The development and market launch of orphan drugs from 1980 – 2019: a quantitative analysis

Deliverable 5.3

17th January 2021

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Version	Date	Contribution
V1	15th December 2020	ICL
Final version	17th January 2021	All partners

The Rare2030 project is co-funded by the European Union Pilot Projects and Preparatory Actions Programme (2014- 2020). This leaflet is part of the pilot project PP-1-2-2018-Rare 2030. The content represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission or any other body of the European Union.

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Acknowledgments: Marisa Miraldo, Franco Sassi, Mujaheed Shaikh, Bryony Simmons and Charlotte Vrinten acknowledge funding by the European Union Pilot Projects and Preparatory Actions Programme (2014- 2020), as pilot project PP-1-2-2018-Rare 2030. Marisa Miraldo, Lise Rochaix and Eliana Barrenho also acknowledge funding from the "Rare Cancers & Orphan Drugs, innovation and Inequality" from INCa (Institut National du Cancer) (grant number #9580). Authors are grateful to Giovanna Giuffrè, Virginie Hivert, Andrea Ricci, Loredana Marmora, Yann Le Cam, Giovanni Forchini, Jan Panhuysen, Stéphanie Nguegang Wakap, Jack Olney, Zhengnan Zhou, Ana Rath, Charlotte Rodwell, Zoé Fontier, Thelma Arcelin, Clara Medioni Anna Kole and Philippe Gorry for their useful comments and to support in data preparation and analyses. Authors are grateful to Orphanet for granting access to epidemiological data and data on orphan drug designations, and to Ana Rath, Charlotte Rodwell and Stephanie Nuegang Wakap for guidance on the data.

1. Introduction

Although the exact definitions for rare diseases vary across jurisdictions, rare diseases are commonly defined by their low prevalence or incidence. Despite their rarity, rare disease patients are numerous. This is because there are an estimated 6,000-8,000 rare diseases. Based on the epidemiological data available in the Orphanet database, Nuegang Wakap and colleagues have recently estimated that the population prevalence of rare diseases (excluding rare cancers, infectious diseases and poisonings, which are characterised by incidence rather than prevalence) is between 3.5% and 5.9%, equating to 263 to 446 million people globally at any given point in time (Nuegang Wakap et al., 2020).

Historically, research and development (R&D; innovation) of pharmaceutical treatments has been driven by return on investment (with targeting towards larger markets), markets with higher profitability, and areas where disease knowledge is better, and which are scientifically less challenging. Hence, R&D and market launches of pharmaceutical treatments for rare diseases has lagged behind that for more prevalent diseases.

Various jurisdictions have put orphan drug legislation in place to incentivise R&D and market launch of products for rare diseases. Orphan drugs are commonly defined in these types of legislation as pharmaceutical products that target a rare disease or a disease area for which there would not deem to be sufficient return on investment to drive R&D in the absence of the special incentivisation as laid out in the orphan drug legislation. To date, four jurisdictions have put in place such orphan drug legislation: the US in 1983 (Orphan Drug Act), Japan in 1993 (the Act on securing quality, efficacy and safety of pharmaceuticals, medical devices, regenerative and cellular therapy products, gene therapy products, and cosmetics of the Pharmaceutical Affairs Law), the EU in 2000 (Orphan Medicinal Product Regulation), and Switzerland in 2000 (Therapeutic Products Act).

The incentives provided through these pieces of legislation vary, but all aim to incentivise R&D and market launch of treatments for rare diseases. The incentives may, however, be stronger for certain disease areas than for others, such as those rare diseases which are relatively more prevalent, where scientific knowledge of the disease is better, and/or where technologies to develop new treatments already exist (Austin et al., 2018).

In addition, it is important to recognise that the incentives provided by the various pieces of orphan drug legislation may target different stages of the R&D process. For example, some phases, such as the discovery phase, are more scientifically challenging, while others, such as phase III trials, tend to be more expensive and tend to require larger numbers of research participants.

Incentives for innovation will also vary across diseases areas. Scientific complexity of the innovation process, its inherent risk and rate of return on investment largely vary across disease incentivizing investment in profitable

disease areas where it is easier to innovate. These areas might not reflect unmet need thus generating inequalities of access and outcomes.

With this report, our first aim is to historically map the differences in innovation for orphan drugs versus non-orphan drugs, by disease area, ATC, region, and over time. We provide an overview of all orphan versus non-orphan products, but in recognition of the different challenges associated with different R&D phases, we also examine innovation by stage: early stage development (discovery through to phase I trials), late stage development (phase II, III and registration), and market launch.

Secondly based on these the observed heterogeneity of innovation across disease we measure the inequalities in product innovation targeting rare diseases.

Thirdly, based on these historical trends, we aim to measure the stock of innovation to be made available over the next ten years.

This leads to the following research questions that are addressed in this report:

1. *What is the stock of innovation, both orphan and non-orphan, made available between 1980 and 2019?*
2. *What is the stock of innovation, both orphan and non-orphan, that is expected to become available over the next 10 years in the absence of changes to current policies?*
3. *What is the direction and size of inequalities in innovation across rare diseases factoring need proxied by prevalence?*

2. Historical R&D Activity & Forecasts

2.1 Data

In this study, we combine two data sources: (a) IQVIA Pipeline Intelligence database, which provides information on global pharmaceutical R&D from the discovery phase through to market launch, (b) Orphanet data on orphan drug designations in the EU, US, and Switzerland.

2.1.1 IQVIA Pipeline intelligence database

The IQVIA Pipeline Intelligence database (IQVIA, 2018) is used by the pharmaceutical industry to monitor market structure and performance and to inform strategic decision making. It contains event data since 1949 more than 40,000 drug products developed by 7,500 companies in 170 countries worldwide from the Discovery stage through to market launch for more than 700 indications, which are indexed by the IQVIA indication hierarchy and EphMRA ATC code (EphMRA, 2020). Products include small molecules, fixed combination products, and drug delivery systems, as well as biotechnology products and biosimilars, such as cell therapies, gene therapies, vaccines, and monoclonal antibodies. We kept the events that map orphan drug designations, early and late-stage R&D and market launch. The resulting dataset includes 1,930 orphan products, with global activity mapped around 953,979 events across all countries, firms, indications and ATCs and route of administration.

The IQVIA indication hierarchy is a hierarchy of diseases with 6 levels of roughly increasing granularity in the diseases contained at each level, which is used by IQVIA to define the indications for the products contained in their pipeline intelligence dataset. The top level of the hierarchy (Level 1) consists of 12 disease groups that roughly correspond to the EphMRA ATC coding scheme: cancer, cardiovascular disease, CNS disorders, dermatological disorders, endocrine and metabolic disorders, gastrointestinal disorders, genitourinary disorders, infectious disease, musculoskeletal disorders, ophthalmological disorders, respiratory disorders, and "other" disorders, including immunologic disease, medical procedures, multisystem genetic disorders, and trauma.

The pipeline intelligence database is updated daily with information from news sources, major regulators, clinical trial databases, top pharma companies' pipeline updates, interviews with small/medium pharma companies, and through scientific presentations at conferences. Because products can be developed for more than one indication and in several countries, we used the product_country_indication as the unit of our analyses in section 3 and product_indication in section 4. In both sections, indication is defined at IQVIA level 3 (IMS, 2012). We included all

pharmaceutical products containing one or more active ingredients targeting one or more diseases, but excluded diagnostics and products used in medical procedures (e.g., stents) from our analyses as these are outside the remit of this study.

2.1.2 Orphanet orphan drug database

We complemented the orphan drug designation events already contained in the Pipeline Intelligence dataset with information on orphan drug designations from Orphanet (Orphanet, 2019a) with the objective of fine tuning the indications for events of products with ODD recorded in the Pipeline Data but also to identify further ODD missing from the Pipeline Intelligence data. This dataset contains information on orphan drug designations in the EU, US, and Switzerland from 1984 to 2019. It also maps the indications of the orphan drugs to their Orpha code – a unique and stable identifier for groups of rare disorders, rare disorders, and disorder subtypes.

2.1.3 Data cleaning and merging

First, we matched the orphan drug designations in the Orphanet database to the orphan drug designations that were already in the IQVIA Pipeline Intelligence database, based on product name and synonyms, tradename, active ingredient, or CAS number; orphan indication; and country or region. Where needed to identify a match, we brought in additional data from the Orphanet database or from the main regulators (EU, US, Japan) on the sponsor of the orphan designation and the route of administration of the product. Where this information did not already exist in the Pipeline Intelligence database, we manually searched for it online, using pipeline intelligence resources, company pipeline information, and information from the main regulators. Where product names did not match between databases (for example, if the orphan drug designation used the chemical compound name and the IQVIA database used the international non-proprietary name), we used fuzzy matching methods and PubChem and other online sources to identify a match.

Secondly, we manually matched Pipeline products to orphan drug designations from the Orphanet dataset for which no orphan indication was captured in the Pipeline Intelligence dataset, thereby extending the coverage of orphan drug designations captured in the Pipeline Intelligence dataset. For new orphan drug designation events identified in this manner, the event was assigned an indication from the IQVIA hierarchy described above. Matching to the appropriate indication was achieved using the ICD-10 codes (extracted from the Orphanet datasets), medical dictionaries, and expert knowledge.

Using these methods, we were able to capture a total of 3451 current and historical orphan drug designations in the US, EU, Switzerland, and Japan in the Pipeline Intelligence dataset for 1890 unique products. We were unable to match 692 orphan drug designations from the Orphanet database to products in the Pipeline Intelligence dataset.

Some of these could not be matched because no common product identifier could be found (not even through extensive manual searching), while some orphan drug development processes (for example those by individual clinical teams rather than companies) may not have been captured by IQVIA's Pipeline Intelligence database.

For the analyses we build two sets of indicator variables to identify events related to: i) products with orphan designations (used for research objectives 1 & 2) and ii) products for rare diseases, regardless of when the product has been awarded an orphan drug designation (used for research objective 3). For the orphan designation indicator for products with an orphan drug event, a time-invariant binary orphan drug designation variable was built so that each event prior and post orphan drug designation related to that product indication and jurisdiction was flagged as an event of an orphan drug. That variable assumes value equal to 1 if the event occurs for the product indication and country for which an ODD was attributed. As in early stages of R&D the indications tend to be broad, the orphan variable assumes a value equal to 1 also for events that refer to indications that nest the indication of the ODD. The variable assumes value zero otherwise. This implies that products that target rare indications in countries for which the product does not have an ODD were also coded as zero.

