Output current R&D ecosystem

Analysis of pharmaceutical market introductions since 1995

January 2023

SiRM. Strategies in Regulated Markets

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1 Study objective and conclusions

1.1 Background

In June 2022, the Dutch minister of Health, Welfare and Sports ('VWS') submitted the report *The Financial Ecosystem of Pharmaceutical R&D*[1] to the House of Representatives of the Netherlands. This report describes how the current financial ecosystem of drug research and development (R&D) operates, and concludes that a drug's expected financial return ultimately determines whether it is developed, not the expected societal impact. VWS is now considering whether better prioritisation of societally relevant drugs is possible given the current financial ecosystem.

As a first follow-up to the report, VWS wants to know for which conditions the current ecosystem produces many or few new drugs. This information can then form the starting point for follow-up research into the largest 'pharmaceutical gaps' in the Netherlands.

1.2 Research questions and methods

In this context, the Department of Pharmaceutical Affairs and Medical Technology ('GMT') of VWS has asked consultancy and research firm SiRM – Strategies in Regulated Markets – to draw up an overview of drugs that the current R&D ecosystem produces, focusing on conditions with major societal impact in terms of the total burden of disease. GMT asked SiRM the following specific research questions:

- Which drugs for which conditions with high burden of disease have been newly registered in the Netherlands between 1995-2021? Differentiate between European Medicines Agency (EMA) approval and presence/absence on the Dutch market.[2]
- Which drugs for which conditions with high burden of disease are listed on the current edition of the Dutch Horizon Scan?[3]

Breaking down innovation to specific patient groups, such as paediatric use, was beyond the scope of this study. GMT asked SiRM to provide the overview as spreadsheets accompanied by a short report.

To answer these questions, we used the following methods:

- **Identifying relevant conditions with the highest annual total burden of disease.** We started by identifying forty conditions with the highest annual total burden of disease in the Netherlands, measured in terms of disability-adjusted life years (DALYs). The total burden of disease is the burden of disease per patient multiplied by the number of patients in the Netherlands. We then solely included conditions for which medication is (or could be) an

[1] https://www.sirm.nl/en/publications/the-financial-ecosystem-of-pharmaceutical-r-d
[2] Before drugs are accessible to patients, they need to undergo registration and market authorisation by the EMA. Afterwards, drugs may or may not be introduced to a national market and may or may not be reimbursed by health insurance.
[3] The Dutch Horizon Scan aims to provide an overview of future new drugs and indication extensions. It is published at https://www.horizonscangeneesmiddelen.nl/

important part of treatment. Additionally, we included conditions listed as a 'key pharmaceutical gap' by the WHO.[4] This resulted in a total of 33 conditions for our study (Table 1).

- **Mapping developed drugs for the included conditions.** Based on European Public Health Assessment Reports (EPARs)[5] by the EMA, we examined which drugs (brand names) have been authorised on the European market for each included condition since 1995. We linked the conditions to therapeutic area information of the EPARs. We also linked this information to two Dutch drug claims databases[6] to analyse which of these drugs were prescribed in the Netherlands between 2019-2021.
- **Assessing which drugs may be introduced to the market in the coming years.** Based on the Dutch Horizon Scan of the National Health Care Institute ('Zorginstituut Nederland'), we assessed which drugs may be introduced to the market in the coming years for each included condition.

During the preparation of this report, we were supported by a group of three Dutch pharmacists (two hospital pharmacists and one community pharmacist) who provided us with feedback in their personal capacity. Appendix 1 contains a more detailed description of our methodology.

Table 1. We included 33 conditions in this study.

Included conditions in alphabetical order		
Anxiety disorders	Diabetes mellitus	Multiple sclerosis
Arthrosis	Eye disorders	Non-Hodgkin lymphoma
Asthma	Hearing disorders	Oesophageal cancer
Brain cancer	Heart failure	Pancreatic cancer
Breast cancer	HIV infections	Parkinson's disease
Cardiac arrhythmias	Hypertension	Prostate cancer
Colon cancer	Leukaemia	Rheumatoid arthritis
Contact eczema	Lower respiratory infections	Schizophrenia
COPD	Lung cancer	Skin cancer
Coronary heart disease	Mood disorders	Stroke
Dementia	Multiple myeloma	Upper respiratory infections

[4] World Health Organization (2004), Priority medicines for Europe and the world.
[5] https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
[6] The GIPdatabank (https://www.gipdatabank.nl/, published by the National Health Care Institute) and SFK (https://www.sfk.nl/, a foundation created by the Dutch national association of pharmacists).

1.3 Conclusions

Analysing the EMA brand name registrations for the 33 included conditions we observe different patterns of development:

- A quarter of the conditions have seen continuous drug development since 1995.
- Thirty percent of the conditions show a more erratic pattern: a clear increase in the last decade preceded by limited development.
- Fifteen percent have seen little or no development in the past decade after a period of greater development.
- For about thirty percent of the conditions there has been little to no drug development. This can be caused by various reasons, such as the lack of clear pharmacological targets or the existence of other (non-pharmacological) treatment options.

There are also different degrees of innovativeness within all registered pharmaceutical brand names. For approximately 20% of substance names, multiple brand names have been registered for the same condition and treatment setting. For example, the 75 registered brand names for diabetes mellitus are based on 45 unique active substances.[7]

Almost 95% of all drugs developed for the included conditions are accessible to Dutch insurees, most often under the same brand name but also regularly under a different brand name. About five percent of drugs are not on the market in the Netherlands.

[7] Drugs regularly consist of combinations of several active substances. For clarity of writing, in this report we always use the singular form when referring to 'active substance.'

