causes are reported using a categorisation scheme, these schemes are not standardised between Member States, complicating sharing of information and comparative research. To improve this situation, in 2019 the SPOC network introduced a root causes classification scheme, comprising eight categories, which is used to recode root causes. [11]

[8] https://data.europa.eu/doi/10.2875/211485

[9] Belgium, Denmark, Germany, Ireland, the Netherlands and Portugal classify causes using their own definitions; Finland, Germany and Spain use classifications based on the SPOC definitions; Austria, Estonia, Latvia, Slovenia and Sweden do not record root causes.

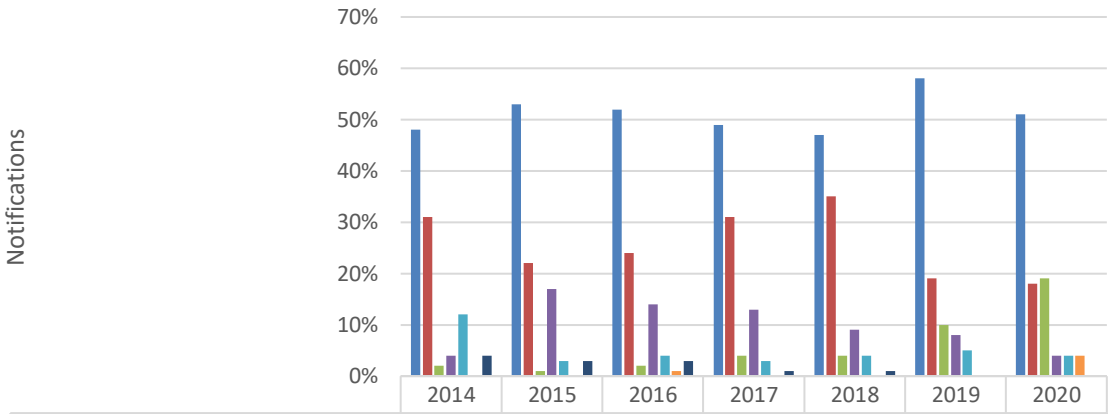
[10] These countries are Austria, Belgium, Croatia, Estonia, France, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Spain and Sweden.

[11] HMA/EMA (22 January 2020).

A trend analysis of reported root causes by start year of notification shows that, between 2014 and 2020, (Figure SM-3):

- Quality & Manufacturing issues were consistently the main root cause of shortages, accounting for around half of all notifications; the relative contribution remained between 48% and 58% of all notifications.12
- Commercial reasons as a reported cause of shortages strongly increased between 2015 and 2018 up to a third (31%) of all notifications; this has since declined again to around a fifth (18-19%) of notifications.
- Unexpected increased demand strongly increased as a reported root cause in 2019 and 2020, becoming the second most reported reason (19%). For 2020, this includes the effects of COVID-19
- Distribution issues have steadily declined as a reported root cause of shortages since 2015.
- Regulatory issues have never been responsible for more than 5% of notifications (with a reported root cause) since 2015.
- Until 2019, unpredicted major events or natural disasters had been reported only sporadically as a root cause of shortages; however, 2020 saw a noticeable increase in reporting of this cause following the COVID-19 outbreak

Figure SM-3: Time trends in reported root causes of shortages (2014-2020)



	2014	2015	2016	2017	2018	2019	2020
Quality & Manufacturing issues	48%	53%	52%	49%	47%	58%	51%
Commercial reasons	31%	22%	24%	31%	35%	19%	18%
Unepected increased demand	2%	1%	2%	4%	4%	10%	19%
Distribution issues	4%	17%	14%	13%	9%	8%	4%
Regulatory issues	12%	3%	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	0%	0%	1%	0%	0%	0%	4%
Other issues	4%	3%	3%	1%	1%	0%	0%

Source: Technopolis Group, based on notifications in national shortage registries. Share expressed as the number of shortages reporting a particular root cause relative to all shortages with a reported root cause that year.

[12] All percentages reported as a share of all notifications for which a root cause was included in the reporting.

SM-4: Proportion of generic products in shortage

The study "Future-proofing pharmaceutical legislation: study on medicine shortages".[13] Found that shortages can arise for any type of medicine, but those at highest risk include pain relief medication, antihypertensives, anti-infectives and oncology medicines. Most shortages involve older, off-patent and generic medicines, which has been widely attributed to the low profit margins associated with these products. Just over half of all reported shortages (52%) involve generic medicines[14] while non-generic medicines account for 37% of reported shortages, with non-generic medicines including both still-patented medicines and original medicines that are not (or no longer) protected.

Table SM-4 shows the number of generic products in shortage by country. Portugal tops the list with 2558 products in shortage, followed by Czech Republic and Netherlands with 1602 and 1390 products in shortage, respectively.

Potentially an even more relevant distinction than that between generic and non-generic medicines is that between multisource and single source products. A multisource product can hereto be defined as a product for which there are multiple providers in a market offering an interchangeable product (based on equivalent active ingredient(s), strength and form). A recent White Paper by IQVIA finds that 52%-79% of shortages[15] involve generic products, which it assumes to be mainly 'multisource products'.[16] Additionally, it is estimated that 3.5% to 28%[17] of shortages involve 'no longer protected, original products' for which there are alternative generics or parallel import products available and that thus can be considered multisource products.

Table SM-4: Number of generic products in reported shortage per country

Country	Number of generic products in shortage
Portugal	2558
Czech Republic	1602
Netherlands	1390
Spain	1202
France	1156
Belgium	845
Slovenia	758
Italy	607
Slovakia	590

[13] https://data.europa.eu/doi/10.2875/211485

[14] Indicated in the IQVIA MIDAS data set as: generic product, early entry generic product or biocomparable product. Other categories not shown here are 'non categorized' and 'other' products.

[15] The unit of analysis used by IQVIA is the 'stock keeping unit' (SKU), used to normalize data across countries.

[16] Troein P, Newton M, Wasik AM, Coucoravas C, Scott K. (2020). Reporting of medicine shortages in Europe: white paper. IQVIA.

[17] The paper indicates that 5% to 40% of reported SKUs are 'no longer protected' original products and goes on to state that 70% of these have alternative generics or parallel import products. Thus, it can be said that 70% x (5% to 40%) = 3.5% to 28% of this group of products are multisource products.

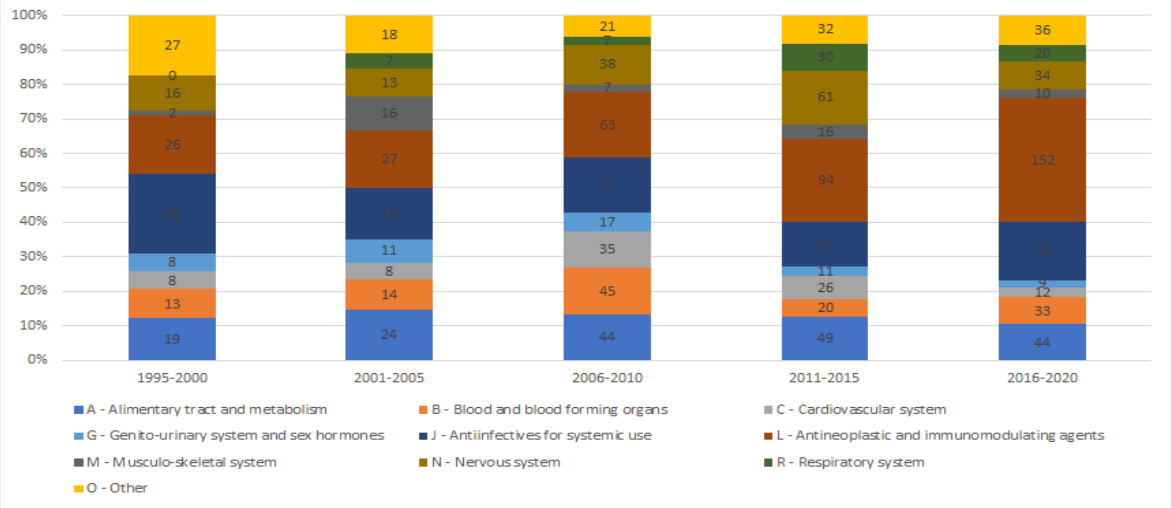
Finland	481
Estonia	476
Ireland	440
Sweden	305
Norway	259
Hungary	228
Romania	228
Germany	206
Austria	138
Croatia	72
Greece	17
UK	17
Latvia	5
Denmark	2
Iceland	2
Switzerland	1

Source: Technopolis Group, based on notifications in national shortage registries.

SM-5: Number of centrally authorised medicines per class, therapeutic area

To create an overview of the number of authorised medicines per therapeutic area we relied on level 1 ATC classification (main anatomical/pharmacological groups) of all products in the dataset in Figure SM-5.1.

Figure SM-5.1: Authorisations by EMA per ATC-L1 code per year



Source: Utrecht database.

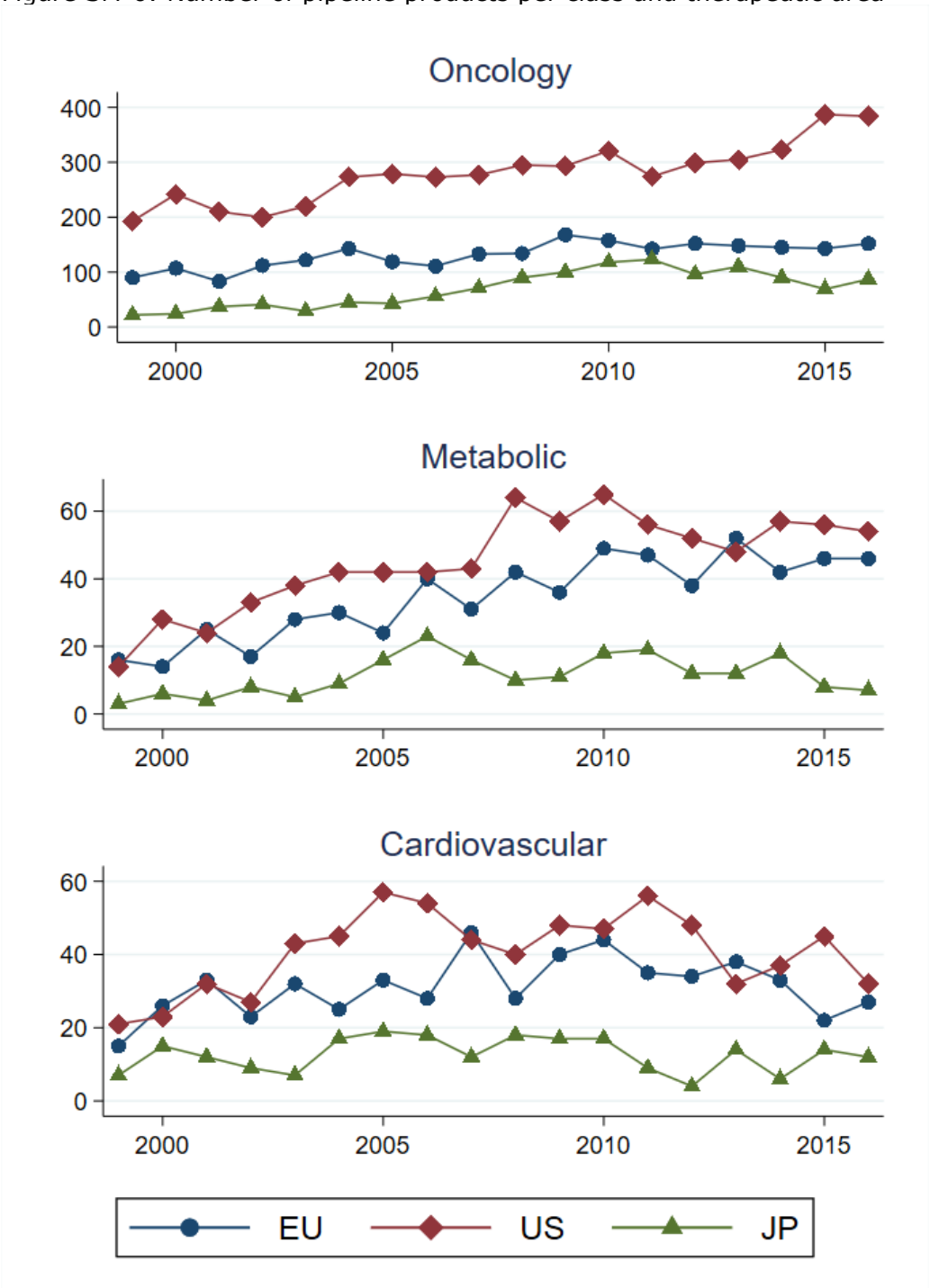
Over time, we see an increase in authorisation of antineoplastic and immunomodulating drugs.