Similarly, we built a time invariant variable non-orphan that is equal to 1 for all observations for which are i) related to product-indication-country combinations that have never received orphan designation and ii) for observations where an orphan-designation has been granted for that product-indication-country, but we cannot be sure that the event relates solely to the orphan designation (e.g., when then indication is at a broader level and might relate to both orphan and non-orphan activity). The non-orphan variable is equal to zero for all other observations.

We use similar methodology to build the time invariant rare disease indicators. We identify product-indications as rare or non-rare, using the IQVIA indication hierarchy and ORPHA code as described in Section 2.3. We used the European definition to identify rare diseases and only consider diseases which are currently considered rare. As with the orphan designation indicators, we assign all events related to the product-indication and any product-indication event that is nested in the rare disease indication as rare disease events. To identify events associated with rare diseases we proceeded in several steps. We first flagged events as being associated with a rare disease if the product of the event had an orphan designation anywhere globally and that orphan designation was for a EU rare disease. For products that do not have any orphan drug designation but could target rare diseases we proceeded by searching manually for the Pipeline event indication in the Orphanet dataset making use of a disease dictionary that provided different disease synonymous enabling more accuracy in the matching. We mark any event of a product with an indication that is nested within the product-indication identified as rare, as a rare observation. The remainder observations were flagged as non-rare.

The resulting dataset contains information of R&D events of all pharmaceutical products from 1949-2019, across all disease areas and ATCs globally. Events are coded at product, indication, country level and event date level, and include all phases in the drug development process namely discovery, pre-clinical R&D, Phase I-III clinical trials, registration, market launches, and orphan drug designations. The total number of observations in our data is 953,979. We start by excluding products for which dates for events is 'Unknown'. This leads to 20,080 observations being excluded from the analysis. For products where the event date is partial i.e., instead of month and year, we observe quarter and year, we consider the middle month of the quarter. Similarly, for first and second half of the

year. Since we are interested in mapping R&D activity and market launch, we exclude orphan drug designations from our final dataset (n=43,852).

2.2 Historical analyses

2.2.1 Sample and Statistical analyses

The analyses consisted of descriptive statistics where we compare global R&D activity (early and late stage) and market launches of orphan and non-orphan products. We also look at the distribution of global R&D activity and market launch across diseases, ATCs (using the EphMRA ATC classification) and regions.

We considered as unit of observation the product-indication-country level, with the indication level set to IQVIA indication level 3. For simplicity, we present the analyses by disease area at IQVIA level 1 of the disease hierarchy. In addition, to simplify exposition, we shall refer to the product-indication-country level observations as "products" throughout, but the reader should note that each product can be observed more than once for different indications and countries.

We use the observations of the variable orphan equal to 1 to identify events associated with orphan products and the observations of the variable non-orphan equal to 1 to identify events associated with non-orphan products. The exception is in the t-tests where we use the binary variable orphan to identify both orphan (when orphan=1) and non-orphan products (when orphan=0). We run a robustness check using the non-orphan variable to identify the orphan and non-orphan events and results remain qualitatively the same.

We exclude observations with missing information on ATC class or diseases, and also duplicate events for the same product. Any products with missing information on country or indication are also excluded. We then cluster events into – early stage and late stage R&D and marketed. Early-stage R&D includes all events from Discovery to Phase 2 completed or stopped. Late stage R&D includes all events from Phase 3 to Registration. A product is considered 'launched' if the product shows a marketed event. We do not consider events such as discontinued, withdrawn, suspended, trial stopped etc. within the scope of the two R&D stages we defined. These observations are therefore excluded from the analysis as are other observations that do not have any information on events. This leaves us with 331,224 observations in total across 28,953 unique products.

2.2.2 Results

2.2.2.1 All R&D and market launch events

From the 331,224 product events more than 13,000 orphan products events and more than 310,000 non-orphan products events. From the 28,953 unique products from 1949 to 2019, of approximately 5% were orphan designated products in any of the jurisdictions with orphan drug designation regulations in place: the USA, Japan, European Union, or Switzerland. Thus, orphan designated products only comprised a small proportion of total products observed between 1981 and 2019.

Of all events that we observe, 23.5% are early stage R&D events (of which 1.8% are for orphan designated products), 67.8% are late stage R&D events (of which 4.6% are for orphan designated products), and 8.6% are market launch events (of which 5% are for orphan designated products).

By disease area

Figure 1 presents the distribution for all events combined (i.e., early stage R&D, late stage R&D and market launch) by disease area, for orphan designated and non-orphan products. Most products targeted cancer (26.6%), and this was true for both orphan designated (2.1%) and non-orphan products (24.5%). For orphan designated products, this was followed by products targeting endocrine and metabolic disorders (0.5% of all products across all stages) and cardiovascular disease (0.4%), while for non-orphan drugs the most targeted disease areas after cancer were CNS disorders and infectious diseases (13.1% and 12.7%, respectively) and endocrine and metabolic disorders (10.0%).

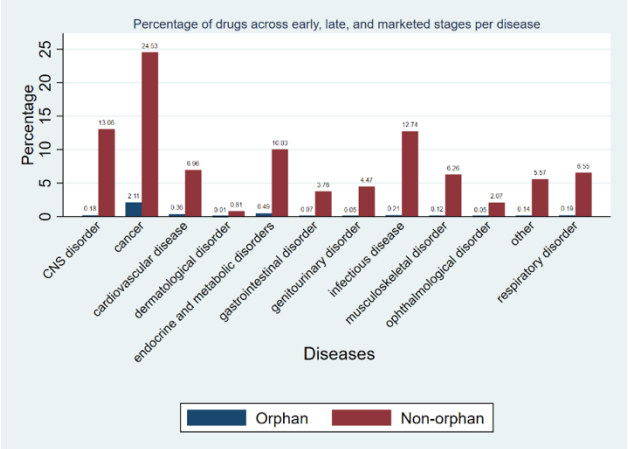


Figure 1. Percentage of all orphan and non-orphan products combined across early stage R&D, late stage R&D and market launch by disease area, for orphan designated and non-orphan designated products.

We also examined the percentage of products across all stages by disease area separately for orphan and non-orphan products. Figure 2 describes the distribution of products by disease area, separately for orphan designated products and non-orphan products, across early stage R&D, late stage R&D and market launch. This figure shows that of all orphan products events, more than half (53%) targeted cancer, followed by endocrine and metabolic disorders (12%) and cardiovascular disease (9%). Of all non-orphan products events, a quarter (25%) targeted cancer, followed by CNS disorders and infectious diseases (both 13%), and endocrine and metabolic disorders (12%).

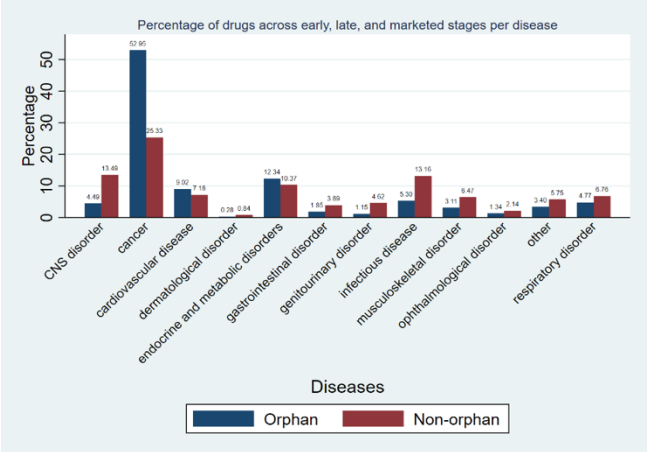


Figure 2. Percentage of R&D activity products across early stage R&D, late stage R&D and market launch by disease area, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total orphan (non-orphan) products across all diseases.

By ATC

Figure 3 shows the distribution for all events and products combined (i.e. early stage R&D, late stage R&D and market launch, and orphan designated and non-orphan products) by EphMRA ATC code, for orphan designated and non-orphan products. Most products were antineoplastic and immunomodulating agents (29.1%, ATC class L), and this was true for both orphan designated (2.1%) and non-orphan products (27.0%). For orphan designated products, this was followed by products targeting the alimentary tract and metabolism (0.44%, ATC class A) and blood and blood forming organs (0.36%, ATC class B), while for non-orphan products, this was followed by products targeting the nervous system (13.4%, ATC class N), systemic anti-infectives (12.0%, ATC class J), and products targeting the alimentary tract and metabolism (11.6%, ATC class A).

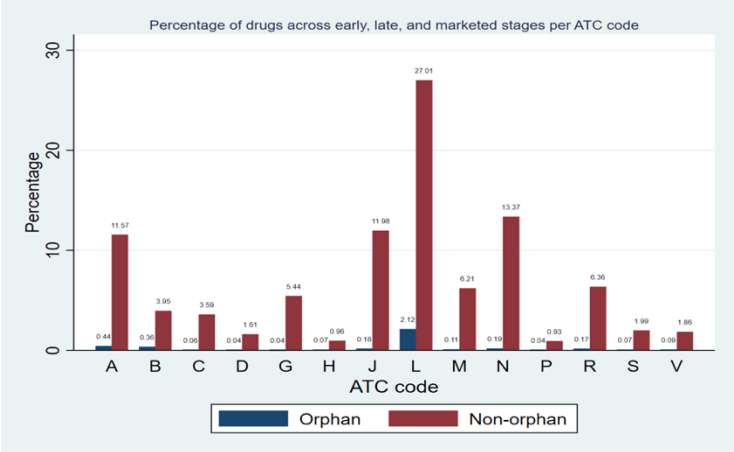


Figure 3. Percentage of all orphan and non-orphan products combined across early stage R&D, late stage R&D and market launch by ATC code, for orphan designated and non-orphan designated products. Shares for orphan (non-orphan) represent the ATC share out of the total orphan (non-orphan) products across all ATCs. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, T = Diagnostic agents, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses.