2 EMA brand name registrations

A total of 464 pharmaceutical brand names have been registered with the EMA since 1995 for the 33 included conditions. The Dutch Horizon Scan contains an additional 126 brand names for these conditions that may be introduced to the market between 2022 and 2024. Not all these 126 brand names will reach the market because ongoing clinical studies may still show disappointing results.

In this chapter, we first elaborate on the different patterns of drug development for the included conditions based on EMA registrations and the Horizon Scan (§2.1). We then discuss varying degrees of innovativeness of the developed drugs (§2.2). Appendix 2 contains a complete overview of the (expected) brand name registrations for each included condition.

2.1 Different patterns of drug development

Over the past 25 years, the 33 included conditions show different patterns of drug development. Broadly speaking, we identified four patterns, which we describe in this paragraph.

2.1.1 Continuous development

Almost a quarter of included conditions show a pattern of continuous drug development since 1995, as illustrated in Figure 1 for five conditions with 10 or more new brand names since 1995. Not all registered new brand names are the result of the development of new active substances. We will explain this further in §2.2.

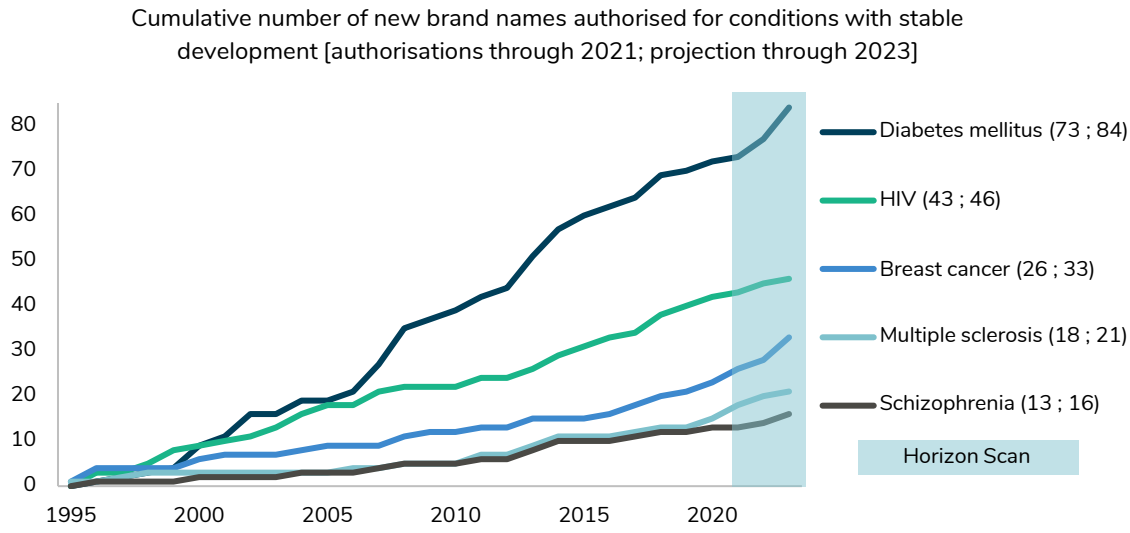

Figure 1. Diabetes mellitus, HIV, breast cancer, multiple sclerosis and schizophrenia have seen continuous drug development since 1995.

In addition, new brand names are listed in the Dutch Horizon Scan for these conditions, especially for diabetes mellitus and breast cancer. The actual number of new brand names introduced in the

coming years is likely to be lower, however, since not all of these items will be introduced to the market.

2.1.2 Upturn after limited development

About thirty percent of included conditions show an increase in the number of drugs developed after a period of more limited development. Examples include lung cancer, leukaemia, COPD and multiple myeloma (Figure 2). The growth in new drugs for lung cancer, leukaemia and multiple myeloma is expected to continue over the next two years, but this is not the case for COPD.

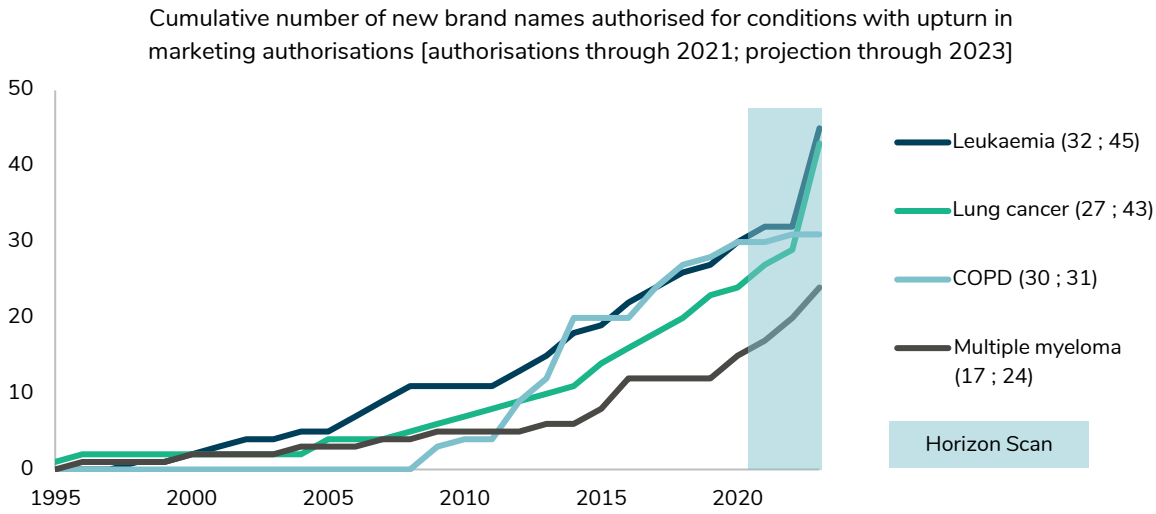

Figure 2. After a period with little innovation lung cancer, leukaemia, COPD and multiple myeloma have seen an upturn in EMA registrations.