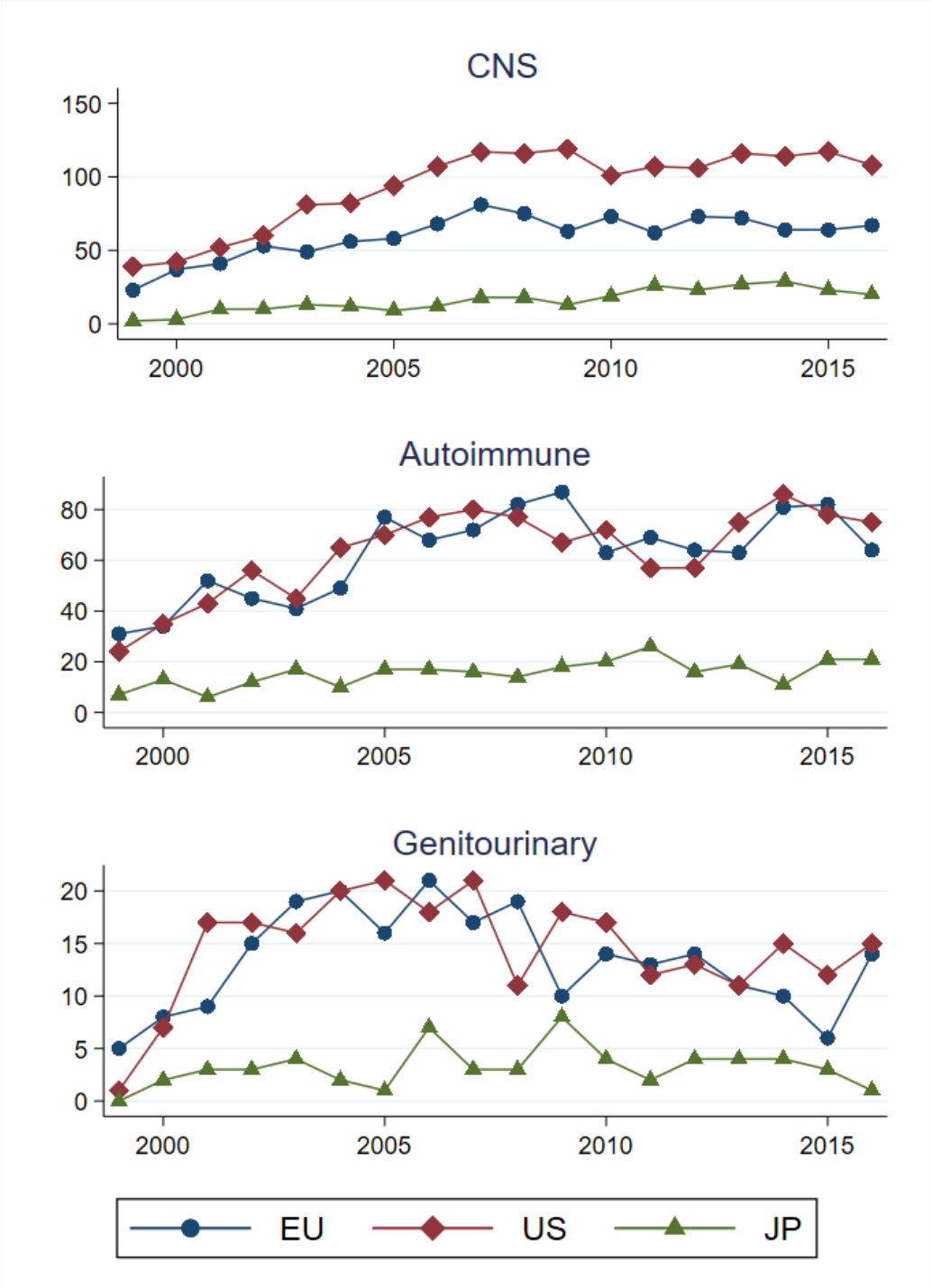
SM-6: Number of pipeline products per class and therapeutic area

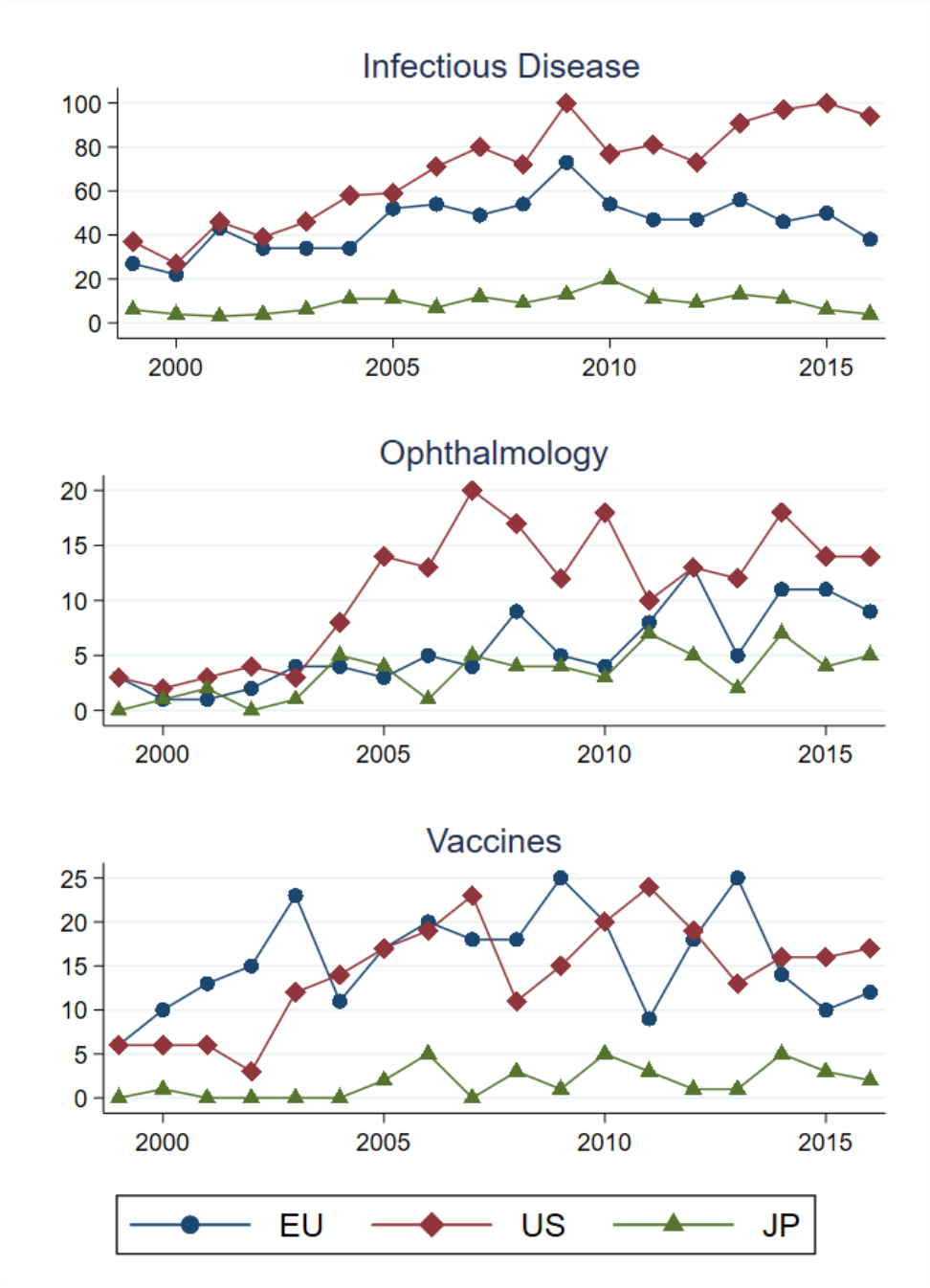
Indicator SM-6 is akin to RI-1 in that it shows the number of new candidate drugs per year; it differs from RI-1 in that it shows the new candidate drugs broken down by therapeutic area that they are being tested for.

We differentiate the same nine therapeutic areas as before: i) oncology, ii) metabolic/endocrinology, iii) cardiovascular, iv) CNS, v) autoimmune/inflammation, vi) genitourinary, vii) infectious diseases, viii) ophthalmology, and ix) vaccines.

Figure SM-6: Number of pipeline products per class and therapeutic area




CNS
150
100
50
0
2000
2005
2010
2015
Autoimmune
80
60
40
20
0
2000
2005
2010
2015
Genitourinary
20
15
10
5
0
2000
2005
2010
2015
EU
US
JP


Infectious Disease
100
80
60
40
20
0
2000
2005
2010
2015
Ophthalmology
20
15
10
5
0
2000
2005
2010
2015
Vaccines
25
20
15
10
5
0
2000
2005
2010
2015
EU
US
JP

1.6 EFFICIENCY INDICATORS

Indicator name	Indicator description
EFF-1	Time from start of Phase1 to completion of Phase 3 clinical trials
EFF-2	Number of EMA approvals by year
EFF-3	EMA assessment times including accelerated assessments

EFF-1: Time from start of Phase 1 to completion of Phase 3 clinical trials

Indicator definition and relevance with respect to the evaluation

Efficiency indicator 1 is a measure of the time spent in each development phase for medicinal products on average across the same four analysis regions/countries used for IEC-1-4 and IEC-6 and RI-1-6. However, for EFF-1, instead of assessing the productivity or innovation of each region, it is changes in efficiency in terms of the average length of time that medicinal products spend in different phases of clinical development that is assessed. Therefore, the aim was to observe if the EU demonstrated changes in efficiency following the implementation of the general pharmaceutical legislation, or if the USA, Japan, or Switzerland demonstrated changes in efficiency during the same period but of course without being influenced by the implementation of the general pharmaceutical legislation.

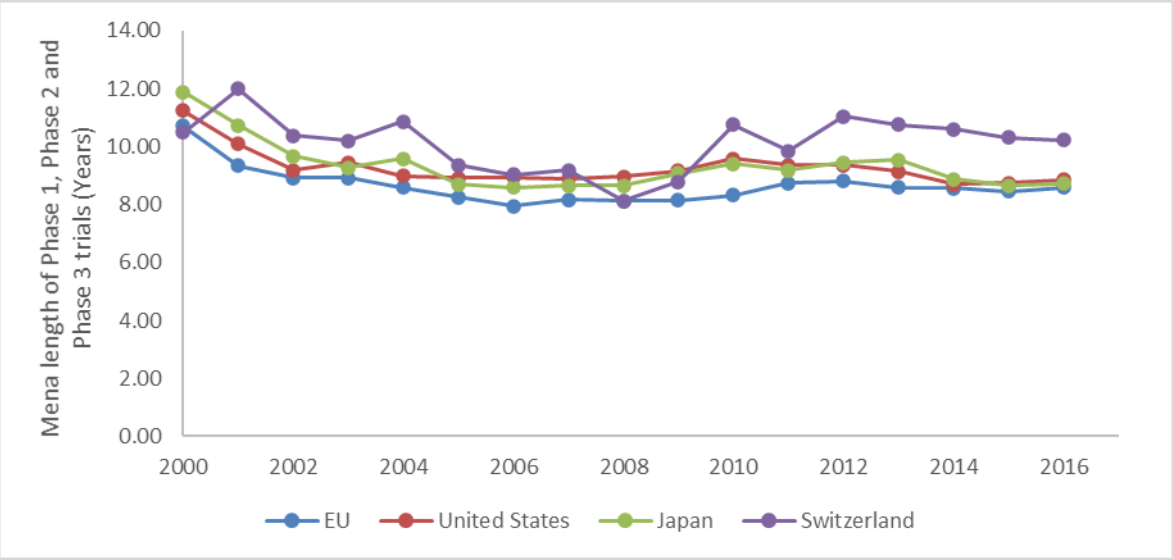
Methodology

The base dataset for EFF-1 is the same as that used for IEC-6 and IEC-9 and consists of over 172,000 Phase 1, Phase 2, and Phase 3 clinical trials contained in Trialtrove with start dates between 2000 and 2020. Each trial was assigned a development phase and an analysis region (USA, EU, Japan, or Switzerland) based on the information contained in Trialtrove. In addition, only trials with known start dates and known or anticipated end dates were included. The countries in what was the EU28 were treated as always having been in the EU for the entire period of the analysis (2000-2020). The clinical trials included in the mean length of trial calculations do not take into account the number of patients recruited in each region or country (such data are not available), so a trial with a least one site and therefore one or more patients per region or country is of necessity counted for that region or country. So as to not unduly bias the data, the mean length of trial calculations were cut off at 2017, as many trials in later years are those that were terminated early, thus making the average length of the trials appear shorter than in reality. Furthermore, any trials recorded as being terminated due to business or other nonclinical reasons (i.e., not related to either the safety or the efficacy of the medicinal product under investigation) were also excluded. Trials conducted in multiple regions or countries were included, as later phase trials are almost exclusively run globally or in at least two or more of the seven major pharmaceutical markets. The mean number of clinical trials starting each year in each phase in each analysis region or country and standard deviations were determined for both the pre and post periods. As with IEC-1-4, Shapiro-Wilk tests were conducted to check data distribution prior to

parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post groups.

EFF-1 investigated the total length of time taken for products to begin Phase 1 and end Phase 3 with trials starting in each year in each of the markets under investigation, namely the EU, the USA, Japan, and Switzerland, in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing each analysis region or country are shown in Figure EFF-1 and Table EFF-1. In all analysis regions, no significant difference was observed between the pre and post periods.

Figure EFF-1 Total mean length of Phase 1, Phase 2, and Phase 3 trials conducted in the EU, the USA, Japan, and Switzerland by start year, 2000-2017.



Source Trialtrove (2000-2017).