We also examined the percentage of products across all stages by ATC separately for orphan and non-orphan products. Figure 4 describes the distribution of products by ATC, separately for orphan designated products and non-orphan products, across early stage R&D, late stage R&D and market launch. The findings are similar to those by disease area, with more than half of all orphan products being antineoplastic and immunomodulating agents (53%; ATC class L), followed by products targeting the alimentary tract and metabolism (11%; ATC class A) and the blood and blood forming organs (9%; ATC class B). For non-orphan products, just over a quarter were antineoplastic and immunomodulating agents (28%; ATC class L), followed by products targeting the nervous system (14%; ATC class N), and general systemic anti-infectives (12%; ATC class J).

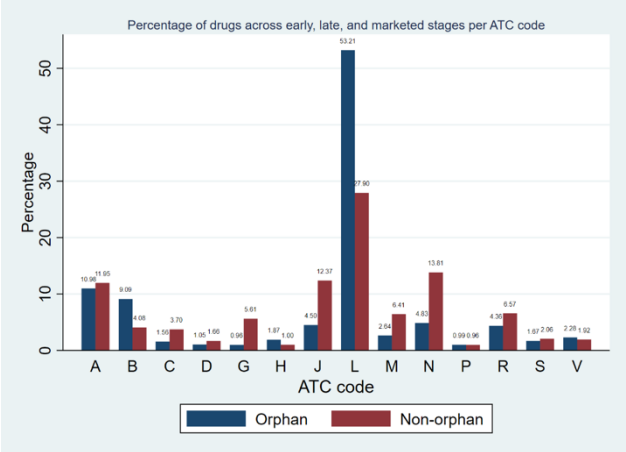


Figure 4. Percentage of products across early stage R&D, late stage R&D and market launch by ATC, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total orphan (non-orphan) products across all ATCs. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, T = Diagnostic agents, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses.

By country and region

Figure 5 shows the distribution for all events combined (i.e., early stage R&D, late stage R&D and market launch) by comparing those countries/regions with orphan medicinal product legislation in place (USA, Japan, Europe, and Switzerland) versus the rest of the world (ROW).

Around 95% of total R&D activity and market launches relates to non-orphan products and only a small fraction to orphan products. The US conducts most of the R&D activity and market launches for both orphan and non-orphan products, followed by the EU. The ROW exhibits equivalent levels of activity and launches than Europe for non-orphan drugs but a negligible level for orphan. Negligible activity and launches for orphan products is also observed in Switzerland and Japan.

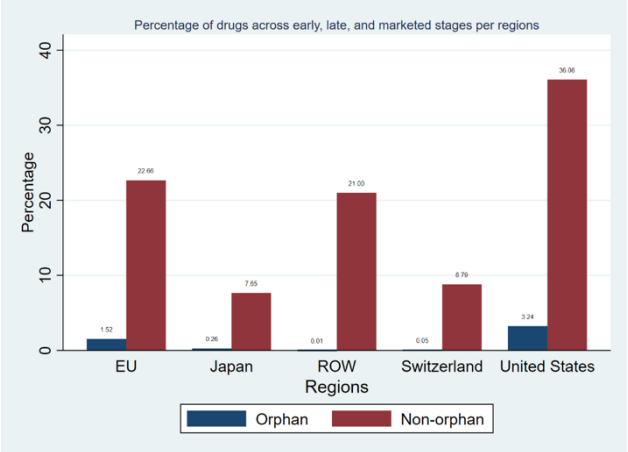


Figure 5. Percentage of all orphan and non-orphan products combined across early stage R&D, late stage R&D and market launch for the EU, US, Switzerland, Japan, and the rest of the world (ROW), for orphan designated and non-orphan designated products. Shares for orphan (non-orphan) represent the region share out of the total orphan and non-orphan products across all regions.

We also examined the percentage of products across all stages by these regions separately for orphan and non-orphan products. Figure 6 describes the distribution of products for the EU, US, Switzerland, Japan, and ROW, separately for orphan designated products and non-orphan products, across early stage R&D, late stage R&D and market launch. Nearly all orphan drug development and market launches took place in the US (64%) and EU (30%), compared with 37.52% and 23%, respectively, for non-orphan drug development and market launches.

For non-orphan products, most market launches (37.5%) took place in the US, followed by EU and Switzerland (32%), ROW (21.81) and Japan (7.95%).

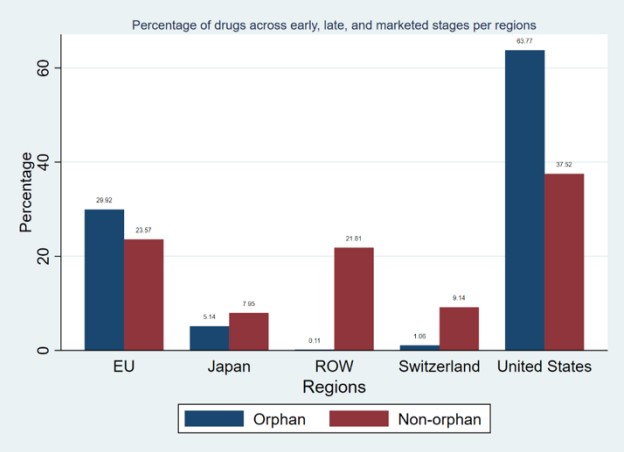


Figure 6. Percentage of products across early stage R&D, late stage R&D and market launch for the EU, US, Switzerland, Japan, and the rest of the world (ROW), separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the region share out of the total orphan (non-orphan) products across all regions.

2.2.2.2 Early stage R&D activity

By disease area

Figure 7 shows the percentage of products in early stage R&D by disease area, separately for orphan designated and non-orphan products. Most orphan designated products in the early stage of R&D targeted cancer (46.28%), followed by infectious disease (10.08%) and respiratory disorders (9.31%). Of all non-orphan products in the early stage of R&D, the distribution is more equal with most (17.03%) target CNS disorders, followed by infectious disease (16.54%) and cancer (16.07%).

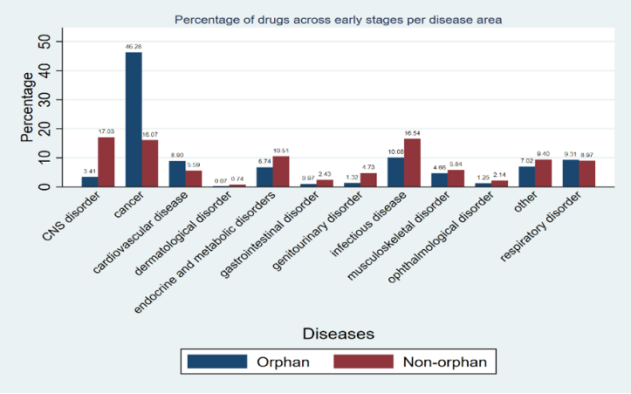


Figure 7. Percentage of products across early stage R&D, late stage R&D and market launch by disease area, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total early stage orphan (non-orphan) products across all diseases.

Comparing early stage activity across orphan and non-orphan products (Table 1) we observe that there is more R&D activity for non-orphan than orphan drugs in most disease areas with the highest statistically significant differences being observed in CNS disorders (Mean Difference (MD)=0.137, p-value<0.001) followed by infectious diseases (MD=0.066, p-value<0.001) and endocrine and metabolic disorders (MD=0.038, p-value<0.001). For cancer and cardiovascular disease instead, there is more early stage activity for orphan than non-orphan products (MD=-0.304, p-value<0.001; MD=-0.033, p-value<0.001 respectively).

	Non-orphan (1)	Orphan (0)	Diff (1-0)	St_Err	t_value	p_value
CNS	.171	.035	.137	.01	13.7	0.000
Cancer	.16	.464	-.304	.01	-30.95	0.000
CVS	.056	.088	-.033	.006	-5.3	0.000
Dermatological	.007	.001	.007	.003	2.95	0.003
Endocrine	.105	.068	.038	.008	4.65	0.000
GIT	.024	.009	.015	.004	3.55	0.001
Genitourinary	.048	.013	.034	.005	6.1	0.000
Infectious diseases	.166	.1	.066	.01	6.65	0.000
Musculoskeletal	.058	.046	.011	.006	1.9	0.060
Ophthalmology	.022	.013	.009	.004	2.35	0.020
Other	.094	.07	.024	.007	3.05	0.002
Respiratory	.089	.093	-.004	.007	-.45	0.655

Table 1: Early stage activity mean differences for orphan vs. non-orphan products by disease[1].

By ATC

Of all observed products by ATC, about half were in the early stage of R&D, and this was true for both orphan products (51%) and non-orphan products (52%).

[1] Two-sample t test with equal variances performed over the sample of all early stage activity across all disease areas considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to 0. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

Figure 8 shows that of all orphan designated products in the early stage of R&D, about half (50.73%) were antineoplastic and immunomodulating agents (ATC class L), followed by the blood and blood forming organs (10.42%; ATC class B), products targeting the respiratory system (7.64%, ATC class R) and general anti-infectives systemic products (7.37%, ATC class J). Most non-orphan products in the early stage of R&D were also antineoplastic and immunomodulating agents, although these formed a smaller percentage of all non-orphan R&D in the early stage (20.65%), followed by products targeting the nervous system (18.56%; ATC class N), and infectious diseases (15.14%, ATC class J).

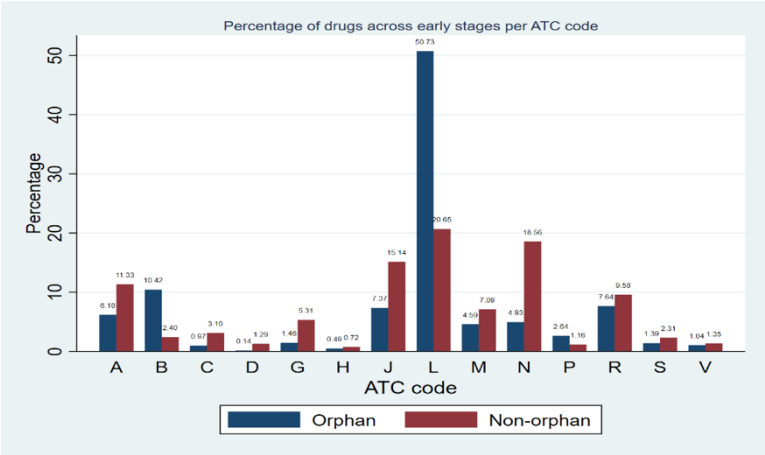


Figure 8. Percentage of products across early stage R&D by ATC, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total early stage orphan (non-orphan) products across all ATCs. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020).