2.1.3 Stagnant development

For approximately 15% of the included conditions, we see stagnation after a period of greater development. For example, for hypertension and coronary heart disease hardly any new brand names have been registered since 2011 (Figure 3). The same pattern exists for dementia and mood disorders since 2015.

No new brand names are expected for hypertension, coronary heart disease and dementia in the next two years. Based on the Dutch Horizon Scan, new brand names are expected for mood disorders, although it is likely that not all of these expected brand names will be introduced to the market.

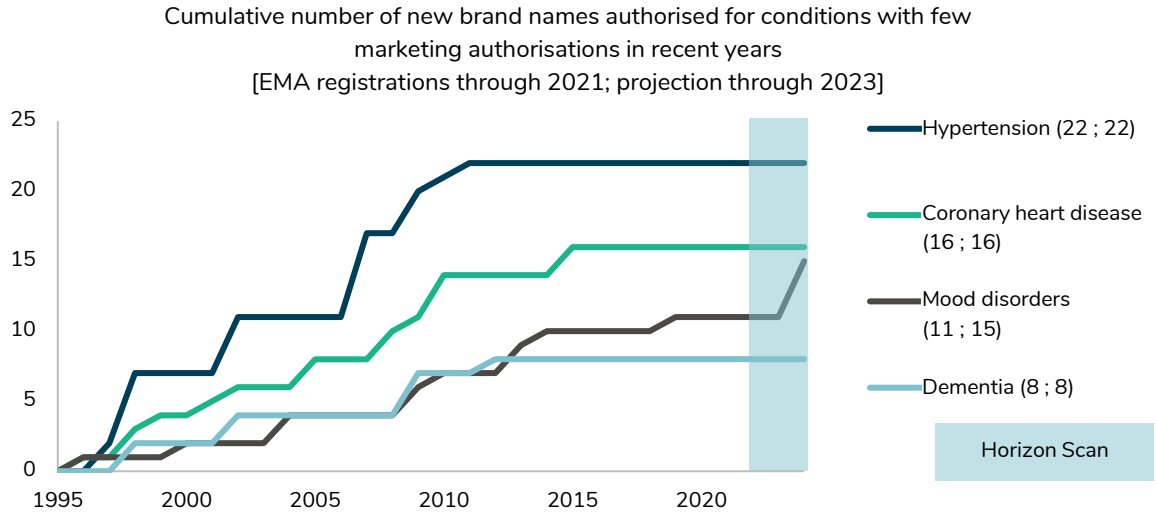

Figure 3. Few new drugs have been registered with the EMA since 2011/2012 and 2015 respectively for hypertension, coronary heart disease, mood disorders and dementia.

2.1.4 Limited development

About thirty percent of included conditions have shown limited development since 1995. Six or fewer new brand names have appeared for these conditions since 1995:

- Heart failure (6)
- Stroke (5)
- Cardiac arrhythmias (5)
- Anxiety disorders (2)
- Upper respiratory infections (2)
- Arthrosis (1)
- Brain cancer (1)
- Oesophageal cancer (1)
- Contact eczema (0)
- Hearing disorders (0)

This limited development can be the result of a variety of reasons, such as a lack of clear pharmacological targets or the existence of other (non-pharmacological) treatment options. For oesophageal cancer and brain cancer, the Horizon Scan contains three and two items respectively. New brand names may therefore be introduced for these two conditions in the period up to and including 2023.

2.2 Varying degrees of innovativeness

The brand names registered with the EMA differ in degree of innovativeness. A new brand name based on a new active substance is considered more innovative than a new brand name based on an existing one. New active substances for a condition for which there are no current pharmacological options are more innovative than new active substances for a condition for which pharmacological treatment is already available. Novel methods of administration can also reflect innovativeness.

The brand names registered with the EMA regularly overlap in active substance. For example, there are five brand names registered for the classic TNF-α inhibitor infliximab. These five brand names have the same active substance and ATC code. Infliximab was first registered with the EMA in 1999. The other four items are what are known as branded generics and were registered between 2013 and 2018 after the original patent on infliximab expired.

Within the included conditions, the number of brand names differs per (combination of) active substance(s). Figure 4 illustrates this for the six conditions with the most market authorisations since 1995. Seventy-five brand names have been registered for diabetes mellitus, based on 'only' 49 unique active substances. For COPD there are 31 brand names, 19 of which are unique active substances. In contrast, almost all brand names introduced for HIV, leukaemia and lung cancer are based on unique active substances.