Table EFF-1 Descriptive statistics for the total mean length of Phase 1, Phase 2, and Phase 3 trials conducted in the EU, the USA, Japan, and Switzerland

Analysis region	Pre or post	MEAN (years)	STDEV	LOW	HIGH	N number	MANN-WHITNEY U TEST (P-value)
EU	Pre	9.29	0.75	8.55	10.04	3,159	**0.078**
EU	Post	8.49	0.25	8.24	8.74	10,699	
USA	Pre	9.79	0.81	8.97	10.60	3,983	**0.135**
USA	Post	9.10	0.32	8.77	9.42	14,431	
Japan	Pre	10.23	0.96	9.27	11.19	388	**0.064**
Japan	Post	9.06	0.33	8.73	9.39	3,615	
Switzerland	Pre	10.78	0.64	10.14	11.43	400	**0.092**
Switzerland	Post	9.96	0.89	9.07	10.85	1,154	

Source: Trialtrove. Mean total length of Phase 1, Phase 2, and Phase 3 trials starting each year in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

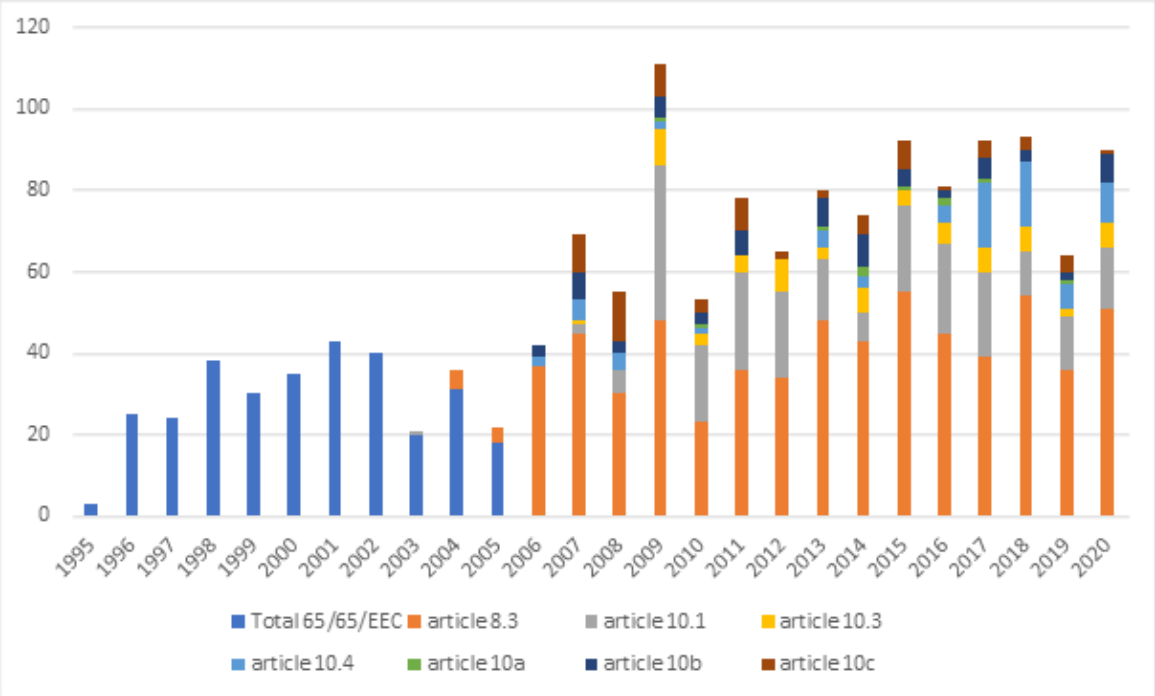
Interpretation of possible causes for changes in EFF-1

EFF-1 demonstrates that the EU has not lost any efficiency compared with other jurisdictions in terms of the overall length of time taken for products to transition from Phase 1 to Phase 3 as a result of the implementation of the general pharmaceutical legislation, although the same trend was observed for all analysis regions or countries. So, while attrition rates and overall difficulty in drug development have been seen to increase in the past 20 years, in terms of the overall length of trials, with the caveats explained above regarding the trials included, the implementation of the general pharmaceutical legislation does not seem to have had a significant effect on the overall length of time taken for products to progress from Phase 1 to Phase 3.

EFF-2: Number of EMA approvals by year

In Figure EFF-2.1 the number of medicinal product authorisations as reported in ACC-1 is stratified by legal bases. The Figure confirms an increase in the number of approvals by year, including a small upward trend in the number of authorisations based on a complete dossier (article 8(3)) as well as an increase in the number of similar biological applications (article 10(4)).

Figure EFF-2.1: Number of EMA approvals by legal basis (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

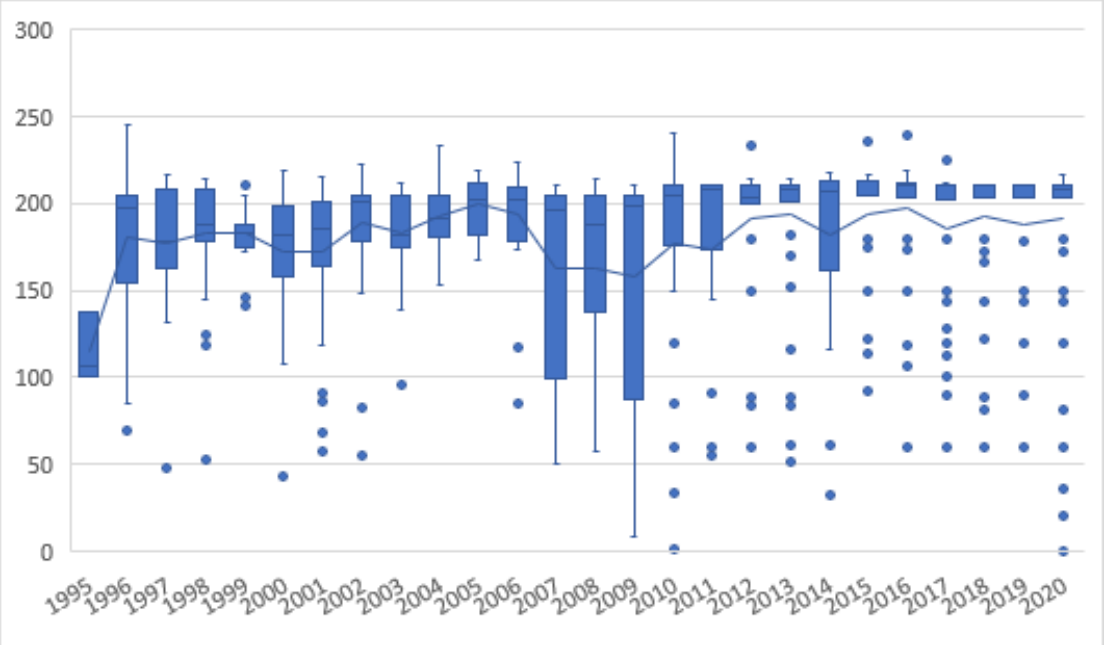
EFF-3: EMA assessment times including accelerated assessments

Figures EFF-3.1 and EFF-3.2 provide a detailed picture of EMA assessment times by year by distinguishing between active time (Figure EFF-3.1) and clock-stop time (Figure EFF-3.2). Moreover, Regulation (EC) No 726/2004 allowed for accelerated assessment of certain marketing authorisation applications. Figure EFF-3.3 provides an overview of the number of accelerated assessments that were granted by CHMP at the start of the marketing authorisation procedure as well as the number of assessments that were executed with accelerated timelines.

Figure EFF-3.4 compares executed accelerated assessments by EMA with executed priority reviews by the FDA, focusing on the subset of matched NASs/NMEs. A Priority

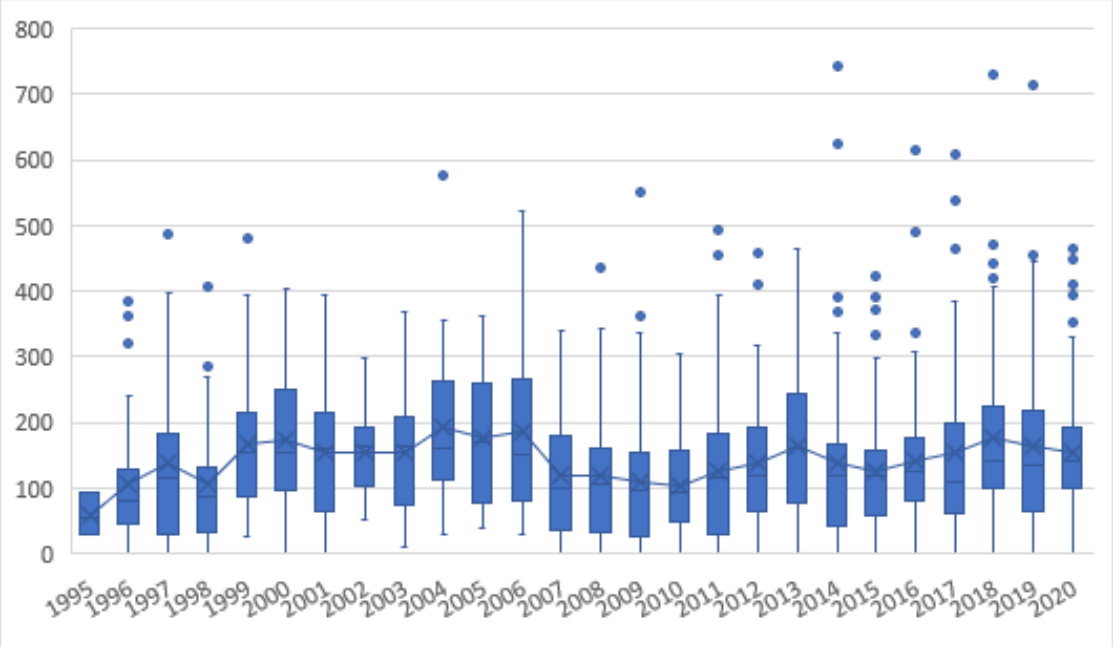
Review designation means FDA's goal is to take action on an application within 6 months. Accelerated Assessment permits a reduction in active assessment time from 210 to 150 days.

Figure EFF-3.1: Active assessment times for EMA authorised medicines (yearly, 1995-2020)



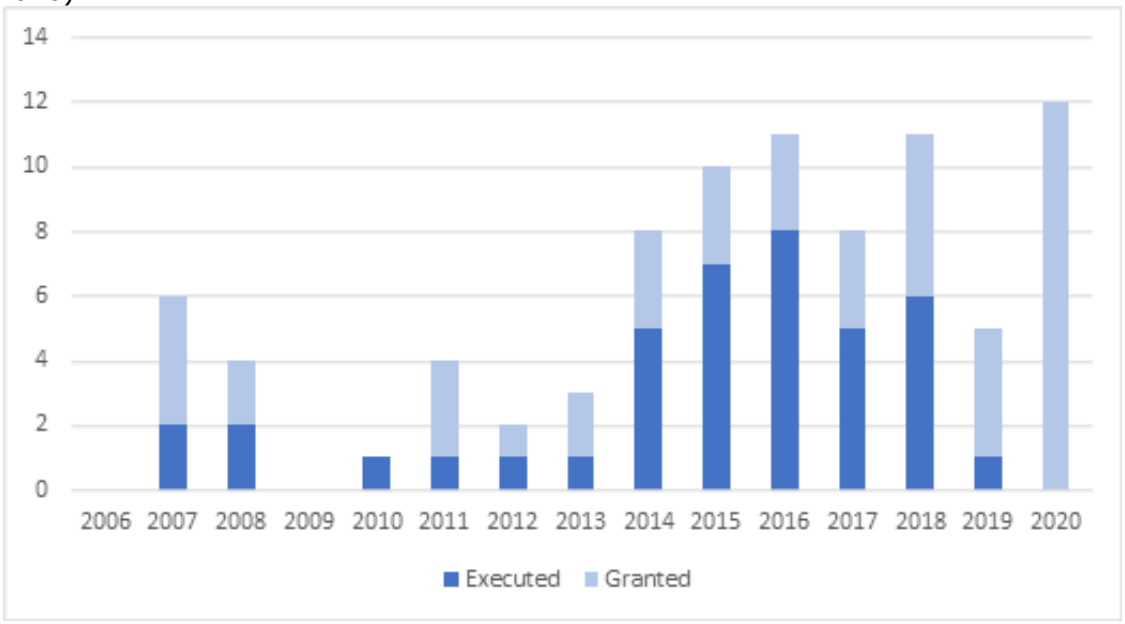
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.2: Clock-stop assessment times for EMA authorised medicines (yearly, 1995-2020)



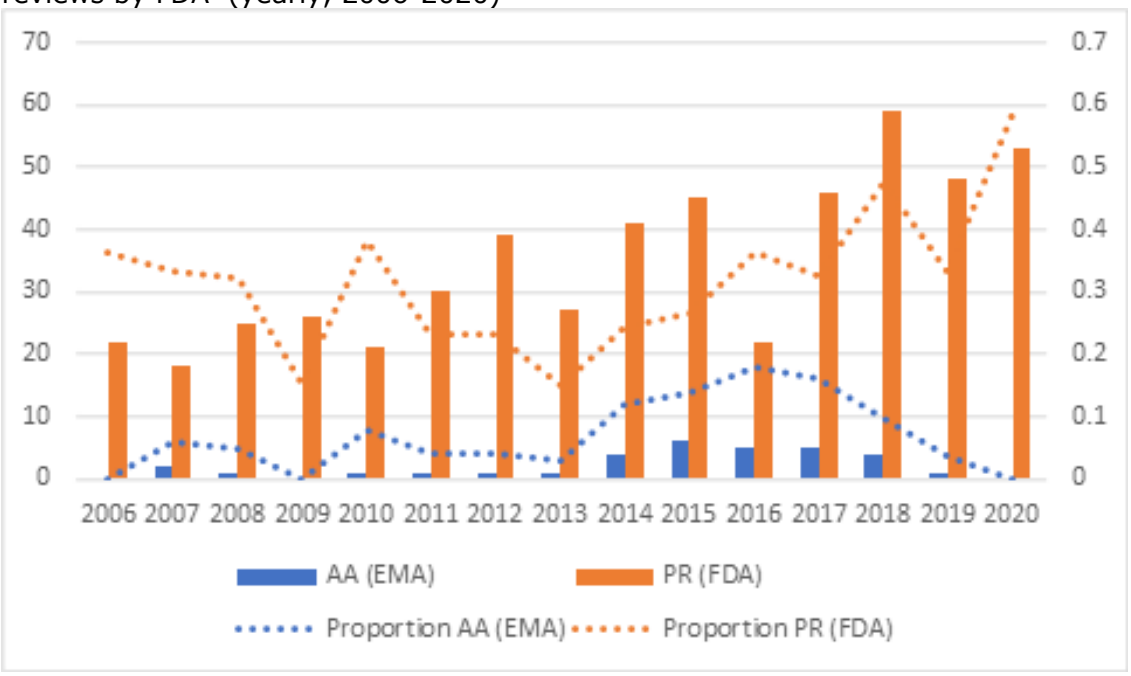
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.3: Executed and granted accelerated assessments by EMA (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.4: Number and proportion of accelerated assessments by EMA and priority reviews by FDA (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It is found that:

- There is no clearly discernible trend is visible in active assessment time and clock stop time at EMA
- The number of granted accelerated assessments is increasing over time
- The number of executed accelerated assessments increases up to 2018, but has been relatively low in 2019-2020
- The number and proportion of accelerated assessments executed by EMA is relatively low compared to the number of priority reviews executed by FDA.