Comparing early stage activity across orphan and non-orphan products (Table 2) we observe that there is more early stage R&D activity in most ATCs for non-orphan than for orphan products, with the highest statistically significant differences being observed in ATC N-Nervous System (MD=0.137, p-value<0.001), followed by ATC J-General anti-infectives systemic (MD=0.073, p-value<0.001) and ATC A-Endocrine and Metabolic Disorders (MD=0.052, p-value<0.001).

For ATCs L-Antineoplastic and immunomodulating agents, B-Blood and blood forming organs and P-Parasitology, there is, instead more early-stage activity for orphan than non-orphan products (MD=-0.303, p-value<0.001; MD=-0.08, p-value<0.001; MD=-0.015, p-value<0.001, respectively).

	Non-orphan (1)	Orphan (0)	Diff (1-0)	St_Err	t_value	p_value
ATC A	.114	.062	.052	.009	6.15	0.000
ATC B	.024	.104	-.08	.004	-19.35	0.000
ATC C	.031	.009	.022	.005	4.65	0.000
ATC D	.013	.002	.011	.003	3.85	0.000
ATC G	.053	.015	.038	.006	6.5	0.000
ATC H	.007	.005	.003	.002	1.05	0.292
ATC J	.152	.073	.079	.009	8.3	0.000
ATC L	.206	.509	-.303	.011	-28	0.000
ATC M	.071	.046	.025	.007	3.65	0.001
ATC N	.186	.05	.137	.011	13.25	0.000
ATC P	.011	.026	-.015	.003	-5.1	0.000
ATC R	.096	.076	.019	.008	2.45	0.013
ATC S	.023	.014	.009	.004	2.35	0.020
ATC V	.013	.009	.004	.003	1.2	0.227

Table 2: Early stage activity mean differences for orphan vs. non-orphan products by ATC.

A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020)[2].

By country and region

We analysed early R&D activity by comparing those countries/regions with orphan medicinal product legislation in place (USA, Japan, Europe, and Switzerland) versus the rest of the world.

[2] Two-sample t test with equal variances performed over the sample of all early stage activity across all ATCs considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to zero. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

Figure 9 shows that early R&D activity for all orphan designated products is indeed concentrated EU followed by the US. Nearly all early stage R&D activity for orphan designated products takes place in Europe (60%) and the US (38%). Similar patterns are found for non-orphan products early R&D in the US and the EU: 47.81% and 14.36% respectively. However, the ROW assumes an important role in the early stage development of non-orphan drugs accounting for 34% of global early stage activity.

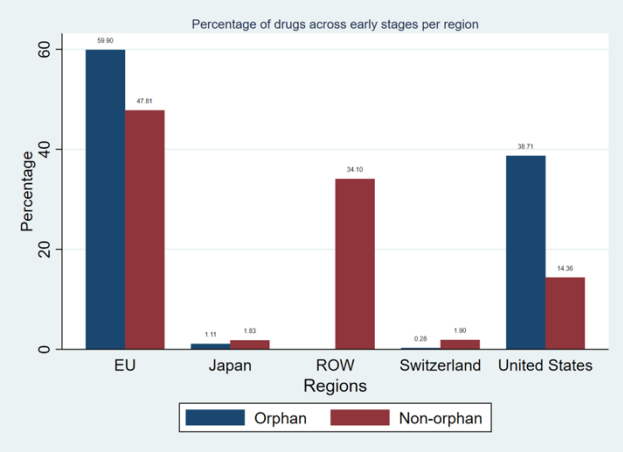


Figure 9. Percentage of products in early stage of R&D development for the European Union (EU), Switzerland, United States of America, Japan, and the rest of the world (ROW), for orphan designated and non-orphan products. Shares for orphan (non-orphan) represent the region share out of the total early stage orphan and non-orphan products across all regions.

2.2.2.3 Late stage R&D activity

By disease area

Figure 10 shows the percentage of all products in late stage R&D by disease area, for both orphan designated and non-orphan products.

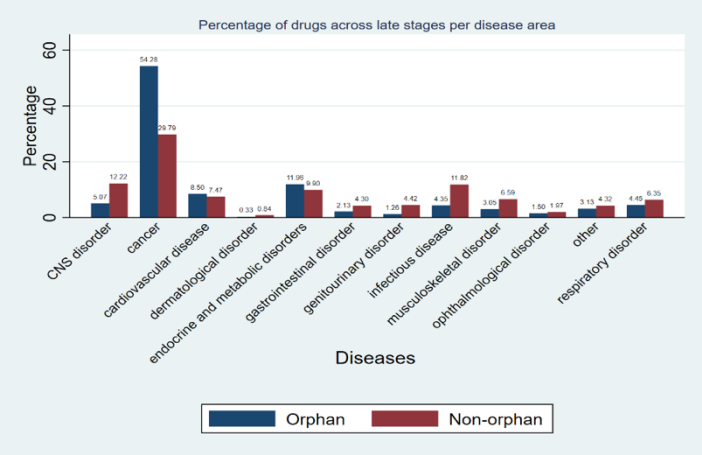


Figure 10. Percentage of products across late stage R&D by disease area, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total late stage orphan (non-orphan) products across all diseases.

Of all orphan designated products in the late stage of R&D, more than half (54.28%) targeted cancer, followed by endocrine and metabolic disorders (11.996%), cardiovascular disease (8.5%), and CNS disorders (5.07%). Similarly, most non-orphan products targeted cancer (29.79%), followed by CNS disorders (12.22%), and infectious diseases (11.82%).

Comparing late stage activity across orphan and non-orphan products by disease (Table 3) we observe that there is more R&D activity for non-orphan than orphan products in most disease areas with the highest statistically significant differences being observed in Infectious Diseases (MD=0.076, p-value<0.001) followed by CNS disorders (MD=0.068, p-value<0.001) and Musculoskeletal disorders (MD=0.036, p-value<0.001).

For cancer, endocrine and metabolic disorders, and dermatological disorders instead, there is more late stage activity for orphan than non-orphan products (MD=-0.238, p-value<0.001; MD=-0.026, p-value<0.001; and MD=-0.009, p-value<0.001, respectively).

	Non-orphan (1)	Orphan (0)	Diff (1-0)	St_Err	t_value	p_value
CNS	.12	.052	.068	.004	20.2	0.000
Cancer	.31	.548	-.238	.005	-48.95	0.000
CVS	.073	.082	-.009	.003	-3.1	0.002
Dermatological	.009	.004	.005	.001	5.35	0.000
Endocrine	.098	.123	-.026	.003	-8.15	0.000
GIT	.044	.022	.022	.002	10.4	0.000
Genitourinary	.044	.013	.031	.002	14.65	0.000
Infectious diseases	.113	.037	.076	.004	23.2	0.000
Musculoskeletal	.066	.03	.036	.003	13.85	0.000
Ophthalmology	.019	.015	.004	.002	2.85	0.004
Other	.041	.029	.012	.002	5.8	0.000
Respiratory	.062	.044	.018	.003	7.45	0.000

Table 3: Late stage activity mean differences for orphan vs. non-orphan products by disease[3].

By ATC

Figure 11 shows the percentage of orphan designated and non-orphan products in the late stage of R&D by their ATC class.

Of all orphan designated products in the late stage of R&D, more than half were antineoplastic and immunomodulating agents (54.21%; ATC class L), followed by products targeting the alimentary tract and metabolism (10.67%; ATC class A) and products for blood and blood forming organs (8.29%; ATC class B). Fewer than 1% of orphan designated products in the late stage of R&D target the genitourinary system or sex hormones, or parasitic infections (ATC classes G and P, respectively).

Of all non-orphan products in the late stage of R&D, more than a third were antineoplastic or immunomodulating agents (31.91%, ATC class L), followed by systemic anti-infectives and products targeting the nervous system

[3] Two-sample t test with equal variances performed over the sample of all late stage activity across all disease areas considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to 0. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

(12.17%, ATC class N) and products targeting the alimentary tract and metabolism (11.8%, ATC class A) and general anti-infectives systemic products (11.25%, class J).

The proportion of late stage innovation was higher for orphan designated products than non-orphan products for products targeting blood and blood forming organs (8.29% vs. 4.5%), systemic hormonal preparations (1.97% vs 1.01%), antineoplastic and immunomodulating agents (54.21% vs. 31.91%,) and products targeting the sensory organs (1.91% vs. 1.78%).

The proportion of late stage innovation was higher for non-orphan than for orphan designated products for all other ATCs and notably higher for products targeting the cardiovascular system (3.76% vs. 1.71%), the genitourinary system and sex hormones (5.42% vs. 0.99%), general infections (11.25% vs. 3.84%), musculoskeletal system (5.88% vs 2.61%), and the nervous system (12.17% vs. 5.28%), while is differences are milder for the remainder ATCs.

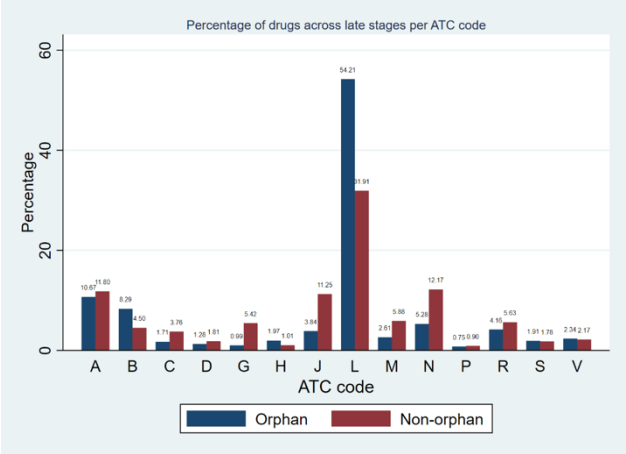


Figure 11. Percentage of products in late stage of R&D development by EphMRA ATC code, for orphan designated and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total late stage orphan (non-orphan) products across all ATCs. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculoskeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses.

Comparing late stage R&D activity across orphan and non-orphan products (Table 4) we observe that there is more late stage R&D activity for non-orphan than orphan in most ATCs with the highest statistically significant differences being observed in ATC N-Nervous System (MD=0.064, p-value<0.001), followed by ATC G - Genito-urinary system and sex hormones (MD=0.044, p-value<0.001) and ATC M -Musculo-skeletal system (MD=0.032, p-value<0.001).