Number of new brand names (solid lines) and new unique substance names (dotted lines) for the six conditions with the most marketing authorisations since 1995

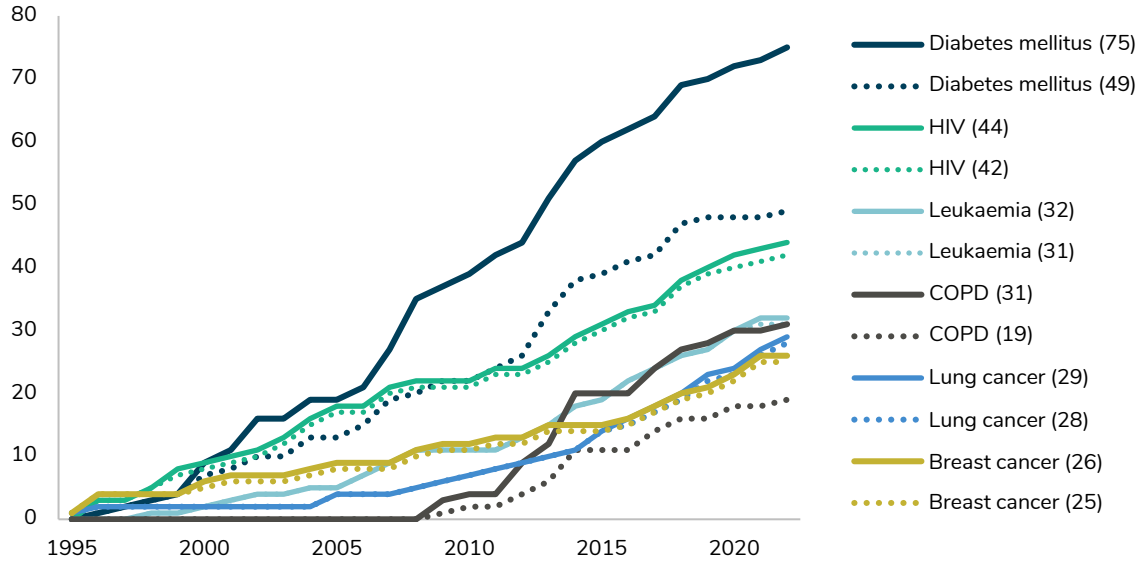

Figure 4. For diabetes mellitus there have been 75 registered brand names, consisting of 'only' 49 unique active substances. For COPD there are 31 brand names and 19 unique active substances. For the other four conditions with >25 registrations since 1995, the number of brand names almost corresponds to the number of active substances introduced.

More than 40% of the 75 authorised brand names for diabetes mellitus are different brand names for the same active substance (Figure 5). The registrations for various forms of insulin represent 28% of these brand names.

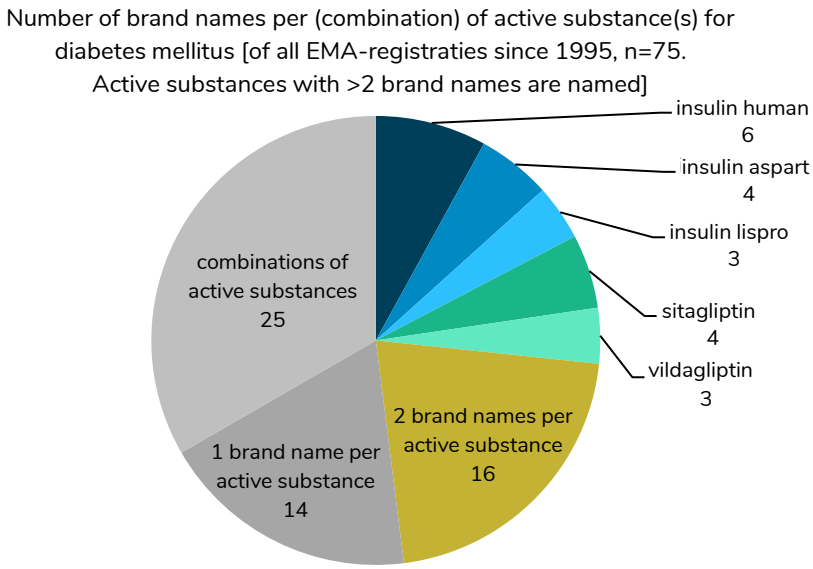

Figure 5. More than 40% of the 75 authorised brand names for diabetes mellitus are different brand names for the same active substances.

For COPD there are also many different brand names for the same active substances. For this condition, 65% of all EMA registrations concern different brand names for the same active substances, see Figure 6. There are four (combinations of) active substances that have three registered brand names each.

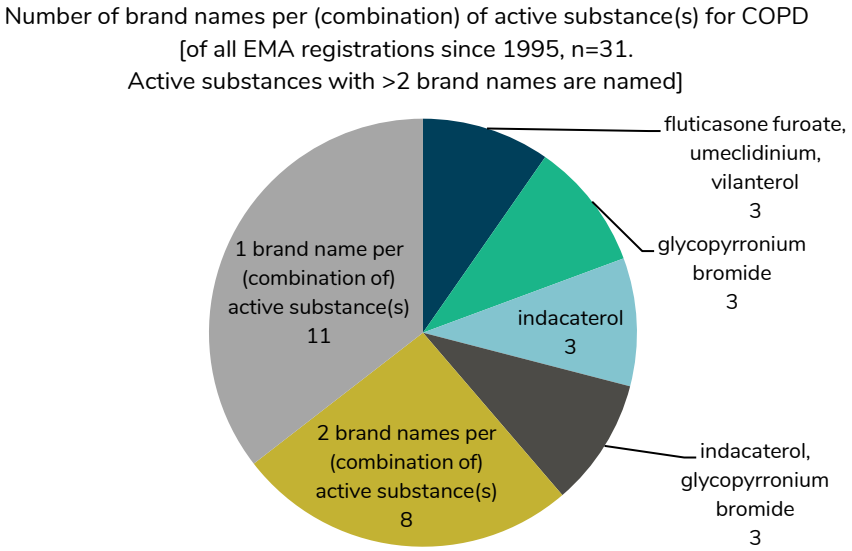

Figure 6. For COPD, 65% of EMA registrations are different brand names for the same active substances.