1.7 MANUFACTURING INDICATORS

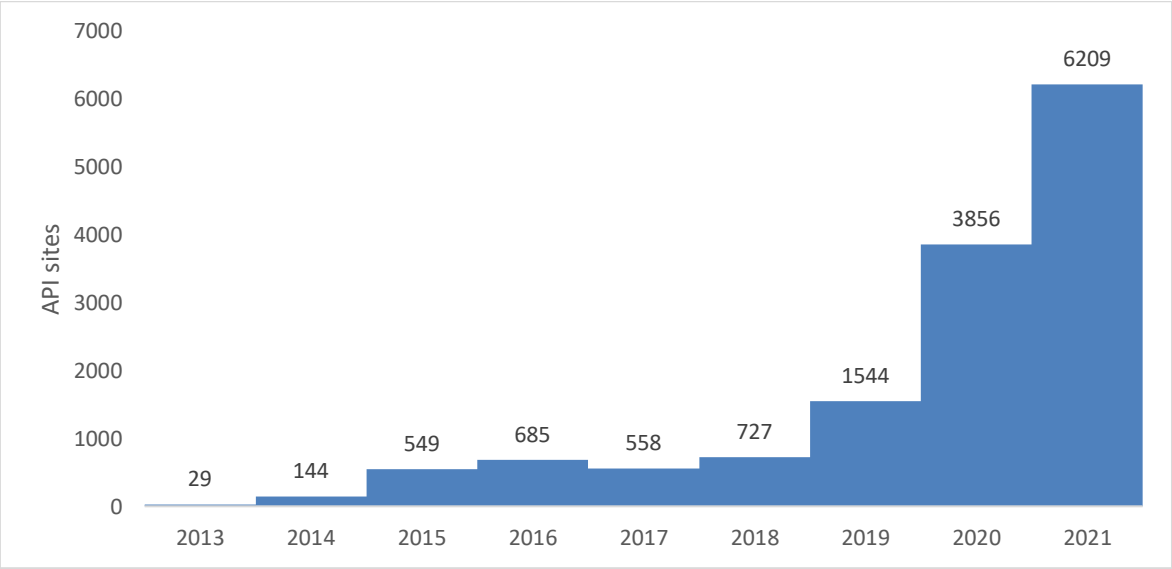
Indicator name	Indicator description
MI-1	Number of third-country API sites, stratified by geography
MI-2	Number of EU-registered API sites, stratified by MS
MI-3	Number of non-compliance of GMP, stratified by countries

MI-1: Number of third-country API sites, stratified by geography

The community format for the API registration certificate was established in accordance with art. 47 of directive 2004/27/EC and art. 51 of directive 2004/28/EC, amending directives 2001/83/ec and 2001/82/EC respectively. For the manufacturing indicators in this section we use the EudraGMDP database, which is the Community database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing (GMP) and good-distribution-practice (GDP) certificates. A public version of the database has been available since 2011.

As shown in Figure MI-1, the number of third country registered API sites remained somewhat stable in 2015-2018 (averaging 630 sites per year). However, since 2019 this number has almost doubled every year. By 2021, there were 6209 API sites registered in third countries (with links to companies with a main site registered in the EU).

Figure MI-1: Number of third country registered API sites

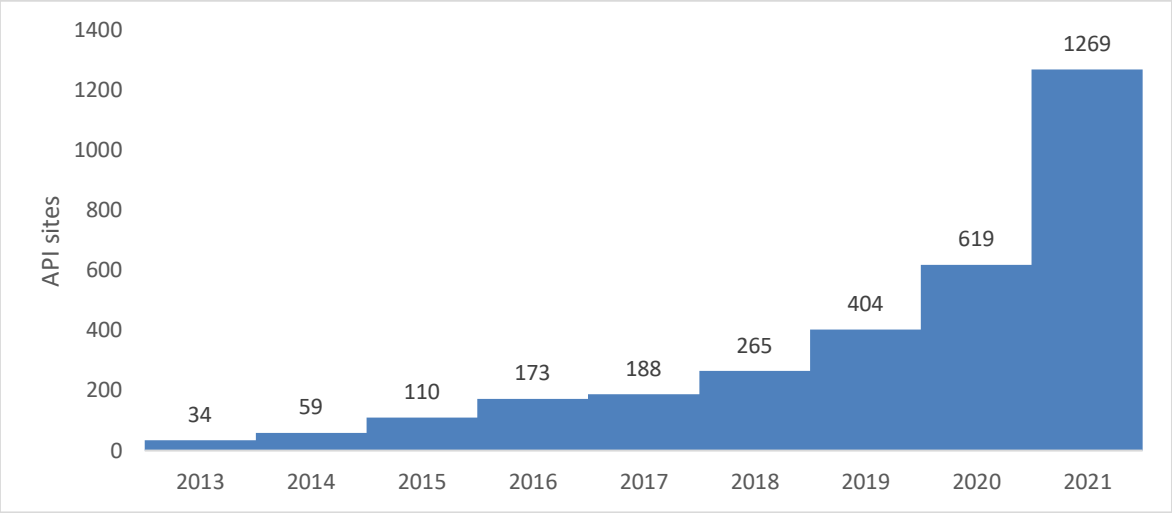


Source: EudraGMDP. This figure is based on information reported by 23 EU countries and the UK. Denmark, Estonia, Luxemburg and Romania are excluded.

MI-2: Number of EU-registered API sites

On the other hand, the number of API sites registered in the EU has seen a steady growth since 2013, although it almost doubled in 2021 when there were 1269 registered API sites (Figure MI-2).

Figure MI-2: Number of EU-registered API sites

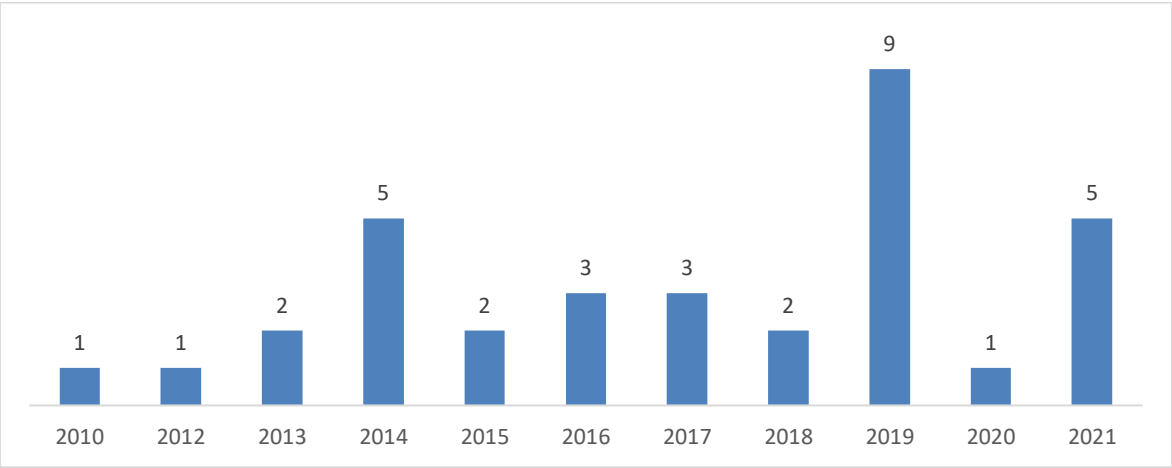


Source: EudraGMDP. This graph presents information for 26 EU countries and the UK. Romania is excluded.

MI-3: Number of non-compliance of GMP, stratified by countries

The General Pharmaceutical Legislation aimed to harmonise Good Manufacturing Practices (GMP) across the EU. To this end, a Community format for GMP Certificate was established in accordance with Art. 47 of Directive 2004/27/EC and Art. 51 of Directive 2004/28/EC, amending Directives 2001/83/EC and 2001/82/EC respectively. Only few EU counties report non-compliance of GMP, among them Austria, Czechia, Denmark, Spain, France, Hungary, Italy, Netherlands and Romania. There is no clear pattern in the number of non-compliance reports per year, however, as shown in Figure MI-3, more of these reports were issued in 2014, 2019 and 2021.

Figure MI-3: Number of non-compliance of GMP reports



Source: EudraGMDP. This graph presents the number of non-compliance of Good Manufacturing Practice reports reported by 9 EU countries and the UK. The 9 EU countries include Austria, Czechia, Denmark, Spain, France, Hungary, Italy, Netherlands and Romania. Date of data retrieval: October 28, 2021.

1.8 INDICATORS SPECIFIC TO ANTIMICROBIAL RESISTANCE

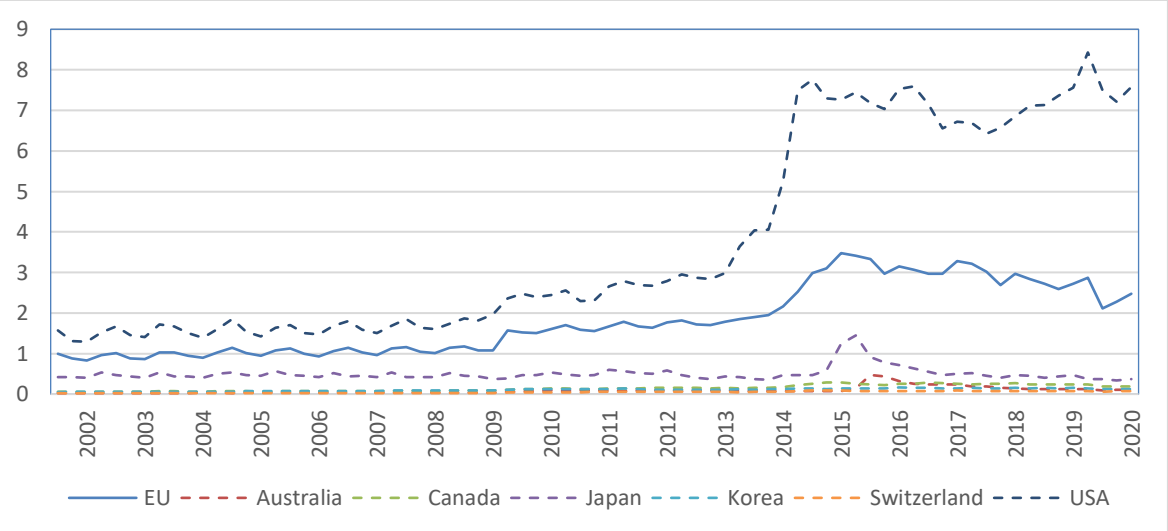
Indicator name	Indicator description
AMR-1	Sales volume of antibiotics
AMR-2	Number of antibiotics withdrawn from EU markets*
AMR-3	Number of antibiotics approved per year
AMR-4	Number of antibiotic medicine candidates in the R&D pipelines

* Note that this indicator was not calculated

AMR-1: Sales volume of antibiotics

To construct AMR-1, we use the IQVIA-MIDAS dataset (see the 'Affordability and Single Market Indicators' section for a detailed description of the data and caveats). We add up all drug sales falling into the ATC categories J01 (antibiotics), but also J02 (antifungals), J03 (antimycobacterials) and J05 (antivirals). Figure AMR-1.1 reports the resulting time series. Total sales of antibiotics in the EU have slowly increased from 2002 to 2014, then rapidly risen until 2016 and have since declined again. The US display a similar pattern of even more rapidly rising antibiotics expenses in 2014 which have since stabilized at a high level. Most other comparators, except Japan, are dwarfed by the total sales of antibiotics in the US and the EU.

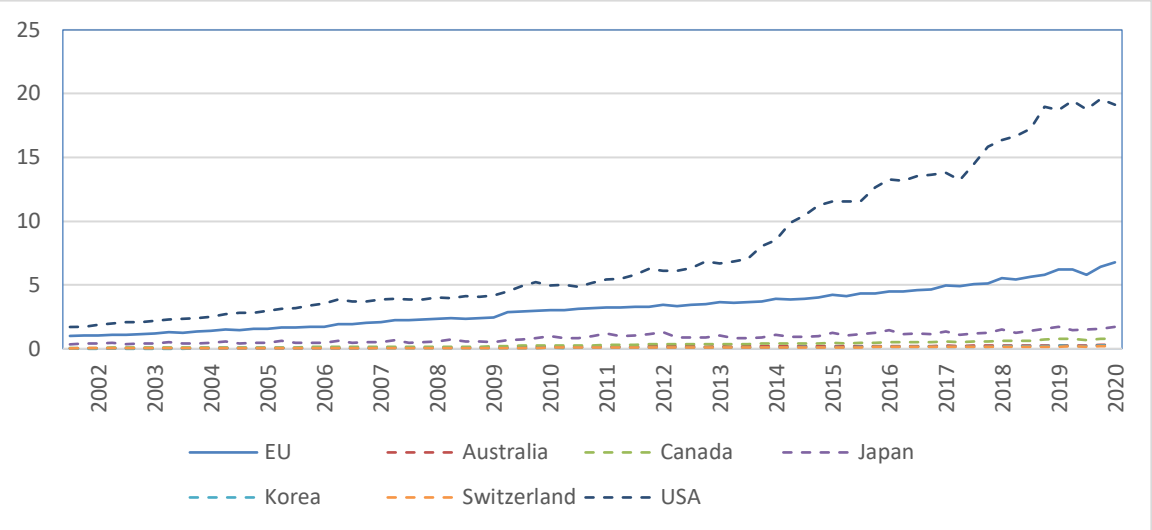
Figure AMR-1.1: Total sales of antibiotics



Source: IQVIA-MIDAS

Figure AMR-1.2 presents total sales by region for biological drugs. Sales of biological drugs in the EU have steadily increased in the EU and are now at more than six times their 2002 level. The increase in the sales of biological drugs is even more pronounced in the US. Again, other comparators – except Japan – are relatively small compared to the US and the EU.