For ATCs L-Antineoplastic and immunomodulating agents, B-Blood and blood forming organs and H-Systemic hormonal preparations, excluding sex hormones, there is, instead more late-stage activity for orphan than non-orphan products (MD=-0.215, p-value<0.001; MD=-0.032, p-value<0.001; MD=-0.011, p-value<0.001, respectively).

	Non-orphan (1)	Orphan (0)	Diff (1-0)	St_Err	t_value	p_value
ATC A	.118	.11	.007	.004	2.3	0.022
ATC B	.045	.077	-.032	.002	-14.2	0.000
ATC C	.038	.018	.021	.002	10.3	0.000
ATC D	.018	.013	.005	.002	3.3	0.001
ATC G	.054	.01	.044	.003	19	0.000
ATC H	.01	.021	-.011	.001	-9.85	0.000
ATC J	.108	.036	.073	.003	22.8	0.000
ATC L	.332	.548	-.215	.005	-43.65	0.000
ATC M	.058	.026	.032	.003	13.3	0.000
ATC N	.118	.054	.064	.004	19.1	0.000
ATC P	.009	.005	.004	.001	4.3	0.000
ATC R	.053	.04	.013	.003	5.7	0.000
ATC S	.017	.019	-.002	.002	-1.6	0.107
ATC V	.022	.025	-.003	.002	-1.85	0.061

Table 4: Late stage activity mean differences for orphan vs. non-orphan products by ATC. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses[4].

[4] Two-sample t test with equal variances performed over the sample of all late stage activity across all ATCs considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to 0. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

By country and region

We analysed the late stage R&D activity by comparing those countries/regions with orphan medicinal product legislation in place (USA, Japan, Europe, and Switzerland) versus the rest of the world.

Figure 12 shows the percentage of products in the late stage of R&D for the countries/regions with orphan medicinal product legislation in place, for orphan designated and non-orphan products. The patterns of the regional distribution of late stage R&D activity are similar to those of the early stage activity, though with a higher role played by the EU when compared to the US (90% vs. 9% of total late stage activity). There is virtually no late stage R&D activity in Japan, Switzerland and the ROW region.

This distribution is in contrast with the distribution of late stage activity for non-orphan drugs for which the ROW leads late stage development accounting for around 52% of global activity, followed by the EU with 42%. The US ranks third albeit being responsible for less than 4% of total R&D late stage activity. Switzerland and Japan do not play a significant role in this stage of R&D.

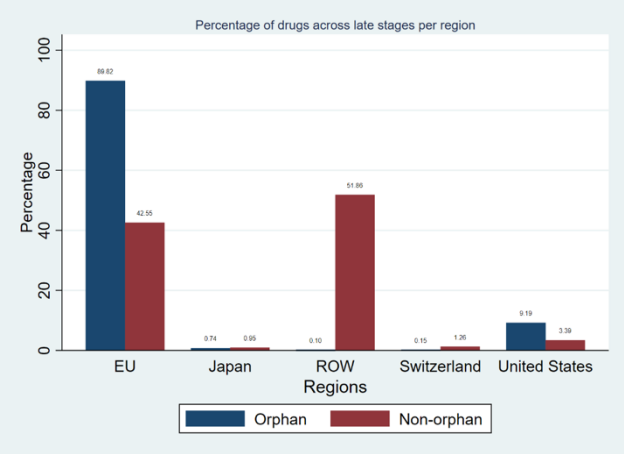


Figure 12. Percentage of products in late stage of R&D development for the European Union (EU), Switzerland, United States of America, Japan, and the rest of the world (ROW), for orphan designated and non-orphan products. Shares for orphan (non-orphan) represent the region share out of the total late stage orphan and non-orphan products across all regions.

2.2.2.4 Market launch

By disease area

Figure 13 shows the percentage of all marketed products by disease area, separately for orphan designated and non-orphan products. Most orphan designated products that were marketed between 1980 and 2019 targeted cancer (50.87%), followed by endocrine and metabolic disorders (20.51%), cardiovascular disease (12.54%), and infectious disease (7.21%).

Less than one per cent of all marketed orphan designated products targeted dermatological disorders, gastrointestinal disorders, genitourinary disorders, or ophthalmological disorders.

Of all non-orphan products that were marketed, most targeted cancer (16.11%) infectious diseases (14.21%), followed by CNS disorders (13.57%) and endocrine and metabolic disorders (13.62%).

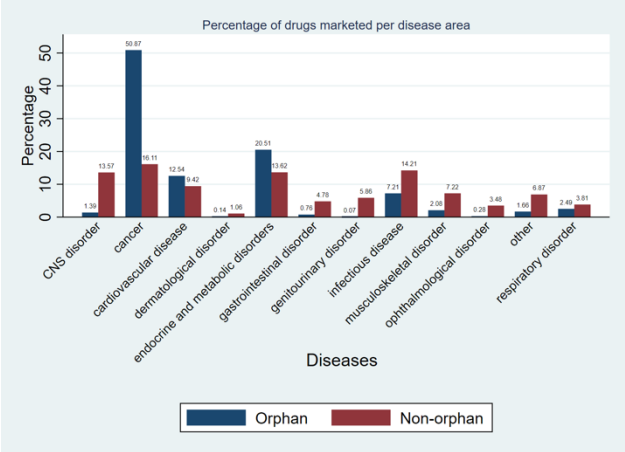


Figure 13. Percentage of marketed products by disease area, separately for orphan designated products and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the marketed total orphan (non-orphan) products across all diseases.

Comparing global market launches across orphan and non-orphan products by disease (Table 5) we observe that there are more launches of non-orphan than orphan products for most disease areas with the highest statistically significant differences being observed in CNS disorders (MD=0.165, p-value<0.001), followed by infectious diseases (MD=0.056, p-value<0.005) and genitourinary disorders (MD=0.064, p-value<0.001).

Cancer is the only disease area in which there are more market launches for orphan than non-orphan products (MD=-0.555, p-value<0.001).

	Non-orphan (1)	Orphan (0)	Diff (1-0)	St_Err	t_value	p_value
CNS	.165	0	.165	.034	4.85	0.000
Cancer	.136	.692	-.555	.032	-17.6	0.000
CVS	.091	.117	-.026	.026	-1	0.327
Dermatological	.007	.009	-.002	.007	-.25	0.818
Endocrine	.143	.108	.035	.032	1.05	0.283
GIT	.056	0	.056	.021	2.65	0.007
Genitourinary	.064	0	.064	.022	2.85	0.004
Infectious diseases	.137	.067	.07	.032	2.2	0.026
Musculoskeletal	.052	0	.052	.021	2.6	0.010
Ophthalmology	.036	0	.036	.017	2.1	0.036
Other	.088	0	.088	.026	3.4	0.001
Respiratory	.026	.009	.018	.015	1.2	0.229

Table 5: Market launch activity mean differences for orphan vs. non-orphan products by disease[5].

By ATC

Figure 14 shows all marketed products by ATC, for orphan designated and non-orphan products. Of all orphan designated products that were marketed between 1980 and 2019, more than a third were antineoplastic or immunomodulating agents (49.06%, ATC class L), followed by products targeting the alimentary tract and metabolism (17.95%, ATC class A), and the blood and blood forming organs (13.24%, ATC class B).

For non-orphan marketed products, antineoplastic or immunomodulating agents are also the ATC with the highest share of activity (16.06%, ATC class L), followed by products targeting the alimentary tract and metabolism (14.85%, ATC class A), and general anti-infectives systemic as well as nervous system with around 13% of observations in each (ATC classes J and N).

[5] Two-sample t test with equal variances performed over the sample of all market launches across all disease areas considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to zero. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

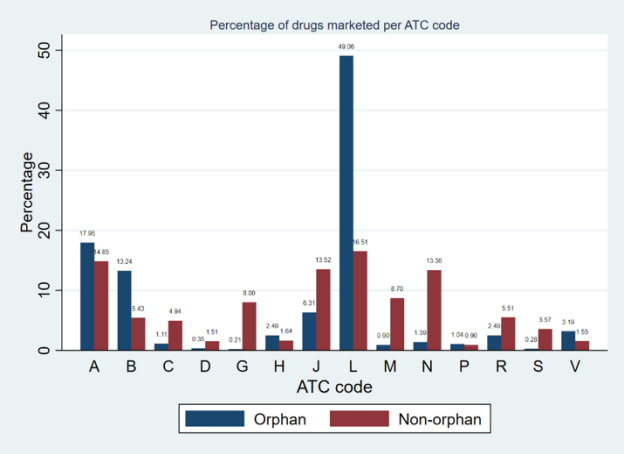


Figure 14. Percentage of marketed products by ATC code, for orphan designated and non-orphan products. Shares for orphan (non-orphan) represent the disease share out of the total orphan (non-orphan) marketed products across all ATCs. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculoskeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses.

Comparing market launch activity across orphan and non-orphan products (Table 6) we observe that there is more late stage R&D activity for non-orphan products than for orphan in most ATCs with the highest statistically significant differences being observed in ATC N-Nervous System (MD=0.163, p-value<0.001), followed by ATC G - Genito-urinary system and sex hormones (MD=0.091, p-value<0.001) and ATC M-Musculo-skeletal system (MD=0.075, p-value<0.001).

For ATCs L- Antineoplastic and immunomodulating agents and B-Blood and blood forming organs there is, instead more late-stage activity for orphan than non-orphan products (MD=-0.518, p-value<0.001; MD=-0.062, p-value<0.001 respectively).

	Non-orphan (1)	Orphan (0)	Diff(1-0)	St_Err	t_value	p_value
ATC A	.154	.138	.016	.033	.5	0.627
ATC B	.044	.105	-.062	.018	-3.35	0.001
ATC C	.059	.017	.043	.022	2	0.044
ATC D	.009	.008	.001	.009	.05	0.965
ATC G	.091	0	.091	.026	3.5	0.001
ATC H	.019	0	.019	.013	1.55	0.118
ATC J	.123	.057	.067	.03	2.25	0.025
ATC L	.14	.658	-.518	.032	-16.4	0.000
ATC M	.075	0	.075	.024	3.15	0.002
ATC N	.163	0	.163	.034	4.9	0.000
ATC P	.012	.008	.004	.01	.4	0.683
ATC R	.057	.008	.049	.021	2.35	0.019
ATC S	.04	0	.04	.018	2.25	0.024
ATC V	.013	0	.013	.01	1.25	0.211

Table 6: Market launches mean differences for orphan vs. non-orphan products by ATC. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, D = Dermatologicals, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). ATC class T was excluded from these analyses[6].