Whether a new brand name also concerns a new active substance is an indication of innovativeness. Another determinant of the innovativeness of a new brand name is whether it is considered substitutable with an existing drug. In the Netherlands, this factor of innovativeness forms the basis of the Medicines Reimbursement System ('GVS'), the closed reimbursement system for drugs used outside of the hospital. The GVS has different annexes for drugs that are or are not mutually substitutable with others, respectively. GVS annex 1A lists drugs in different groups of mutual substitutability. These groups comprise drugs that can be used in a similar

therapeutic area, with a comparable mode of administration and within comparable patients.[8] Drugs on annex 1A have a reimbursement limit. Therefore, if the price of the drug is above this limit, a co-payment is required. This incentivises care providers and patients to use cost-effective drugs. Annex 1B lists so-called unique drugs which are considered to lack a substitute. The costs of these drugs are always fully reimbursed by health insurers.

Of the four included conditions with the largest number of out-of-hospital health insurance claims, diabetes mellitus has the largest share – more than 90% – of drugs listed on appendix 1A (Figure 7). For COPD, this share is only 63%.

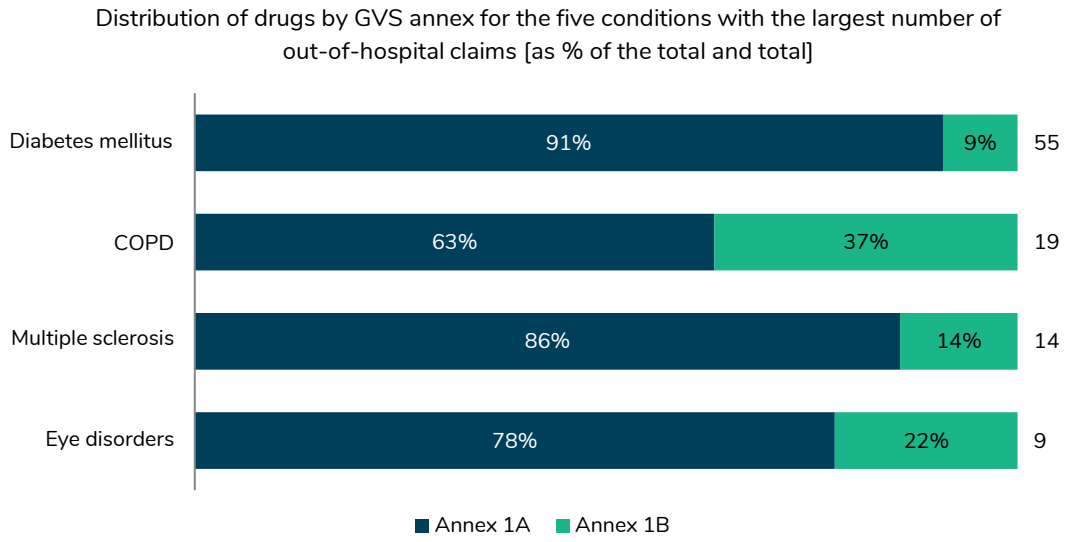

Figure 7. For COPD almost 40% of drugs are not considered substitutable, in diabetes mellitus this is only slightly less than 10%.

Incidentally, there are also exceptions which lead to mutually substitutable drugs being placed on annex 1B. For example, since 2000, HIV has been considered an exception in the GVS by Dutch ministerial regulation whereby all drugs treating HIV are automatically placed on annex 1B. This precludes out-of-pocket payments by patients for this medication with the aim of promoting therapy adherence and preventing resistance development.

[8] Explained further (in Dutch) on the website of the National Health Care Institute: https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/vergoeding-van-extramurale-geneesmiddelen-gvs

3 Accessibility of EMA registered drugs in the Netherlands

Almost 95% of the 464 brand names registered with the EMA for the 33 included conditions since 1995, are accessible to Dutch insurees or are expected to be so in the near future (Figure 8).

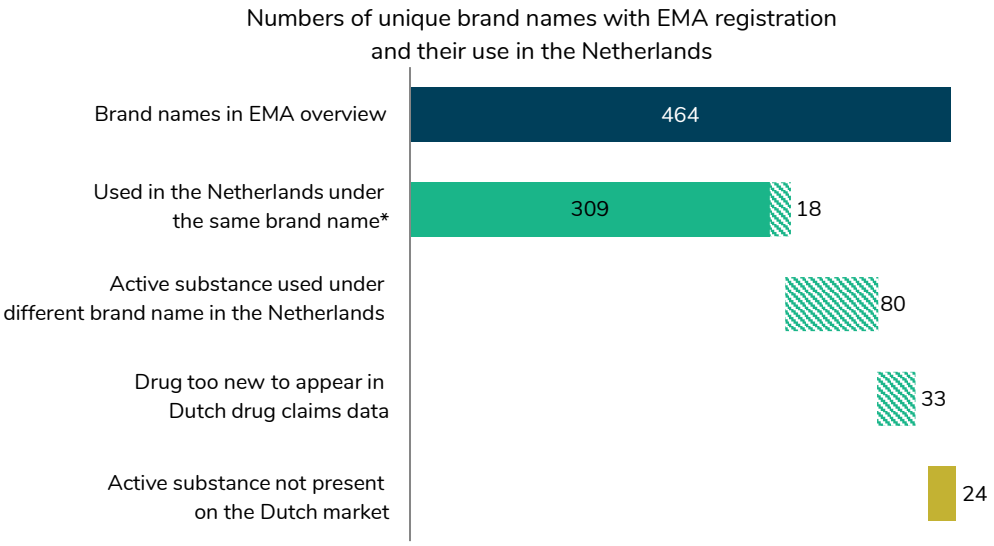

Figure 8. Almost 95% of developed drugs are accessible in the Netherlands. *The shaded part comprises of drugs that do appear in the Dutch drug registry, but not in the drug claims data.