Figure AMR-1.2: Total sales of biological drugs



Source: IQVIA-MIDAS

AMR-3-4: Indicator definition and relevance with respect to the evaluation

Antimicrobial resistance is one of the most significant healthcare challenges of the next decade or sooner, and there is a very real possibility that humanity will truly enter a post antibiotic era where, for example, currently routine lifesaving procedures become very high risk due to the possibility of secondary infection. Despite this, it has been over 30 years since a new class of antibiotic was discovered and brought to market, and the economics to drive such discovery are at odds with worldwide drug discovery driven by private business. Any new antibiotic, even if discovered and brought to market, is, by necessity, usually reserved as a last line treatment and only prescribed carefully and rarely to treat infections shown to be resistant to all other classes of antibiotic. This means that the economics of developing a new antibiotic are heavily stacked against profit driven development. Therefore, legislation and the related financial incentives that any legislation might facilitate are likely to be required to promote development of new antibiotics. It is the intention of AMR-3 and 4 to assess the relative productivity of various regions and countries with respect to the development of antimicrobial products, in terms of final output as measured by approved antimicrobials (AMR-3), and overall productivity of clinical research as measured by the number of clinical trials and products in the development pipeline (AMR-4).

Methodology – AMR-3 and AMR-4

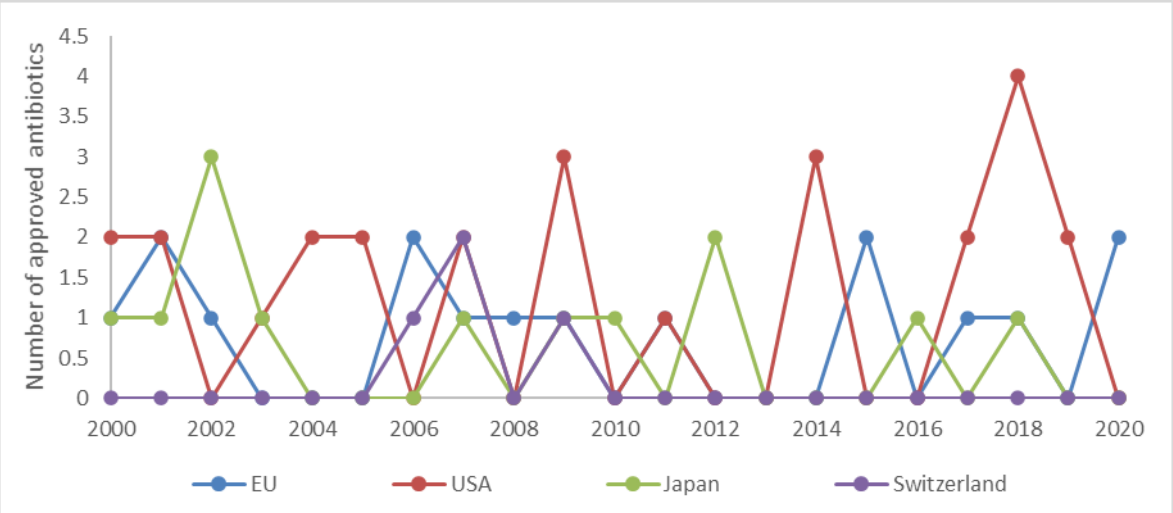
Throughout, all drug approval data are based on that contained in Pharmaprojects and Biomedtracker as of August 2021. The base dataset for AMR-3 contained 4,981 products with a known approval date anywhere in the world. The approval year was set as first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. Therefore, in the case of approvals in the EU, no distinction is or can be made between drugs approved via the centralised or decentralised procedures using data from Pharmaprojects. Furthermore, all member states currently in the EU plus the UK were treated as always having been part of the EU for the entire analysis period. The scope of Pharmaprojects is also limited in that while the majority of medicinal products in development are covered, including biosimilars and reformulations relating to fixed dose combinations and route of administration reformulations by originator companies, approvals of generics or drug combinations are not recorded. Antibiotic products were selected based on recorded

therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Pre or post refers to the analysis period before (pre defined as 2000-2004) or after (post defined as 2007-2020) the implementation of the general pharmaceutical legislation. Mean approvals per year and standard deviations were calculated for both the pre and post periods. For all analyses, if the number of observations (number of approved products or clinical trials) was less than 30, no statistical testing was performed or reported. For AMR-4, the clinical trial dataset used for previous indicators was curated to extract those trials for known antimicrobials as found using the criteria outlined above for AMR-3 for approved products and for those in the pipeline. Both the number of trials starting each year and the number of antimicrobial compounds in trials were counted for each year and each analysis region. As with AMR-3, n numbers were not sufficient for statistical analysis.

AMR-3: Number of antibiotics approved per year

AMR-3 investigated approvals of antibiotic medicines in the EU, the USA, Japan, and Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the four analysis regions for all antibiotic products, not including reformulations, are shown in Figure AMR-3 and Table AMR-3. Reformulations are excluded as they are not expected to contribute to preventing the continued rise of AMR. In keeping with known trends, in the EU, the USA, and Japan, the mean number of antibiotics approved was shown to decrease in the post period vs the pre period, but n numbers were not sufficient for statistical analysis. In Switzerland, the average number of antibiotics was shown to increase in the post period vs the pre period, but, again, n numbers were not sufficient for statistical analysis.

Figure AMR-3 Number of approved antibiotics by year in the EU, the USA, Japan, and Switzerland.



Source: Pharmaprojects 2000-2020.

Table AMR-3 Descriptive statistics for the number of antibiotics approved in the EU, the USA, Japan, and Switzerland (excluding reformulations)

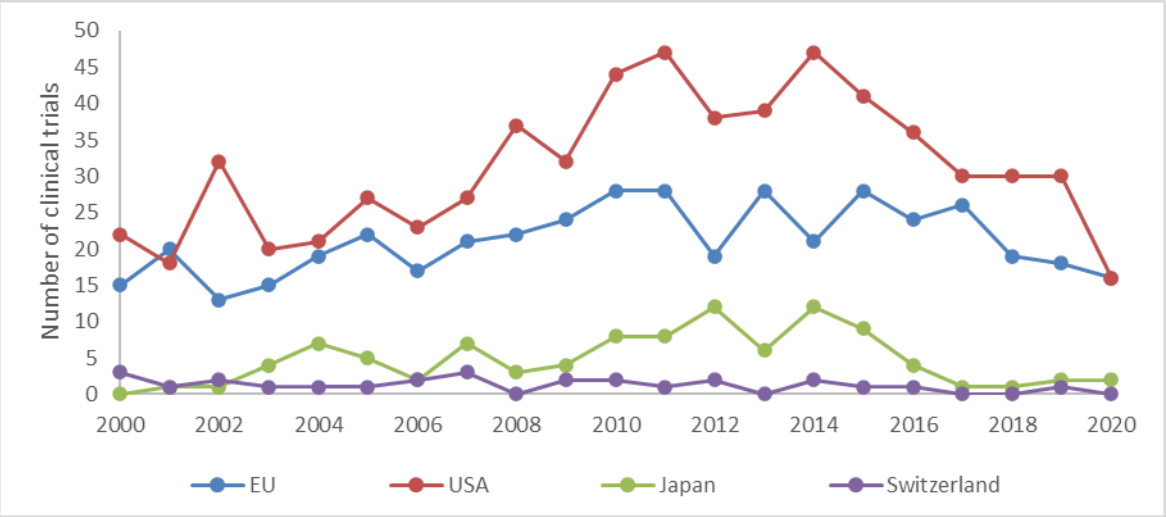
Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
EU	Pre	0.80	0.75	0.05	1.55
EU	Post	0.71	0.70	0.01	1.41
USA	Pre	1.40	0.80	0.60	2.20
USA	Post	1.21	1.37	-0.16	2.59
Japan	Pre	1.20	0.98	0.22	2.18
Japan	Post	0.50	0.63	-0.13	1.13
Switzerland	Pre	0.00	0.00	0.00	0.00
Switzerland	Post	0.21	0.56	-0.34	0.77

Source: Pharmaprojects (2021) and Biomedtracker (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

AMR-4: Number of antibiotic medicine candidates in the R&D pipeline

AMR-4 investigated the number of antibiotic medicine candidates in the R&D pipeline in the EU, the USA, Japan, and Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the number of trials starting each year in the four analysis regions for all antibiotic products, not including reformulations, are shown in Figure AMR-4.1 and Table AMR-4.1. The number of products in the R&D pipeline with trials starting in each year in each analysis region are shown in Figure AMR-4.2 and Table AMR-4.2. As with AMR-3, reformulations were excluded, as they are not expected to contribute to preventing the continued rise of AMR. In the EU and the USA, more trials for antibiotics were found to start on average in each year in the post period compared to the pre period. The tailing off of trial numbers in the US towards the end of the time period may be attributable to what is often perceived as the failure of Generating Antibiotic Incentives Now (GAIN), which was passed in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). While GAIN may have stimulated some trial activity in the early period from 2012, the failure to target Qualified Infectious Disease Product (QIDP) criteria tightly enough to match unmet need may have led to the subsequent fall in trial numbers. The number of trials starting in each year was shown to increase in Japan and decrease in Switzerland, but the n numbers were not sufficient for statistical analysis. The number of products in the R&D pipeline in each year increased in the EU, the USA, and Switzerland in the post period compared to the pre period. In Japan, the number of products also increased in the post period, but the n number was not sufficient for statistical analysis.

Figure AMR-4.1 Number of clinical trials for antibiotics starting in each year in the EU, the USA, Japan, and Switzerland.



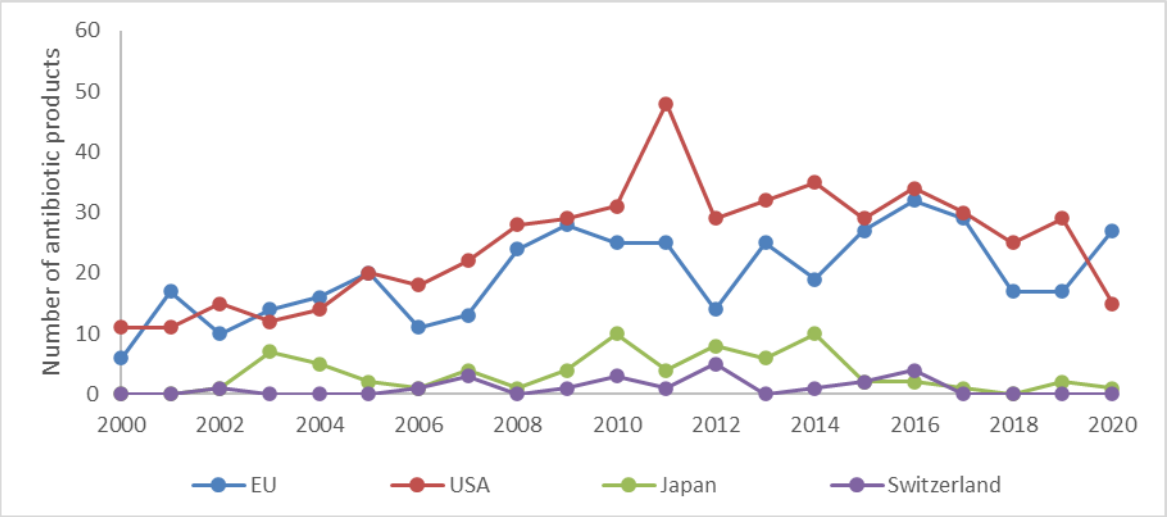
Source: Trialtrove 2000-2020.

Table AMR-4.1 Descriptive statistics for the number of clinical trials for antibiotics in the EU, the USA, Japan, and Switzerland (excluding reformulations)

Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
EU	Pre	16.40	2.65	13.75	19.05
EU	Post	23.00	4.02	18.98	27.02
USA	Pre	22.60	4.88	17.72	27.48
USA	Post	35.29	8.21	27.08	43.49
Japan	Pre	2.60	2.58	0.02	5.18
Japan	Post	5.64	3.66	1.99	9.30
Switzerland	Pre	1.60	0.80	0.80	2.40
Switzerland	Post	1.07	0.96	0.11	2.03

Source: Pharmaprojects (2021) and Trialtrove (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Data were not split by phase to preserve the n number for the number of trials in Japan and Switzerland. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Figure AMR-4.2 Number of antibiotic products with clinical trials starting in each year in the EU, the USA, Japan, and Switzerland.



Source: Trialtrove 2000-2020.

Table AMR-4.2 Descriptive statistics for the number of antibiotics in the R&D pipeline in the EU, the USA, Japan, and Switzerland (excluding reformulations)

Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	WELCH'S T-TEST (P-value)
EU	Pre	11.75	4.15	7.60	15.90	**0.012**
EU	Post	21.86	6.36	15.50	28.21	
USA	Pre	12.25	1.64	10.61	13.89	**0.001**
USA	Post	29.93	6.61	23.32	36.53	
Japan	Pre	2.00	2.92	-0.92	4.92	0.360
Japan	Post	3.93	3.24	0.69	7.17	
Switzerland	Pre	0.25	0.43	-0.18	0.68	**0.026**
Switzerland	Post	1.50	1.59	-0.09	3.09	

Source: Pharmaprojects (2021) and Trialtrove (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Data were not split by phase to preserve the n number for the number of trials in Japan and Switzerland. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Interpretation of possible causes for changes in AMR-3-4

Due to the relatively low level of activity in the pharmaceutical industry in terms of the development of antibiotics or antimicrobials, it was not possible to assess any statistically significant differences. However, while the number of approved products was shown to not change over time in any analysis region or country (AMR-3), there is an observable trend that the number of trials for antimicrobials starting in each year increases in the post period, as does the number of products in trials in each year (AMR-4). However, in addition to the EU, this trend was observed in the other analysis regions, so the impact on the EU of the general pharmaceutical legislation is unknown.