By country and region

Figure 15 shows the percentage of all marketed products for the countries/regions with orphan medicinal product legislation in place, for orphan designated and non-orphan products. Nearly all market launches for orphan designated products takes place in Europe (79%) and the US (16.29%) followed by Japan that plays only a marginal role on global orphan products market launch (3.4%). For non-orphan drugs the patterns are similar to those of late stage R&D with ROW being the top region with market launch activity accounting for 47% of total activity.

[6] Two-sample t test with equal variances performed over the sample of all global market launches across all ATCs considering the orphan variable to flag orphan products when the variable assumed value equal to 1 and non-orphan products when the variable assumed the variable equal to 0. Robustness checks where carried using the binary variable non-orphan and results remain qualitatively the same.

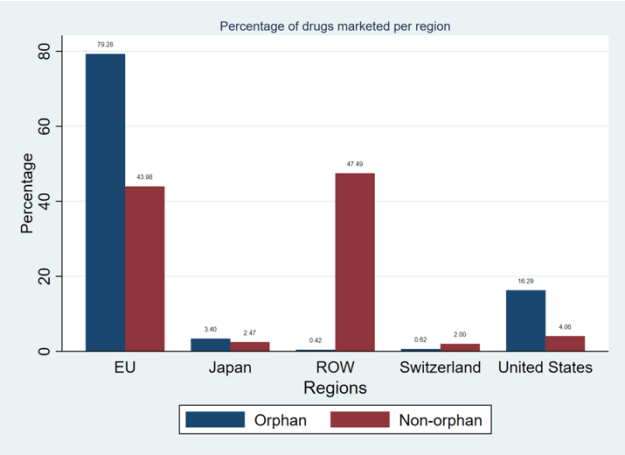


Figure 15. Percentage of marketed products for the European Union (EU), Switzerland, United States of America, Japan, and the rest of the world (ROW), for orphan designated and non-orphan products. Shares for orphan (non-orphan) represent the region share out of the marketed orphan and non-orphan products across all regions.

2.2.2.5 Historical trends in R&D development

We also analysed the development of R&D activity and market launches over time for both orphan designated and non-orphan products. Figure 16 shows the percentage of orphan designated and non-orphan products for each year between 1981 and 2019 out of total orphan and non-orphan activity in each of those years, across all stages of development (early stage R&D, late stage R&D, and market launch). As can be seen from this figure, orphan designated products form an increasing proportion of yearly pharmaceutical innovation.

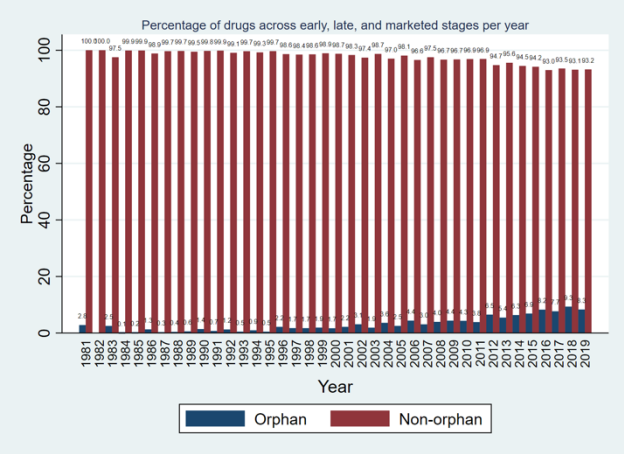


Figure 16. Percentage of orphan designated and non-orphan products across early, late, and marketed stage per year between 1981 and 2019, out of total number of orphan designated and non-orphan products for each year.

Figure 17 shows the orphan and non-orphan activity in each year out of the overall total (i.e., orphan and non-orphan) activity across all years. The increase of orphan drug development as a proportion of total yearly innovation (Figure 16) may be due to non-orphan drug development showing a decreasing trend since the mid-2000s, while the percentage of orphan drug development as a percentage of all drug development has remained stable at about 0.22% of all drug development (Figure 17).

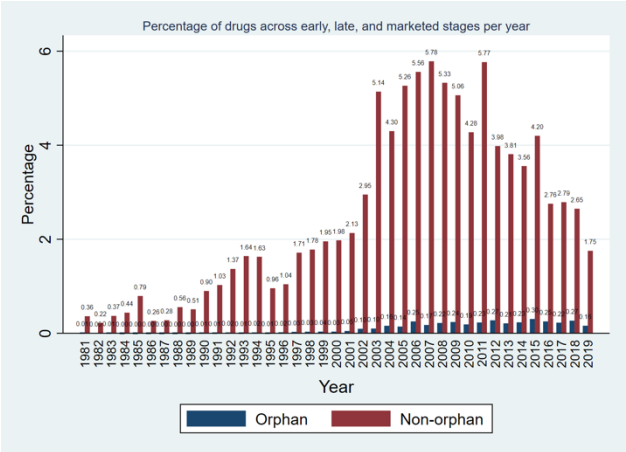


Figure 17. Percentage of orphan designated and non-orphan products across early, late and marketed stages for each year between 1981 and 2019, out of all products observed across all these years.

In what follows we replicate the same analyses stratifying by stage.

Early stage R&D activity

Figure 18 shows the percentage of orphan designated and non-orphan products for each year between 1981 and 2019, out of the total number of products in the early stage of R&D for each of those years.

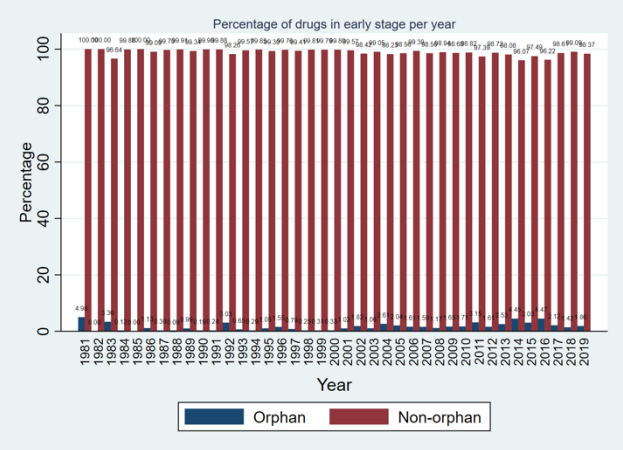


Figure 18. Percentage of orphan designated and non-orphan products in early stage R&D for each year between 1981 and 2019, out of total products in the early stage for each year.

We further examined the regional distribution of products in the early stage of R&D for orphan designated and non-orphan products, using the four regions with orphan drug legislation (US, Japan, EU, Switzerland) and other regions.

Figure 19 presents the regional distribution for early stage products for non-orphan products. This figure shows that about half of all non-orphan early stage drug development since the 1990s takes place in the US, with the remainder 40% taking place in the rest of the world and the EU. The share of early stage activity conducted in Switzerland and Japan was prominent (around 30% combined) in the beginning of the 1980s but has declined steadily since then, exhibiting less than 5% of early stage activity in recent years. The ROW region exhibits an increasing proportion of activity over the years amounting to around a quarter of global early stage R&D activity in recent years.

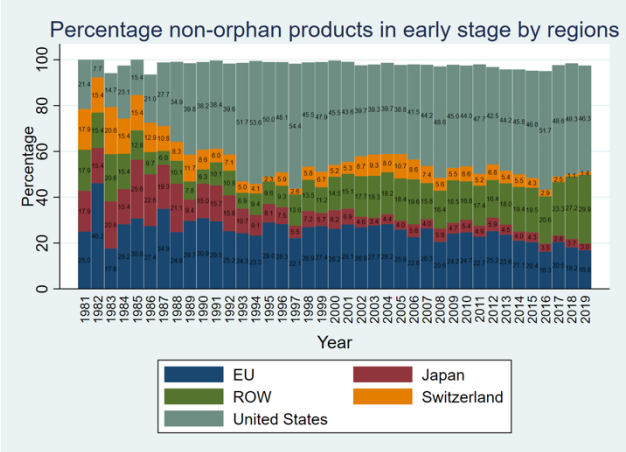


Figure 19. Regional distribution (%) of non-orphan products in the early stage of R&D for each year between 1981 and 2019 (out of total orphan designated and non-orphan early stage products in each year).

Figure 20 shows the regional distribution for early stage products for orphan-designated products. This shows that most early stage orphan designated drug development takes place in the US and the EU, with almost hardly any early stage R&D for orphan designated products in Japan, Switzerland and ROW. The figure also shows that early stage R&D for orphan designated products became more stable in the EU from about 2001 onwards, potentially due to the Orphan Medicinal Product Regulation legislation, but the share of global orphan early stage R&D activity has declined in recent years.

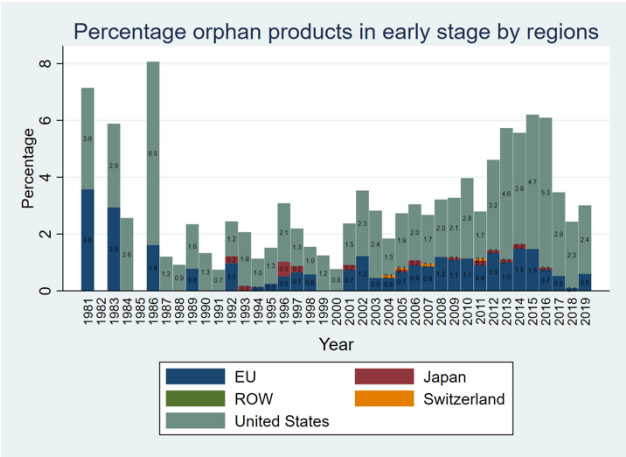


Figure 20. Regional distribution (%) of orphan designated products in the early stage of R&D for each year between 1981 and 2019 (out of total orphan designated and non-orphan early stage products in each year).

Late stage R&D activity

Figure 21 shows the percentage of orphan designated and non-orphan products for each year between 1981 and 2019, out of the total number of products in the late stage of R&D for each of those years. This shows that in the last decade, late stage R&D for orphan products has formed an increasing proportion of overall late stage R&D activity.