Almost 95% of EMA registered drugs are used under the same or a different brand name in the Netherlands – either now or expected to be soon:

- 327 drugs (70%) are used under the same brand name in the Netherlands. This also includes drugs that do not appear in the Dutch drug claims data[9] that we accessed but are included in the Dutch registry of accessible drugs[10] and are reimbursed (18). Because of the way Dutch hospital care expenses are billed, these may be inexpensive drugs that are only used in-hospital, or they simply are not used. Together, these groups make up approximately 70% of all brand names.
- For 80 brand names (17%), the same active substance is used under a different brand name in the Netherlands. In some cases, pharmaceutical companies adjust their brand names per market, for example per European market segment. In addition, companies may not market some brands in the Netherlands, because they are deemed to have little chance of commercial success if another brand already has a strong market position.
- 33 brand names (7%) have been introduced too recently to appear in the drug claims data we accessed. We analysed claims data from 2019 to 2021, which means that brand names introduced in 2022 are not yet available. In addition, claims data of expensive in-hospital

[9] The GIPdatabank, https://www.gipdatabank.nl/
[10] The Farmacotherapeutisch Kompas, https://www.farmacotherapeutischkompas.nl/

drugs[11] are often recorded with some delay, which leads to potentially still incomplete data in 2021.

There are 24 brand names, 5% of the total, which, as far as we could assess, are not accessible in the Netherlands because the active substance is not marketed in the Netherlands. In this study, we do not distinguish between drugs that have been withdrawn from or have never been introduced to the Dutch market. The main reasons for pharmaceutical companies to refrain marketing of drugs on the Dutch market are:

- There are other drugs to treat the condition on the market with the same mechanism of action. The (expected) sales may therefore be too low. An example of this is the DPP-4 inhibitor alogliptin. This diabetes mellitus drug is not present on the Dutch market, but four other DPP-4 inhibitors are.
- The drugs have been assessed by the Dutch National Health Care Institute as being of insufficient added therapeutic value. This causes the use of these drugs to not be reimbursed, which could also make expected sales too low.[12]
- The drugs are not (or no longer) available in the Netherlands for other economic reasons. Possible considerations in this regard are that the Dutch market is perceived to be too small and/or that pharmaceutical prices are perceived as too low in the Netherlands.

It is also possible that some of the drugs that are not present in the Dutch market will still be used in exceptional cases. In that case, they must be imported from abroad after approval from the Dutch Health Care Inspection ('IGJ'). This happens when conditions that are rare in the Netherlands require specific drugs that are otherwise absent.

[11] Called 'add-on medicines' in the Dutch system - https://www.nza.nl/zorgsectoren/medisch-specialistische-zorg/registreren-en-declareren-van-geneesmiddelen

[12] The three drugs to which this applies are the antiarrhythmic drug Multaq (active ingredient dronedarone, considered inferior to amiodarone and with serious side effects), Ceplene (active ingredient histamine dihydrochloride) in leukaemia and Ranexa (ranolazine) in patients with stable angina pectoris.

Appendix 1 - Methodology

This appendix contains the methodology used to create the overviews in the chapters of this report and of Appendix 2. It describes the datasets used, the steps within the analysis and the selection of included conditions.

Description of the used datasets

We used four datasets for the analysis of the outputs of the current ecosystem of pharmaceutical R&D. These were:

- **European public assessment reports (EPARs)**[13] of the European Medicine Agency (EMA). The overview of EPARs is a publicly available dataset, published at https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section. This dataset contains registrations since the EMA was founded in 1995. The date stamp of the dataset used was 5 September 2022.
- **Drug claims data in the Netherlands** obtained from the National Health Care Institute ('Zorginstituut Nederland') via the Medicines and Devices Information Project ('GIP'). In addition to the publicly available information, we requested additional data from the National Health Care Institute to enable breakdowns by brand name. The data was separated into an in-hospital and an out-of-hospital dataset.
- **An overview of brand names by classification in the Medicines Reimbursement System ('GVS')** obtained through data requested from SFK, a foundation created by the Dutch national association of pharmacists.
- **De Dutch Medicines Horizon Scan** of the National Health Care Institute from both December 2021 and June 2022.[14] These datasets contain overviews of drugs that may see market introduction in the coming years, along with supplementary information. They are publicly available at https://www.horizonscangeneesmiddelen.nl.

Selection of included conditions

In this study, we focused on conditions with a major societal impact in the Netherlands. To select these conditions, we used an overview of burden of disease (expressed in DALYs – disability-adjusted life years – per year) from a Dutch overview of public health information ('VZinfo').[15] VZinfo bases this list on the Public Health Future Outlook ('VTV')[16] of the Dutch National Institute for Public Health and the Environment ('RIVM'). We selected conditions from this list with a disease burden of more than 20,000 DALYs per year. This resulted in forty conditions that

[13] An EPAR contains detailed information on a medicine that has been authorised for use in the European Union.
[14] The December 2022 version of the Dutch Horizon Scan was published during this research. This publication appeared too late to be included in our analyses.
[15] https://www.vzinfo.nl/ranglijsten/aandoeningen-op-basis-van-ziektelast
[16] https://www.rivm.nl/volksgezondheid-toekomst-verkenning-vtv

together accounted for 91% of the total calculated annual burden of disease in the Netherlands. From this, we included conditions that met one of the following criteria:

- Pharmaceuticals play at least a fairly large role in the treatment of the condition. We based this selection on our own knowledge and desk research, and discussed it further with the pharmacists involved.
- The condition is listed as 'key pharmaceutical gap' in the WHO report Priority Medicines 2013.[17]

See Table 2 for an overview of selected conditions from the public health information overview.