1.9 ENVIRONMENTAL IMPACTS INDICATORS

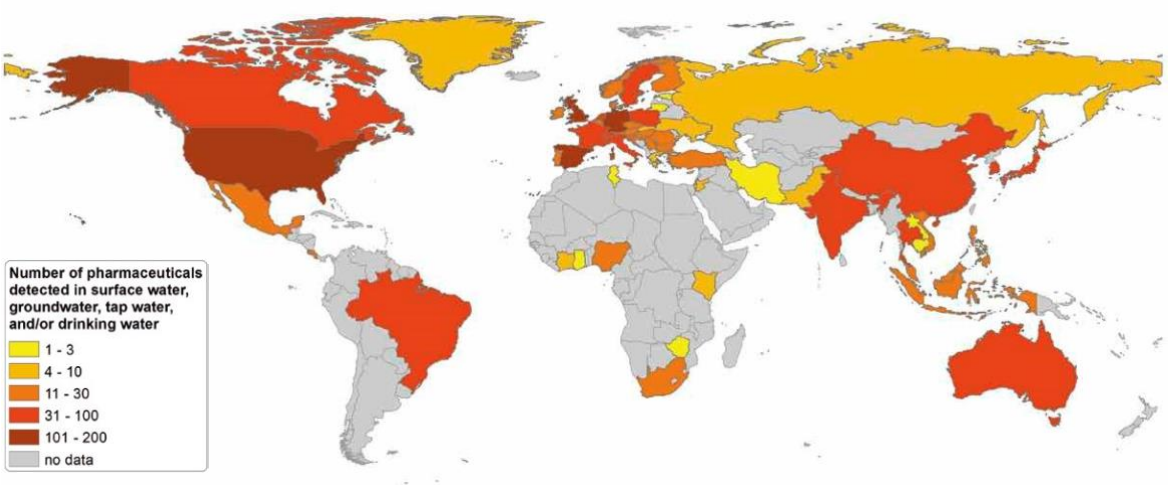
Indicator name	Indicator description
	Presence of pharmaceutical residues in the environment:
EI-1	Concentrations of pharmaceutical residues in the environment
	Emissions from manufacturing plants:
EI-2	Emission intensity/absolute emissions of GHG by the pharmaceutical industry

EI-1: Concentrations of pharmaceutical residues in the environment

Weber et al., (2014) documents that pharmaceutical residues have been detected in 71 countries worldwide in all five UN regional groups (Figure EI-1).[18] Pharmaceuticals were detected in surface water and sewage effluent, but also to a lesser extent on groundwater, manure, soil, and other environmental matrices.

Pharmaceuticals are often found in concentrations of 0.1 µg/L to 1.0 µg/L in rivers and lakes that receive wastewater. However, maximum concentrations in densely populated areas or downstream of sewage treatment plants may be considerably higher. Less data is available on pharmaceuticals in manure and soil, but residues have been detected in 28 countries, especially in the vicinity of intense animal husbandry.

Figure EI-1: Number of pharmaceuticals detected in surface water, groundwater, tap water, and/or drinking water



The report also concludes that the close to 600 active pharmaceutical substances that have been found in the environment belong to 6 therapeutic groups: antibiotics, analgesics, lipid-lowering drugs, beta-blockers, x-ray contrast media, and synthetic estrogens (Table EI-1.1).

[18]https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf

Table EI-1.1: Several globally marketed pharmaceuticals have been found in the aquatic environment of all UN regional groups.

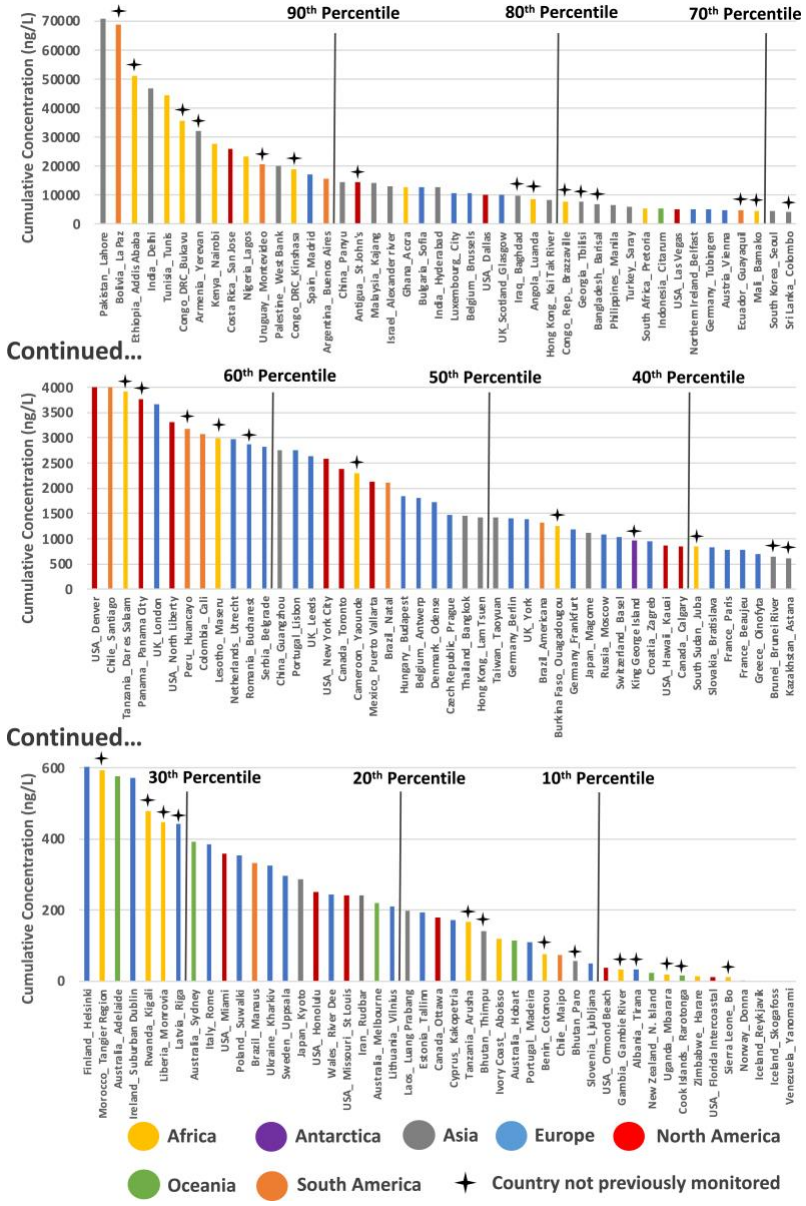
Pharmaceutical	Therapy Group	Number of countries worldwide in which pharmaceuticals have been found in the aquatic environment
Diclofenac	Analgesics	50
Carbamazepine	Antiepileptic drugs	48
Ibuprofen	Analgesics	47
Sulfamethoxazole	Antibiotics	47
Naproxen	Analgesics	45
Estrone	Estrogens	35
17-β-Estradiol	Estrogens	34
17-α-Ethinylestradiol	Estrogens	31
Trimethoprim	Antibiotics	29
Paracetamol	Analgesics	29
Clofibric acid	Lipid-lowering drugs	23
Ciprofloxacin	Antibiotics	20
Ofloxacin	Antibiotics	16
Estriol	Estrogens	15
Norfloxacin	Antibiotics	15
Acetylsalicylic acid	Analgesics	15

Source: Weber et al., (2014).

A more recent study by Wilkinson et al. (2022) covering 1,052 sampling sites located in 104 countries across all continents found that with the exception of Iceland and the Yanomami Village in Venezuela, at least one API was detected in all of the study sites.[19] Figure EI-1.2 shows that the highest mean cumulative concentration was observed in Lahore, Pakistan at 70.8 µg/L. The most polluted European samples were from a site in Madrid, Spain (mean 17.1 µg/L, maximum 59.5 µg/L).

[19] Wilkinson et al. Pharmaceutical pollution of the world's rivers. PNAS. 2022.

Figure EI-1.2: Cumulative API concentrations quantified across 137 studied river catchments organized by descending cumulative concentration (ng/L).

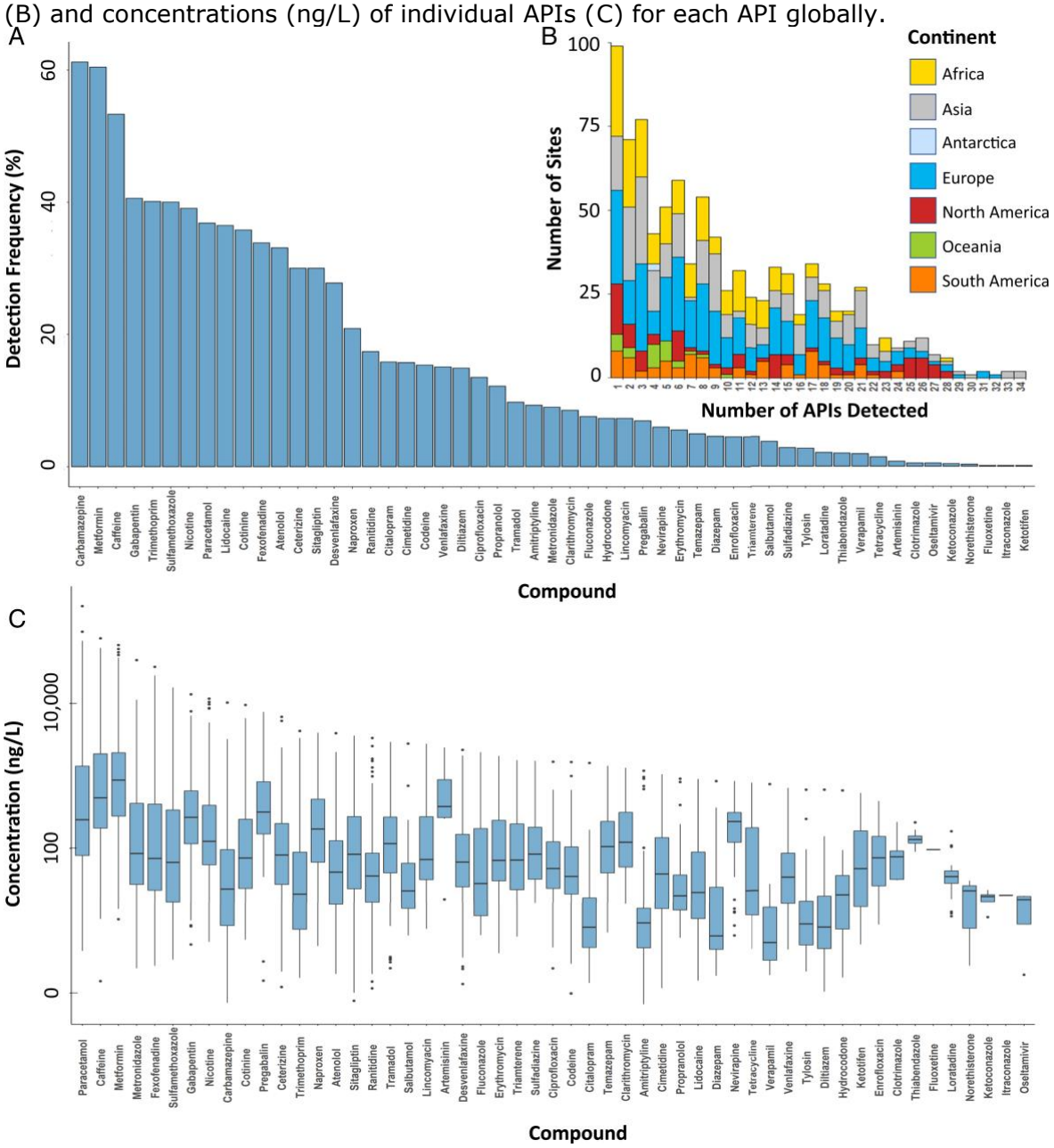


Source: Wilkinson et al. (2022)

Of the 61 targeted APIs in the study, 53 were detected in at least one sampling site. On a continental basis, 45 APIS were found in Europe, 39 in North America, 41 in Africa and 35 in South America (see Figure EI-1.3, panel B). Four APIs were detected across all continents, of which all are considered either lifestyle compounds or over-the-counter APIs: caffeine (stimulant and lifestyle compound), nicotine (stimulant and lifestyle compound), acetaminophen/paracetamol (analgesic), and cotinine (metabolite of a stimulant and lifestyle compound). An additional 14 APIs were detected in all continents except Antarctica: atenolol (β-blocker), carbamazepine (antiepileptic), cetirizine (antihistamine), citalopram (antidepressant), desvenlafaxine (antidepressant), fexofenadine (antihistamine), gabapentin (anticonvulsant), lidocaine (anesthetic), metformin (antihyperglycemic), naproxen (anti-inflammatory), sitagliptin (antihyperglycemic), temazepam (benzodiazepine for insomnia treatment), trimethoprim (antimicrobial), and venlafaxine (antidepressant).

Figure EI-1.3 (panel A) shows that for the detected APIs, overall detection frequencies ranged from 0.1% for fluoxetine (antidepressant), itraconazole (antifungal), and ketotifen (antihistamine), to 62% for carbamazepine within respective river catchments. Metformin and caffeine were also detected at over 50% of all the sampling sites worldwide.

Figure EI-1.3: Detection frequencies (A), number of APIs detected at sampling sites (B) and concentrations (ng/L) of individual APIs (C) for each API globally.