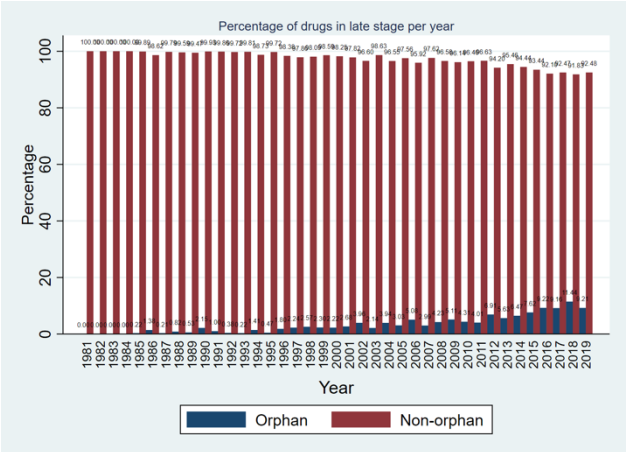


Figure 21. Percentage of orphan designated and non-orphan products in late stage R&D for each year between 1981 and 2019, out of total products in the late stage for each year.

Figure 22 presents the regional distribution for late stage products for non-orphan products. This figure shows that both the US and are responsible for more than a quarter of global late stage R&D activity with the share of global activity increasing since 1983. The share of global late stage activity carried by the ROW region has increased over time amounting to around a quarter of global activity since 2007. Late stage activity for the EU out of total late stage global activity has remained fairly constant over time at around 25%. As for early stage R&D, Switzerland and Japan accounted for 18% of global activity (around 36% combined) in the beginning of the 1980s but the share of activity out of global late stage R&D has declined steadily since then, amounting to around 10% in recent years.

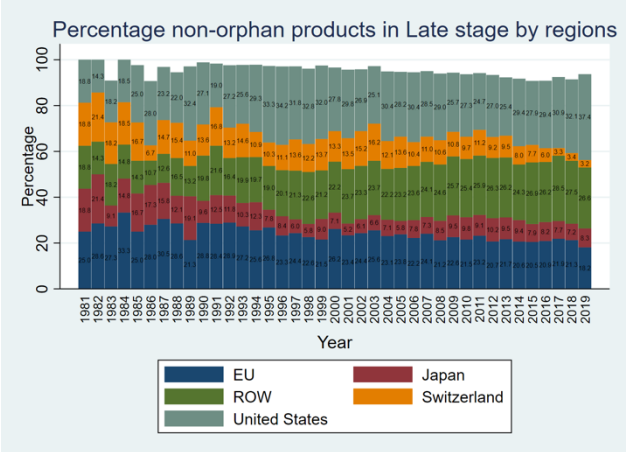


Figure 22. Regional distribution (%) of non-orphan products in the late stage of R&D for each year between 1981 and 2019 (out of total orphan designated and non-orphan late stage products in each year).

Figure 23 presents the regional distribution for late stage products for orphan designated products. Most late stage orphan designated drug development takes place in the US followed by the EU across all years. The proportion of orphan late stage R&D activity in the US has increased over time since 1989. The share of EU late stage R&D for orphan drug designation products has steadily increased over time.

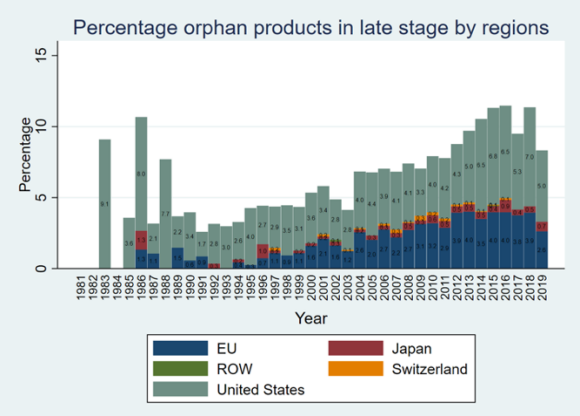


Figure 23. Regional distribution (%) of orphan designated products in the late stage of R&D for each year between 1981 and 2019 (out of total orphan designated and non-orphan late stage products in each year).

Market launch

Figure 24 shows the percentage of orphan designated and non-orphan products marketed for each year between 1981 and 2019, out of the total number of products marketed for each of those years. This shows that orphan designated products form a sizeable proportion of all marketed products each year since the early 2000s after the introduction of Orphan Medicinal Product Regulation.

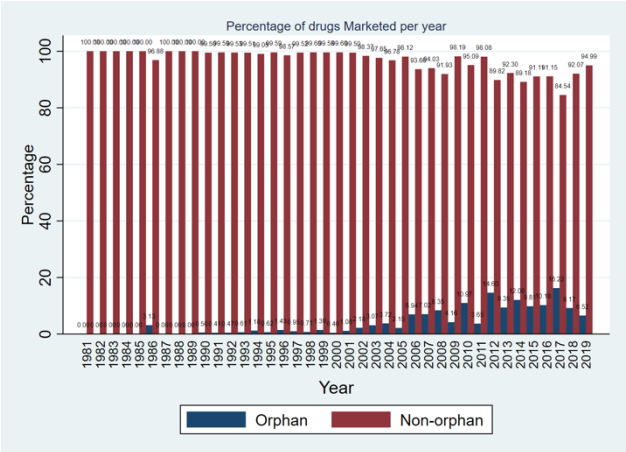


Figure 24. Percentage of orphan designated and non-orphan products that are marketed for each year between 1981 and 2019, out of total products marketed for each year.

Figure 25 presents the regional distribution for marketed products for non-orphan products. It shows that historically most market launches for non-orphan products occurred in the EU and ROW regions although the shares of market launch for these regions over global market launches has declined over time. The US percentage of non-orphan products launches has increased over the years amounting to just below a fifth of global market launches in recent years.

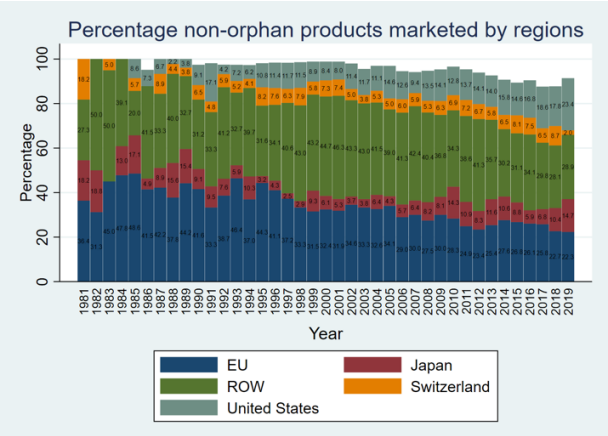


Figure 25. Regional distribution (%) of non-orphan products marketed in each year between 1981 and 2019 (out of total orphan designated and non-orphan marketed products in each year).

Figure 26 presents the regional distribution for marketed products for orphan designated products. Most orphan designated products are marketed in the EU followed by the US. The EU share of global marketed orphan products has increased since 2000 with the introduction of the Orphan Medicinal Product Regulation but decreased in the last year. Japan, Switzerland and ROW regions market launches constitute a small fraction of total global launches amounting to less than 1% of total activity in most years.

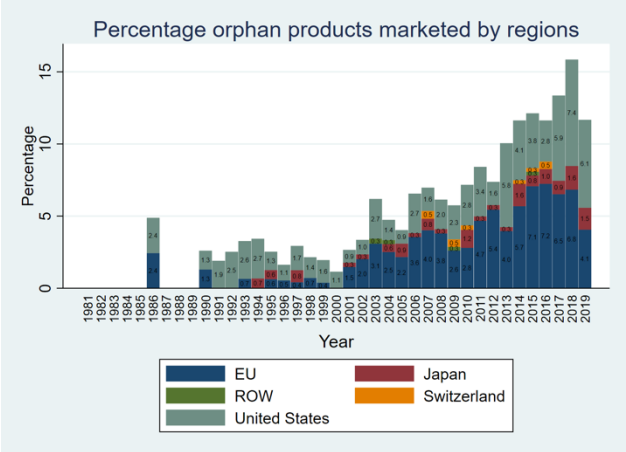


Figure 26. Regional distribution (%) of orphan designated products marketed each year between 1981 and 2019 (out of total orphan designated and non-orphan marketed products in each year).

2.2.3 Key Messages

2.2.3.1 Across all Years

- We observed approximately 1,400 orphan designated and 27,000 non-orphan products between 1980 and 2019.
- For orphan designated products, about 10% were observed in early stage R&D, 78% in late stage R&D and 10% have been marketed between 1980-2019.
- For non-orphan products, about 23% were observed in early stage R&D, 68% in late stage R&D, and 8.5% have been marketed between 1980-2019.
- Looking at orphan designated and non-orphan products by disease area there are similarities on the disease areas that get a higher proportion of R&D activity and innovation with the top diseases being cancer, endocrine and metabolic disorders, cardiovascular and infectious. There are clear differences in activity for orphan and non-orphan products. There is more R&D activity and market launches for non-orphan than for orphan products in CNS disorders and infectious diseases with activity being higher for non-orphan than orphan products all the way from early stage R&D activity to market launch.

- On the other hand, and across all stages from early stage R&D through market launch cancer exhibits a higher proportion of activity for orphan than non-orphan products.
- The activity by ATC reflects these figures. For both orphan and non-orphan antineoplastic and immunomodulating agents as well as alimentary tract and metabolism ATCs receive a disproportionate amount of activity from early stage all the way to market launch.
- There are clear differences in activity for orphan and non-orphan products. There is more R&D activity and market launches for non-orphan than for orphan products in ATCs N-Nervous System, M-Musculo-skeletal system, G-Genito-urinary system and sex hormones with activity being higher for non-orphan than orphan products in early/ late stage R&D and in market launch. On the other hand, and across all stages from early stage R&D through market launch orphan products exhibit a higher proportion of activity for ATCs L-Antineoplastic and immunomodulating agents and B-Blood and blood forming organs.
- In the analyses by region: nearly all R&D activity and market launches for orphan designated products occur in the US followed by Europe although the share of global activity for the US declines as one moves from early stage R&D to market launch. Japan assumes an increasing role on activity as we move from early stage R&D to market launch being responsible for 11% of global orphan products market launch. Also, Switzerland role is increasing over the innovation pathway albeit remaining marginal when compared to other regions. Also, for non-orphan drugs the US assumes a leading position in early and late stage R&D but it declines as we move from early stage R&D to market launch. It is followed by the EU and the ROW regions with the latter becoming the top region with market launches globally. Both Japan and Switzerland have marginal roles on global activity, but with an increasing as we move from early stage to market launch.