Table 2. We included conditions with high burden of disease from the Dutch public health information overview based on the role that drugs play in their treatment and their position in the WHO report 'Priority Medicines 2013'. Conditions sorted in descending order by disease burden per year. Legend: white = included, yellow = excluded.

Conditions #1-10	#11-20	#21-30	#31-40
Coronary heart disease	Hearing disorders	Lower respiratory infections	Non-Hodgkin lymphoma
Stroke	Self-inflicted injuries	Asthma	Cardiac arrest
Diabetes mellitus	Mood disorders	Prostate cancer	Burn-out
COPD	Colon cancer	Pancreatic cancer	Leukaemia
Lung cancer	Breast cancer	Personality disorders	Skin cancer
Arthrosis	Heart failure	Parkinson's disease	Multiple sclerosis
Injuries due to private, work or sports accidents	Eye disorders	Oesophageal cancer	Contact eczema
Dementia	Injuries due to traffic accidents	Endocardial/heart valve conditions	Upper respiratory infections
Neck- and back complaints	Cardiac arrhythmias	Schizophrenia	Brain cancer
Anxiety disorders	Rheumatoid arthritis	Conditions related to alcohol abuse	Autism

This approach results in the omission of conditions in which the annual burden of disease has fallen sharply due to the introduction of new pharmacological treatment. To prevent conditions relevant to this study from being inadvertently omitted, we searched for this in the EPAR overview. We found ten conditions[18] which are not included in the overview of VZinfo and for which at least ten new brand names[19] have been registered since 1995. For these ten conditions we decided to include three more conditions based on qualitative criteria, in consultation with the pharmacists involved. Table 3 contains an overview of the results.

[17] https://www.researchgate.net/publication/249995018_Priority_Medicines_for_Europe_and_the_World_2013_Update_Report
[18] In the EPAR overview: 'therapeutic areas.'
[19] We excluded brand names for generics and biosimilars to find completely new drugs.

Table 3. In addition to the public health information overview, we included three more conditions with a major role of drugs in their treatment and at least ten new brand names since 1995. Legend: white = included, yellow = excluded.

Therapeutic Area #1-10	Motivation
HIV infections	Many drugs developed and relevant due to sharply decreased burden of disease.
Immunisations	Vaccines were outside of our research scope.
Hypertension	Important risk factor for conditions with high disease burden.
Multiple myeloma	Relevant because of large number of drugs developed and expected growth in this.
Haemophilia A	Relatively low disease burden in the Netherlands.
Influenza	Developments are largely vaccines.
COVID-19	Developments are largely vaccines.
Hepatitis B	Relatively low disease burden in the Netherlands.
Hepatitis C	Relatively low disease burden in the Netherlands.
Pulmonary hypertension	Relatively low disease burden in the Netherlands.

Pre-processing of input-data

The first step of our analysis consisted of processing the four described datasets. In the sections below, we describe the activities we performed per dataset.

EPAR overview

We processed the EPARs in Excel and in R before analysis using the following steps:

- **Complementing ATC codes in Excel**. The EPAR overview was not complete for every registration. For missing ATC codes, we used either an updated registration on the EMA website itself or a registration in the Estonian registry of drugs[20] as a source.
- **Deleting registrations out of scope.** These included veterinary drugs, diagnostic drugs, vaccines, generics, biosimilars and items with a registration status other than 'active'. We removed generics and biosimilars from our selection because our research focused on which innovative drugs have entered the market since 1995.

Dutch Medicines Horizon Scan

For the Dutch Horizon Scan we used the editions from June 2022 and December 2021. We removed duplicates based on their registration number. When fields with brand name information

[20] https://www.ravimiregister.ee/en/publichomepage.aspx

were empty, we substituted this with the active substance name.[21] In those cases, we considered the active substance as a provisional brand name for the analysis.

Drug claims data in the Netherlands ('GIPdatabank')

We received separate claims data from GIP for in-hospital and out-of-hospital. We linked these while retaining information about origin, to be able to make a distinction between in-hospital and out-of-hospital use in further analyses. Furthermore, we transformed the table to a different format with rows that were unique combinations of brand name and information on usage per year.

The EPAR overview and the drug claims data sometimes differed in the areas of spelling and degree of detail of substance names (English versus Dutch language use). We corrected this manually to be able to link the datasets.

Overview of brand names by classification in the Medicines Reimbursement System ('GVS')

Of this dataset, we only used information to find the placement of drugs in the appendices of the Medicines Reimbursement System ('GVS') for out-of-hospital drugs. Not every drug analysed was present in this dataset. Using desk research of the GVS, we compiled an additional list of drugs that were not included in the SFK data.

Linking tables

To be able to compare the EPARs and the Horizon Scan based on the selected conditions, we created linking tables in Excel. Based on desk research we divided the indication area for drugs in the EPARs and the Horizon Scan into either one of the included conditions or the category 'none'.

Linking data

We took the following steps to link all input data:

- **Creation of a dataset of EPARs linked to included conditions.** To do this, we first transformed the EPAR data in R into a format with unique rows of brand names and therapeutic area because the EPARs include multiple conditions in the same row. We then linked this data to the table of included conditions. The result was a dataset with a row per unique combination of condition and brand name.
- **Creation of a dataset of the Horizon Scan linked to included conditions.** The Horizon Scan also contains information about expected indication expansions for existing drugs. We excluded these indication expansions when it concerned an expansion within the same condition (for example, for a different subgroup of lung cancer patients) and we included the expansion when it concerned an extension to another condition (for example, a drug registered for breast cancer which could potentially also be used for colorectal cancer). The result was a dataset with one row per unique combination of condition and brand name.