Source: Wilkinson et al. (2022)

EI-2: Emission intensity/absolute emissions of GHG by the pharmaceutical industry

Belkhir et al.,(2018) study the carbon footprint of the global pharmaceutical industry.[20] They examined the Pharma industry over a four-year period from 2012 to 2015 focusing on twenty five major Pharma companies that reported their scope 1 and scope 2 emissions in 2015 and concentrate 70% of the total sector revenues in 2015. Of those firms only fifteen reported their emissions consistently during 2012 -2015. The study found that the pharmaceutical sector is far from being a green sector. In fact, the sector's emission intensity in 2015 was 48.55 Mt-CO2e/$M, which is about 55% higher than that of the Automotive sector of 31.4 Mt-CO2e/$M for that same year. Similarly, in absolute value, the aggregate global emissions of the Pharma sector amount to about 52 MMt-CO2e in 2015 compared to about 46.4 MMt-CO2e emitted by the global automotive sector in that same year (where ”MMt” indicates Million of Metric tons).

[20] Lotfi Belkhir, Ahmed Elmeligi, Carbon footprint of the global pharmaceutical industry and relative impact of its major players, Journal of Cleaner Production, Volume 214, 2019, Pages 185-194, ISSN 0959-6526, https://doi.org/10.1016/j.jclepro.2018.11.204.

ANNEX A: QUANTITATIVE DATA SOURCES

Overview of the main databases available for Task 2 of the study

Database	Summary description
Trialtrove Informa Pharma proprietary clinical trial database	The Trialtrove database is a large database of clinical trial intelligence containing data on over 375,000 clinical trials in over 210 diseases in more than 150 countries. A global team of specialist analysts using information from over 30,000 clinical trial data sources curates the database as a continuously updated reference source for clinical trials research. Information from sources such as company websites, press releases, annual reports and investor presentations, papers in medical journals, and clinical trial registries, goes through a rigorous process of identification, checking, and cleaning before entry into the database by a dedicated analyst team of specialists. The data used in this report allows the tracking of the progress of drugs from Phase 1 to approval. While the dataset nominally ranges 1990-2021, the data thin out considerably in the early and most recent periods; therefore, most analyses focus on the 1998-2020 period. We transform the trial data such that an observation refers to the trial of a specific drug, for a specific indication (drugs may be tested for multiple indications), in a specific year. The resulting dataset tracks the progress of 28,167 drugs in 9 therapy areas of indications through 33,626 different trials. In total, 9,472 drugs were tested in the EU, 15,774 in the USA, and 3,170 in Japan (the sum across regions exceeds the total number of drugs tested, as some drugs were tested in multiple regions for different indications). We track drug development through up to 3 phases of clinical trials. We count a trial as completed successfully if we see the same drug (in the same indication) being trialled in a higher phase at a later point in time. Thus, if we see a drug in a Phase 1 trial in 2002 and in a Phase 2 trial in 2003, we conclude that the Phase 1 trial in 2002 was completed successfully. We count the third and final phase as completed successfully if we see a drug being approved for sale. The

	final dataset contains a total of 13,849 Phase 1 trials, 16,484 Phase 2 trials, and 8,168 Phase 3 trials. Caveats: We observe the geographic location of a trial in the Trialtrove data, which sometimes indicates that a trial took place in multiple locations (e.g., in the EU and the USA jointly). To circumvent this, we added data on a drug's originator (i.e., the original developer) and the respective location from Informa Pharma's Pharmaprojects database. However, for some trials, it remains unclear which jurisdiction a trial should be counted under. We drop some trials that were either i) conducted in multiple geographies, or ii) for which the location of the originator could not be reliably asserted. Combinatorial drug treatments (i.e., trials testing a combination of multiple, different drugs) have been added to the dataset. However, we do not reliably observe when or if combinatorial treatments are approved for marketing. Therefore, we include combinatorial treatments in the analysis of indicators RI-1, RI-2, and RI-3, but we exclude them for RI-4 and RI-6. Data on approval merged from the Pharmaprojects database are only available for around 5,000 drugs, about 2,200 of which could be matched to the analysis dataset. Therefore, the phase progressions in Phase 1 and Phase 2 are not directly comparable to those in Phase 3 and the overall likelihood of approval. However, the overall rate of drugs that end up being approved for marketing is around 10%, which corresponds to experience. The level of data availability in the Trialtrove database is not constant over time. For example, in the figure showing Phase 1 candidate drugs, we see a strong increase in trials over time and close to zero trials in the early 1990s. This is due to the construction of the database and data collection procedures, and is not indicative of a corresponding rise in clinical trials. In the statistical analysis, this is accounted for through the inclusion of year fixed-effects.
Sitetrove Informa Pharma proprietary clinical trial site and investigator database	The Sitetrove database is a large database of clinical trial intelligence containing data on over 510,000 investigators from more than 185,000 clinical trial sites in over 180 countries.

	The database is useful in identifying clinical trial and investigator involvement in the development of drugs, thus complementing Trialtrove in supported detailed county level analysis of clinical trials. The database offers features such as investigator tiering and patient count data, complemented by dynamic and exportable visualizations to aid in data sharing and use.
Pharmaprojects Informa Pharma pharmaceutical product database	The Pharmaprojects database is a large database of pipeline and marketed drug intelligence containing data on over 90,000 drugs in more than 150 countries. A global team of specialist analysts using information on drugs curates the database as a continuously updated reference source for pipeline and marketed drugs. Information from sources such as company websites, press releases, annual reports and investor presentations, papers in medical journals, and clinical trial registries, goes through a rigorous process of identification, checking, and cleaning before entry into the database by a dedicated analyst team of specialists. All drug approval data described in this report are based on the data contained in Pharmaprojects and Biomedtracker as of August 2021. The base dataset for IEC-1-4 contained 4,981 products with a known approval date anywhere in the world. The approval year was set based on first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. The origin of the medical product was set by the HQ country of the originator company as recorded in Pharmaprojects.
Biomedtracker Informa Pharma proprietary pharmaceutical product database	Informa Pharma's Biomedtracker pipeline database provides real time analysis of major market moving events in the pharma and biotech industry, tracking and analysing events in drug development in real time with a US focus. Biomedtracker analysts monitor companies, trials, deals, and regulatory meetings to capture and interpret the most critical events. The database offers features such as likelihood of approval for individual drugs, detailed clinical, regulatory, and partnership event analysis, revenue models, FDA advisory committee insights, analysis of voting patterns of FDA advisory committee

	members, commentary on past meetings, and data on life science company deals including licensing deals and mergers and acquisitions
Datamonitor Healthcare Informa Pharma proprietary pharmaceutical industry database	Detailed company and market specific research and analysis enable expert insight and rapid understanding of complex market dynamics, including forecasts presented as interactive market models. The PharmaVitae module within Datamonitor Healthcare contains detailed company reported data on metrics such as revenues, profits, and R&D spending. Datamonitor Healthcare includes timely, in depth research and expert analysis, with coverage of more than 65 indications. Accurate and objective marketed and pipeline drug sales forecasts and segmented patient-based disease forecasts feature event sensitive analysis and advanced display options. Pipelines are analysed by indication and company, and insights are provided on corporate strategies and trends. Analysis of pricing and reimbursement by indication, plus market access trends and themes are complemented by epidemiology data across all major therapy areas based on expert reviews of the available epidemiological literature to identify the most reliable data sources
Utrecht University MAA database	The Utrecht MAA database provides data on all medicinal products that obtained a centralised marketing authorisation in Europe since the establishment of the European Medicines Agency (EMA) on January 1st 1995 to December 31st 2020. The dataset consists of 1,456 authorised products, of which 317 were approved under Regulation 2309/93 and 1,139 under Regulation 726/2004. For post-marketing data an end-of-follow-up date of December 31st 2020 was used.
EU shortages database dependent on permission from the European Commission	Technopolis has developed a database of reported shortages for the European Commission using shortage datasets received from National Competent Authorities and linked those to IQVIA MIDAS database. It includes over 100,000 reported shortages with 22,500 medicines in shortages identified from 20 European countries over the years of 2007-2021.
IQVIA MIDAS database	Our consortium has intimate familiarity of using the IQVIA dataset through a number of previous studies. The IQVIA

	dataset was made available by the European Commission through a TPA and provided sales volume and revenue data on medicines 2008-2020, for the geographical area Europe and comparator markets.

ANNEX B: LIST OF PRODUCTS IN THE EFPIA-ECIPE REPORT (2020)

Broader Pharmaceutical Category	Pharmaceutical Category	CN Code	Product name
Active Pharmaceutical Ingredients (APIs)	Active Pharmaceutical Ingredients (APIs)	291462	Coenzyme Q10 "ubidecarenone (INN)"
		291469	Quinones (excl. anthraquinone and coenzyme Q10 "ubidecarenone (INN)")
		291639	Aromatic monocarboxylic acids, their anhydrides, halides, peroxides, peroxyacids and their halogenated, sulphonated, nitrated or nitrosated derivatives (excl. benzoic acid, its salts and esters, benzoyl peroxide, benzoyl chloride, phenylacetic acid and its salts, and inorganic or organic compounds of mercury whether or not chemically defined)
		291821	Salicylic acid and its salts (excl. inorganic or organic compounds of mercury)
		291822	o-Acetylsalicylic acid, its salts and esters
		291823	Esters of salicylic acid and their salts (excl. o-acetylsalicylic acid, its salts and esters)
		291899	Carboxylic acids with additional oxygen function and their anhydrides, halides, peroxides and peroxyacids; their halogenated, sulphonated, nitrated or nitrosated derivatives (excl. only with alcohol, phenol, aldehyde or ketone function, and 2,4,5-T (ISO) [2,4,5-trichlorophenoxyacetic acid] and its salts and esters)
		292146	Amfetamine (INN), benzfetamine (INN), dexamfetamine (INN), etilamfetamine (INN), fencamfamine (INN), lefetamine (INN), levamfetamine (INN), mefenorex (INN) and phentermine (INN), and salts thereof
		292149	Aromatic monoamines and derivatives; salts thereof (excl. aniline, toluidines, diphenylamine, 1-naphthylamine "alpha-naphthylamine", 2-naphthylamine "beta-naphthylamine" and their derivatives, and salts thereof, and amfetamine (INN), benzfetamine (INN), dexamfetamine (INN), etilamfetamine (INN), fencamfamine (INN), lefetamine (INN), levamfetamine (INN), mefenorex (INN) and phentermine (INN), and salts thereof)
		292214	Dextropropoxyphene (INN) and its salts
		292219	Amino-alcohols, their ethers and esters; salts thereof (other than those containing > one kind of oxygen function and excl. monoethanolamine, diethanolamine, dextropropoxyphene (INN), their salts, triethanolamine, diethanolammonium perfluorooctane sulphonate, methyldiethanolamine, ethyldiethanolamine and 2-(N,N-Diisopropylamino)ethanol)
		292229	Amino-naphthols and other amino-phenols, their ethers and esters; salts thereof (excl. those containing > one kind of oxygen function; aminohydroxynaphthalenesulphonic acids and their salts)
		292231	Amfepramone (INN), methadone (INN) and normethadone (INN), and salts thereof
		292241	Lysine and its esters; salts thereof
		292244	Tilidine (INN) and its salts
		292249	Amino-acids and their esters; salts thereof (excl. those with > one kind of oxygen function, lysine and its esters, and salts thereof, and glutamic acid, anthranilic acid, tilidine (INN), and salts thereof)
		292250	Amino-alcohol-phenols, amino-acid-phenols and other amino-compounds with oxygen function (excl. amino-alcohols, amino-naphthols and other amino-phenols, their ethers and esters and salts

			thereof, amino-aldehydes, amino-ketones and amino-quinones, and salts thereof, amino-acids and their esters and salts thereof)
		292320	Lecithins and other phosphoaminolipids, whether or not chemically defined
		292411	Meprobamate (INN)
		292424	Ethinamate (INN)
		292429	Cyclic amides, incl. cyclic carbamates, and their derivatives; salts thereof (excl. ureines and their derivatives, salts thereof, 2-acetamidobenzoic acid "N-acetylanthranilic acid" and its salts, ethinamate (INN) and alachlor (ISO))
		292512	Glutethimide (INN)
		292529	Imines and their derivatives; salts thereof (excl. chlordimeform (ISO))
		292630	Fenproporex (INN) and its salts; methadone (INN)-intermediate "4-cyano-2-dimethylamino-4,4-diphenylbutane"
		293190	Separate chemically defined organo-inorganic compounds (excl. organo-sulphur, mercury, tetramethyl lead, tetraethyl lead and tributyltin compounds, and organo-phosphorous derivatives)
		293220	Lactones
		293311	Phenazone "antipyrin" and its derivatives
		293319	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused pyrazole ring, whether or not hydrogenated, in the structure (excl. phenazone "antipyrin" and its derivatives)
		293321	Hydantoin and its derivatives
		293329	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused imidazole ring, whether or not hydrogenated, in the structure (excl. hydantoin and its derivatives, and products of subheading 3002 10)
		293331	Pyridine and its salts
		293332	Piperidine and its salts
		293333	Alfentanil (INN), anileridine (INN), bezitramide (INN), bromazepam (INN), difenoxin (INN), diphenoxylate (INN), dipipanone (INN), fentanyl (INN), ketobemidone (INN), methylphenidate (INN), pentazocine (INN), pethidine (INN), pethidine (INN) intermediate A, phencyclidine (INN) "PCP", phenoperidine (INN), pipradol (INN), piritramide (INN), propiram (INN) and trimeperidine (INN), and salts thereof
		293339	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused pyridine ring, whether or not hydrogenated, in the structure (excl. pyridine, piperidine, alfentanil (INN), anileridine (INN), bezitramide (INN), bromazepam (INN), difenoxin (INN), diphenoxylate (INN), dipipanone (INN), fentanyl (INN), ketobemidone (INN), methylphenidate (INN), pentazocine (INN), pethidine (INN), pethidine (INN) intermediate A, phencyclidine (INN) "PCP", phenoperidine (INN), pipradol (INN), piritramide (INN), propiram (INN), trimeperidine (INN), and salts thereof, and inorganic or organic compounds of mercury)
		293341	Levorphanol (INN) and its salts
		293349	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing in the structure a quinoline or isoquinoline ring-system, whether or not hydrogenated, but not further fused (excl. levorphanol (INN) and its salts, and inorganic or organic compounds of mercury)

		293352	Malonylurea "barbituric acid" and its salts
		293353	Allobarbital (INN), amobarbital (INN), barbital (INN), butalbital (INN), butobarbital (INN), cyclobarbital (INN), methylphenobarbital (INN), pentobarbital (INN), phenobarbital (INN), secbutabarbital (INN), secobarbital (INN) and vinylbital (INN), and salts thereof
		293354	Derivatives of malonylurea "barbituric acid" and salts thereof (excl. salts of malonylurea)
		293355	Loprazolam (INN), mecloqualone (INN), methaqualone (INN) and zipeprol (INN), and salts thereof
		293359	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing a pyrimidine ring, whether or not hydrogenated, or piperazine ring in the structure (excl. malonylurea "barbituric acid" and its derivatives, allobarbital (INN), amobarbital (INN), barbital (INN), butalbital (INN), butobarbital (INN), cyclobarbital (INN), methylphenobarbital (INN), pentobarbital (INN), phenobarbital (INN), secbutabarbital (INN), secobarbital (INN), vinylbital (INN), loprazolam (INN), mecloqualone (INN), methaqualone (INN) and zipeprol (INN), and salts thereof)
		293369	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused triazine ring, whether or not hydrogenated, in the structure (excl. melamine)
		293371	6-Hexanelactam "epsilon-caprolactam"
		293372	Clobazam (INN) and methyprylon (INN)
		293379	Lactams (excl. 6-hexanelactam "epsilon-caprolactam", clobazam (INN), methyprylon (INN), and inorganic or organic compounds of mercury)
		293391	Alprazolam (INN), camazepam (INN), chlordiazepoxide (INN), clonazepam (INN), clorazepate, delorazepam (INN), diazepam (INN), estazolam (INN), ethyl loflazepate (INN), fludiazepam (INN), flunitrazepam (INN), flurazepam (INN), halazepam (INN), lorazepam (INN), lormetazepam (INN), mazindol (INN), medazepam (INN), midazolam (INN), nimetazepam (INN), nitrazepam (INN), nordazepam (INN), oxazepam (INN), pinazepam (INN), prazepam (INN), pyrovalerone (INN), temazepam (INN), tetrazepam (INN) and triazolam (INN), and salts thereof
		293399	Heterocyclic compounds with nitrogen hetero-atom[s] only (excl. those containing an unfused pyrazole, imidazole, pyridine or triazine ring, whether or not hydrogenated, a quinoline or isoquinoline ring-system, not further fused, whether or not hydrogenated, a pyrimidine ring, whether or not hydrogenated, or piperazine ring in the structure, and lactams, alprazolam (INN), camazepam (INN), chlordiazepoxide (INN), clonazepam (INN), clorazepate, delorazepam (INN), diazepam (INN), estazolam (INN), ethyl loflazepate (INN), fludiazepam (INN), flunitrazepam (INN), flurazepam (INN), halazepam (INN), lorazepam (INN), lormetazepam (INN), mazindol (INN), medazepam (INN), midazolam (INN), nimetazepam (INN), nitrazepam (INN), nordazepam (INN), oxazepam (INN), pinazepam (INN), prazepam (INN), pyrovalerone (INN), temazepam (INN), tetrazepam (INN) and triazolam (INN), salts thereof and azinphos-methyl (ISO))
		293410	Heterocyclic compounds containing an unfused thiazole ring, whether or not hydrogenated, in the structure
		293420	Heterocyclic compounds containing in the structure a benzothiazole ring-system, whether or not hydrogenated, but not further fused (excl. inorganic or organic compounds of mercury)
		293430	Heterocyclic compounds containing in the structure a phenothiazine ring-system, whether or not hydrogenated, but not further fused

		293491	Aminorex (INN), brotizolam (INN), clotiazepam (INN), cloxazolam (INN), dextromoramide (INN), haloxazolam (INN), ketazolam (INN), mesocarb (INN), oxazolam (INN), pemoline (INN), phendimetrazine (INN), phenmetrazine (INN) and sufentanil (INN), and salts thereof
		293499	Nucleic acids and their salts, whether or not chemically defined; heterocyclic compounds (excl. with oxygen only or with nitrogen hetero-atom[s] only, compounds containing in the structure an unfused thiazole ring or a benzothiazole or phenothiazine ring-system, not further fused and aminorex (INN), brotizolam (INN), clotiazepam (INN), cloxazolam (INN), dextromoramide (INN), haloxazolam (INN), ketazolam (INN), mesocarb (INN), oxazolam (INN), pemoline (INN), phendimetrazine (INN), phenmetrazine (INN), sufentanil (INN), and salts thereof, and inorganic or organic compounds of mercury whether or not chemically defined, and products of 3002 10)
		293590	Sulphonamides (excl. perfluorooctane sulphonamides)
		293621	Vitamins A and their derivatives, used primarily as vitamins
		293622	Vitamin B1 and its derivatives, used primarily as vitamins
		293623	Vitamin B2 and its derivatives, used primarily as vitamins
		293624	D-Pantothenic or DL-pantothenic acid "Vitamin B3 or B5" and their derivatives, used primarily as vitamins
		293625	Vitamin B6 and its derivatives, used primarily as vitamins
		293626	Vitamin B12 and its derivatives, used primarily as vitamins
		293627	Vitamin C and its derivatives, used primarily as vitamins
		293628	Vitamin E and its derivatives, used primarily as vitamins
		293629	Vitamins and their derivatives, used primarily as vitamins, unmixed (excl. vitamins A, B1, B2, B3, B5, B6, B12, C, E and their derivatives)
		293690	Provitamins and mixtures of vitamins, of provitamins or of concentrates, whether or not in any solvent, and natural concentrates
		293711	Somatropin, its derivatives and structural analogues, used primarily as hormones
		293712	Insulin and its salts, used primarily as hormones
		293719	Polypeptide hormones, protein hormones and glycoprotein hormones, their derivatives and structural analogues, used primarily as hormones (excl. somatropin, its derivatives and structural analogues, and insulin and its salts)
		293721	Cortisone, hydrocortisone, prednisone "dehydrocortisone" and prednisolone "dehydrohydrocortisone"
		293722	Halogenated derivatives of corticosteroidal hormones
		293723	Oestrogens and progestogens
		293729	Steroidal hormones, their derivatives and structural analogues, used primarily as hormones (excl. cortisone, hydrocortisone, prednisone "dehydrocortisone", prednisolone "dehydrohydrocortisone", halogenated derivatives of corticosteroidal hormones, oestrogens and progestogens)
		293750	Prostaglandins, thromboxanes and leukotrienes, their derivatives and structural analogues, used primarily as hormones
		293790	Hormones, natural or reproduced by synthesis; derivatives and structural analogues thereof, used primarily as hormones (excl. polypeptide hormones, protein hormones, glycoprotein hormones, steroidal hormones, catecholamine hormones, prostaglandins,

			thromboxanes and leukotrienes, their derivatives and structural analogues, and amino-acid derivatives, and products of 3002 10)
		293810	Rutoside "rutin" and its derivatives
		293890	Glycosides, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives (excl. rutoside "rutin" and its derivatives)
		293911	Concentrates of poppy straw; buprenorphine (INN), codeine, dihydrocodeine (INN), ethylmorphine, etorphine (INN), heroin, hydrocodone (INN), hydromorphone (INN), morphine, nicomorphine (INN), oxycodone (INN), oxymorphone (INN), pholcodine (INN), thebacon (INN) and thebaine, and salts thereof
		293919	Alkaloids of opium and their derivatives, and salts thereof (excl. concentrates of poppy straw; buprenorphine (INN), codeine, dihydrocodeine (INN), ethylmorphine, etorphine (INN), heroin, hydrocodone (INN), hydromorphone (INN), morphine, nicomorphine (INN), oxycodone (INN), oxymorphone (INN), pholcodine (INN), thebacon (INN) and thebaine, and salts thereof)
		293920	Alkaloids of cinchona and their derivatives; salts thereof
		293930	Caffeine and its salts
		293941	Ephedrine and its salts
		293942	Pseudoephedrine (INN) and its salts
		293943	Cathine (INN) and its salts
		293944	Norephedrine and its salts
		293949	Ephedrines and their salts (excl. ephedrine, pseudoephedrine (INN), cathine (INN), norephedrine, and their salts)
		293951	Fenetylline (INN) and its salts
		293959	Theophylline and aminophylline "theophylline-ethylenediamine" and their derivatives, and salts thereof (excl. fenetylline (INN) and its salts)
		293961	Ergometrine (INN) and its salts
		293962	Ergotamine (INN) and its salts
		293963	Lysergic acid and its salts
		293969	Alkaloids of rye ergot and their derivatives; salts thereof (excl. lysergic acid, ergotamine and ergometrine, and their salts)
		293971	Cocaine, ecgonine, levometamfetamine, metamfetamine (INN), metamfetamine racemate, and salts, esters and other derivatives thereof
		293979	Vegetal alkaloids, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives (excl. alkaloids of opium, alkaloids of cinchons, theophylline, aminophylline "theophylline-ethylenediamine" alkaloids of rye ergot and their salts and derivatives, cocaine, ecgonine, levometamfetamine, metamfetamine (INN), metamfetamine racemate, and salts, esters and other derivatives thereof, caffeine and ephedrines, and their salts)
		293980	Non-vegetal alkaloids, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives
		294200	Separate chemically defined organic compounds, n.e.s.

		300190	Dried glands and other organs for organo-therapeutic uses, whether or not powdered; heparin and its salts; other human or animal substances prepared for therapeutic or prophylactic uses, n.e.s.
		300213	Immunological products, unmixed, not put up in measured doses or in forms or packings for retail sale
	Antibiotics APIs	294110	Penicillins and their derivatives with a penicillanic acid structure; salts thereof
		294120	Streptomycins and their derivatives; salts thereof
		294130	Tetracyclines and their derivatives; salts thereof
		294140	Chloramphenicol and its derivatives; salts thereof
		294150	Erythromycin and its derivatives; salts thereof
		294190	Antibiotics (excl. penicillins and their derivatives with a penicillanic acid structure, salts thereof, streptomycins, tetracyclines, chloramphenicol and erythromycin, their derivatives and salts thereof)
Semi Finished Products (SFPs)	Semi Finished Products (SFPs)	300214	Immunological products, mixed, not put up in measured doses or in forms or packings for retail sale
		300310	Medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof, not in measured doses or put up for retail sale
		300320	Medicaments containing antibiotics, not in measured doses or put up for retail sale (excl. medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof)
		300331	Medicaments containing insulin, not in measured doses or put up for retail sale
		300339	Medicaments containing hormones or steroids used as hormones, not containing antibiotics, not in measured doses or put up for retail sale (excl. those containing insulin)
		300341	Medicaments containing ephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300342	Medicaments containing pseudoephedrine (INN) or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300343	Medicaments containing norephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300349	Medicaments containing alkaloids or derivatives thereof, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale (excl. containing ephedrine, pseudoephedrine (INN), norephedrine or their salts)
		300360	Medicaments containing any of the following antimalarial active principles: artemisinin (INN) for oral ingestion combined with other pharmaceutical active ingredients, or amodiaquine (INN); artelinic acid or its salts; artenimol (INN); artemotil (INN); artemether (INN); artesunate (INN); chloroquine (INN); dihydroartemisinin (INN); lumefantrine (INN); mefloquine (INN); piperaquine (INN); pyrimethamine (INN) or sulfadoxine (INN), not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300390	Medicaments consisting of two or more constituents mixed together for therapeutic or prophylactic uses, not in measured doses or put up for retail sale (excl. antibiotics containing hormones or steroids used as hormones, but not containing antibiotics, alkaloids or derivatives thereof, hormones, antibiotics, antimalarial active principles or goods of heading 3002, 3005 or 3006)

Human Medicinal Products (HMPs)	Finished Pharmaceutical Products (FPPs)	300215	Immunological products, put up in measured doses or in forms or packings for retail sale
		300431	Medicaments containing insulin but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300432	Medicaments containing corticosteroid hormones, their derivatives or structural analogues but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300439	Medicaments containing hormones or steroids used as hormones but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. medicaments containing insulin or corticosteroid hormones, their derivatives or structural analogues)
		300441	Medicaments containing ephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300442	Medicaments containing pseudoephedrine (INN) or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300443	Medicaments containing norephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300449	Medicaments containing alkaloids or derivatives thereof, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing ephedrine, pseudoephedrine (INN), norephedrine or their salts)
		300450	Medicaments containing provitamins, vitamins, incl. natural concentrates and derivatives thereof used primarily as vitamins, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones, alkaloids, or their derivatives)
		300460	Medicaments containing any of the following antimalarial active principles: artemisinin (INN) for oral ingestion combined with other pharmaceutical active ingredients, or amodiaquine (INN); artelinic acid or its salts; artenimol (INN); artemotil (INN); artemether (INN); artesunate (INN); chloroquine (INN); dihydroartemisinin (INN); lumefantrine (INN); mefloquine (INN); piperaquine (INN); pyrimethamine (INN) or sulfadoxine (INN), put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones, alkaloids, provitamins, vitamins, or their derivatives)
		300490	Medicaments consisting of mixed or unmixed products for therapeutic or prophylactic purposes, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones or steroids used as hormones, alkaloids, provitamins, vitamins, their derivatives or antimalarial active principles)
	Antibiotics Finished Pharmaceutical Products (FPPs)	300410	Medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300420	Medicaments containing antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. medicaments containing penicillins or derivatives thereof with a penicillanic structure, or streptomycines or derivatives thereof)

	Vaccines	300220	Vaccines for human medicine

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