[21] Drugs that are still in development regularly do not have a brand name yet.

- **Differentiating registered drugs according to unique substance name and ATC code.** To differentiate between degrees of innovativeness, we analysed whether registered drugs had unique active substances and/or ATC codes. We then used R to analyse whether a combination of unique active substances had previously been registered for the same combination. Finally, we performed the same operation for combinations of ATC codes and conditions.
- **Analysis of drug claims data in the Netherlands.** For this we linked the resulting EPAR dataset to the drug claims data based on brand names.
- **Analysis of drug reimbursement status in the Netherlands.** For this we linked the EPAR dataset to the appendices of the Medicines Reimbursement System ('GVS') as supplied by SFK, based on brand name and ATC code.

The result of the abovementioned linking was an Excel file that we used for further analyses, overviews and visualisations.

Supplementary desk research on results

In addition to graphs of developments within the field of pharmaceutical R&D, we also looked for explanations for the absence of brand names or active substances in the drug claims data. For this, we took the following steps:

- Looking up the brand name in the Medicine Database of the Dutch Medicines Evaluation Board ('CBG').
- Looking up the date of market authorisation for the drug. When this was in or after 2021, the drug may still be too new to appear in drug claims data.
- Looking up the brand name or active substance in the Dutch registry of accessible drugs ('FK') for drugs with a marketing authorisation before 2021. The FK contains information about the reimbursement status of active substances, for example under the name of another specialty drug, or as a generic drug. The FK also contains information about whether the drug is listed in the Dutch Medicine Reimbursement System ('GVS').
- For drugs that were not included in the GVS, we searched the National Health Care Institute overview of drug costs to see whether it concerned medication that is only used in-hospital. Use of in-hospital only drugs cannot be traced separately in Dutch drug claims data unless they concern so-called add-on drugs. Add-on drugs have a separate declaration title because they are drugs with high expenses per patient, and cannot be absorbed in the regular hospital declaration scheme of Diagnostic Related Groups. The fact that in-hospital only drugs cannot be traced separately in drug claims data limits the completeness of the information available for this study.

Appendix 2 – Registrations per included condition

This appendix contains an overview of the number of brand names and unique active substances of drugs for each included condition. The numbers of existing registrations are based on EMA registrations from 1995 up to and including 2022. Numbers for potential future registrations are based on items on the Dutch Horizon Scan from 2022-2024. To provide an indication of development patterns over time, we split EMA registrations into the periods before and after 2010.

Condition	DALYs per year in NL	Registered brand names		Unique active substances		Potential new brand names 2022-2024	Development pattern
		Before 2010	After 2010	Before 2010	After 2010		
Coronary heart disease	271,300	11	5	8	3	0	Stagnant development
Stroke	248,000	3	2	1	1	0	Limited development
Diabetes mellitus	201,000	37	38	20	28	9	Stable development
COPD	188,500	3	28	1	18	0	Upturn after limited development
Arthrosis	165,800	0	1	0	1	0	Limited development
Lung cancer	165,800	6	23	6	21	14	Upturn after limited development
Dementia	163,600	7	1	2	1	0	Stagnant development
Anxiety disorders	127,800	1	1	1	1	0	Limited development
Hearing disorders	113,600	0	0	0	0	0	Limited development
Mood disorders	98,200	6	5	4	4	4	Stagnant development
Colon cancer	90,400	4	7	4	7	1	Stable development

Condition	DALYs per year in NL	Registered brand names		Unique active substances		Potential new brand names 2022-2024	Development pattern
		Before 2010	After 2010	Before 2010	After 2010		
Breast cancer	81,300	12	14	11	14	7	Stable development
Heart failure	72,000	2	4	1	2	0	Limited development
Eye disorders	55,400	8	11	8	10	10	Stable development
Cardiac arrhythmias	51,200	4	1	2	1	0	Limited development
Rheumatoid arthritis	47,500	10	8	10	6	3	Upturn after limited development
Lower respiratory infections	46,700	4	11	4	11	17	Upturn after limited development
Asthma	44,800	1	13	1	10	3	Upturn after limited development
Prostate cancer	44,200	2	9	2	9	7	Upturn after limited development
Pancreatic cancer	42,700	4	5	4	5	1	Upturn after limited development
Parkinson's disease	31,700	13	8	7	3	2	Stagnant development
Oesophageal cancer	30,900	0	1	0	1	0	Limited development
Schizophrenia	26,700	5	9	3	5	2	Stable development
Non-Hodgkin lymphoma	22,500	8	13	8	13	9	Stable development
Leukaemia	21,800	11	21	11	20	13	Upturn after limited development
Skin cancer	21,600	1	13	1	13	6	Upturn after limited development
Contact eczema	21,400	0	0	0	0	0	Limited development

Condition	DALYs per year in NL	Registered brand names		Unique active substances		Potential new brand names 2022-2024	Development pattern
		Before 2010	After 2010	Before 2010	After 2010		
Multiple sclerosis	21,400	5	13	3	13	3	Stable development
Upper respiratory infections	20,200	0	2	0	2	8	Limited development
Brain cancer	20,100	1	0	1	0	0	Limited development
HIV infections	1,810	22	22	21	21	2	Stable development
Hypertension	Not available[22]	20	2	10	2	0	Stagnant development
Multiple myeloma	Not available [22]	5	15	5	14	5	Upturn after limited development

[22] Data on DALYs is based on Dutch public health and care information (https://VZinfo.nl). This source does not mention data on hypertension or multiple myeloma. See Appendix 1.