2.2.3.2 By Year Analyses

- When assessing the percentage of orphan designated and non-orphan products for each year between 1981 and 2019 out of total orphan and non-orphan activity in each of those years, we find that across all stages of development (early stage R&D, late stage R&D, and market launch) orphan designated products form an increasing proportion of yearly pharmaceutical innovation, that is more salient in late stages and marketed albeit in the proportion of orphan (non-orphan) drugs related activity having experienced a decline (increase) in the last couple of years.
- Decomposing these effects by region and year we find that for non-orphan drugs the regional distribution activity is similar across early and late stage R&D. Historically more activity has taken place in the US, followed by the EU and the rest of the world. The US ranking is particularly prominent in early R&D phases. The rest of the world region has gained prominence globally on early and late stages R&D activity over the years while Japan and Switzerland exhibit a decline in early and late stage activity. With regards to market launch ROW and EU historically exhibit a higher, albeit decreasing, proportion of global market launches than the other regions. These are followed by the US that has exhibits an increasing proportion of global marketed products over time.
- For orphan drugs early stage global R&D activity is dominated by the US however the share of early stage activity has increased until 2016 and decreased thereinafter. The US are also the region with the highest share of global late stage R&D activity followed by the EU that has experienced an increase in orphan products R&D activity since around 2000. With regards to market launch activity both the US and the EU account for nearly all orphan products global market launches exhibiting an increasing trend over time since 2000 with the introduction of the Orphan Medicinal Product regulation in the EU

2.3 Forecasts

Based on the historical development of orphan designated and non-orphan products, we predicted the stock of innovation to be made available between 2020 and 2030 in the absence of any changes to current policies. We run the forecasts across all diseases and ATCs, but also stratify the analyses by disease and ATC.

2.3.1 Data

The total number of observations in our data is 953,979. We start by excluding products for which dates for events is 'Unknown'. This leads to 20,080 observations being excluded from the analysis. For products where the event date is partial i.e., instead of month and year, we observe quarter and year, we consider the middle month of the quarter. Similarly, for first and second half of the year. Since we are interested in mapping market launch, we exclude orphan drug designations events from our final dataset (n=43,852).

Given that our data captures very few observations pre-1980, for the forecasts, we use data from 1981 to 2019. The unit of analysis is at the product-indication level where we use IQVIA level 3 indication to define a unique product. We exclude observations with missing information on ATC class or diseases, and also duplicate events for the same product. Any products with missing information on indication are also excluded. We are interested in forecasting market launches; therefore, we exclude all other events and keep only 'marketed' products as input for the forecasting model. This leaves us with approximately 25,000 marketed products across orphan and non-orphan products. However, since we are interested in capturing new products that are launched globally, as input for the model, we use only the first instance when an orphan drug product is launched for a specific indication. If the same product is launched again in another country for the same indication at a later point, we do not include this in the input for the forecasting. However, is the same product is launched in a country for two different indications we consider these as two distinct observations that are included in the forecasts. For simplicity of exposition, we will refer to the pair product-indication as product.

2.3.2 Methods

We use linear time series methods to estimate the number of orphan and non-orphan products that will be launched between 2020 and 2030. We run the forecasts across all disease areas and within each ATC and disease group. Specifically, we use a local linear trend model for observations from a Poisson distribution for forecasting the number of orphan and non-orphan products that will be launched. Local linear trend models are preferred over other types of time-series models since they can be easily adapted to model count data. Such models also allow us

to account easily for missing data, irregularly spaced observations and policy interventions. The local linear trend model with Poisson link is estimated maximum likelihood.

The observations y_t say on orphan drugs have a Poisson distribution with mean λ_t, and $\theta_t = log(\lambda_t)$ is modelled as:

$$\theta_t = \alpha_t \quad (1)$$

$$\alpha_t = \alpha_{t-1} + \beta_t + \varepsilon_t \quad (2)$$

$$\beta_t = \beta_{t-1} + \vartheta_t, \quad (3)$$

where equation (1) describes how the logarithm of the mean of the variable y_t (for example- number of orphan products), and equations (2) and (3) capture the stochastic trend and the shift in trend respectively. The error terms ϵ_t and ϑ_t are assumed to be zero mean, normally distributed, serially uncorrelated and independent of one another. The above model is used to make out-of-sample predictions of the number of products that can be expected to be launched from 2020 to 2030, given the historical pharmaceutical R&D activity. We predict the number of orphan and non-orphan products across disease groups and ATC classes from 2020 to 2030.

2.3.3 Results

By disease area

Figure 27 shows the forecast from 2020 to 2030 by disease area for orphan designated products. This figure shows that 675 orphan designated products can be expected to be launched between 2020 and 2030. About a quarter of these products will target cancer (45%), cardiovascular disease (14%) followed by endocrine and metabolic disorders and musculoskeletal disorders (11% each). In the absence of any incentives and policy changes, the lowest number of forecasted new orphan designated products is expected to be launched for gastrointestinal disorders (0.45%), respiratory diseases (3.3%), and CNS disorders (4.6%). Ophthalmological, genitourinary and dermatological disorders could not be forecasted given the low volumes so it is likely these will be the disease areas with the least innovation in the next decade.

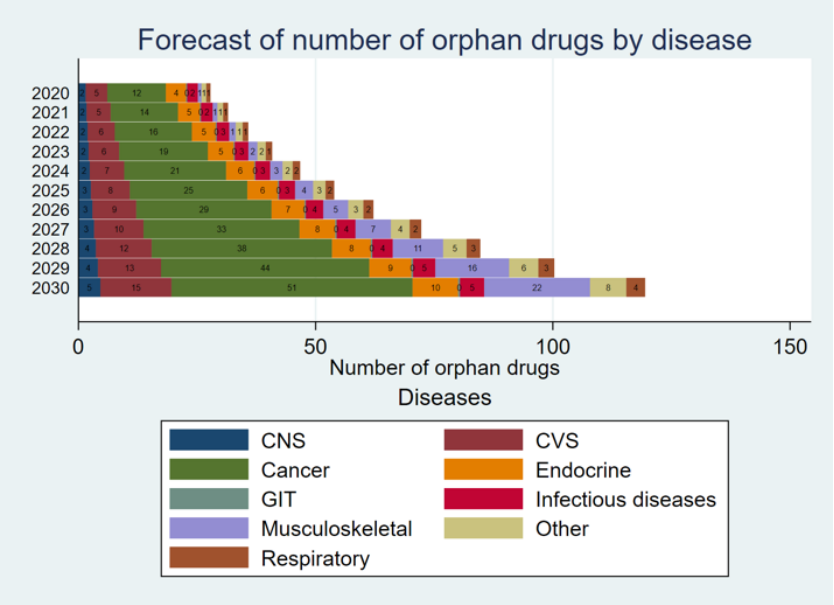


Figure 27. Forecasted orphan designated products to be launched globally between 2020 and 2030 by disease area[7].

Figure 28 shows the forecast from 2020 to 2030 by disease area for non-orphan products. It shows that 2485 non-orphan products can be expected to be launched between 2020 and 2030. More than fifty percent of launches is concentrated in three disease areas cancer (28%) will target of these products target cancers (28%), musculoskeletal (15%) and infectious diseases (11%). The areas that will experience less innovation, in the absence of incentives and policies, are genitourinary and ophthalmological disorders.

[7] Please note that forecasts could not be made for orphan designated products for ophthalmological, genitourinary and dermatological disorders due to low variation in the products launched for these disease categories.

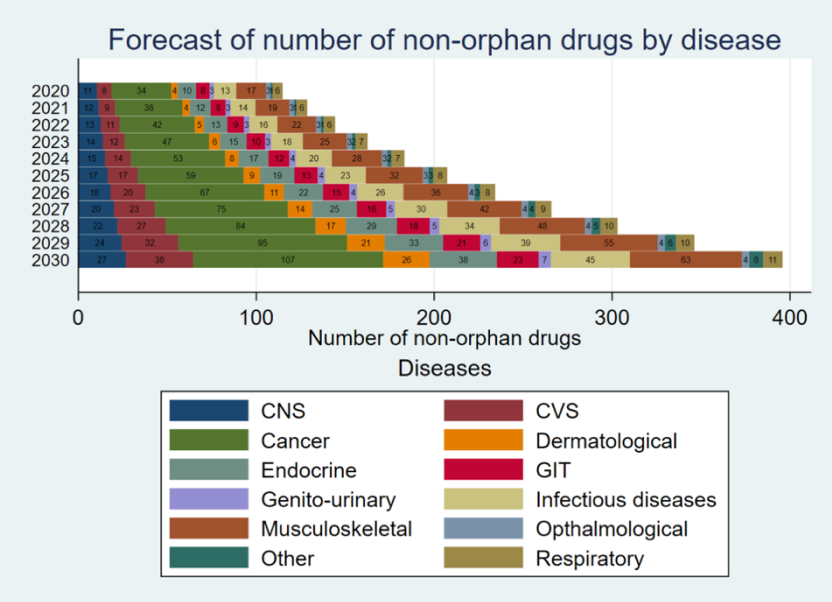


Figure 28. Forecasted non-orphan products to be launched between 2020 and 2030 by disease area.

By ATC

Figure 29 shows the forecast from 2020 to 2030 by ATC for orphan designated products. Based on the historical ATC data, 807 orphan designated products can be expected to be launched between 2020 and 2030. More than fifty percent of these forecasted launches are concentrated in two ATCs: antineoplastic or immunomodulating agents (41%; ATC class L) and products targeting the cardiovascular system (18%; ATC class C). These are followed by ATC B- Blood and blood forming organs that will experience 11% of total market launches.

ATCs D-dermatological, P-parasitology and S-sensory organs could not be forecasted due to the very low level of market launches historically meaning that negligible levels of innovation can be expected in these ATCs in the next decade in the absence of targeted policies and incentives. Form the ATCs for which forecasts could be estimated ATCs H-Systemic hormonal preparations, excluding sex hormones, N-Nervous system and sensory S-Sensory organs are those where the least innovation can be expected in the next ten years (0.16%, 3.5% and 2.7% of total forecasted innovation respectively).

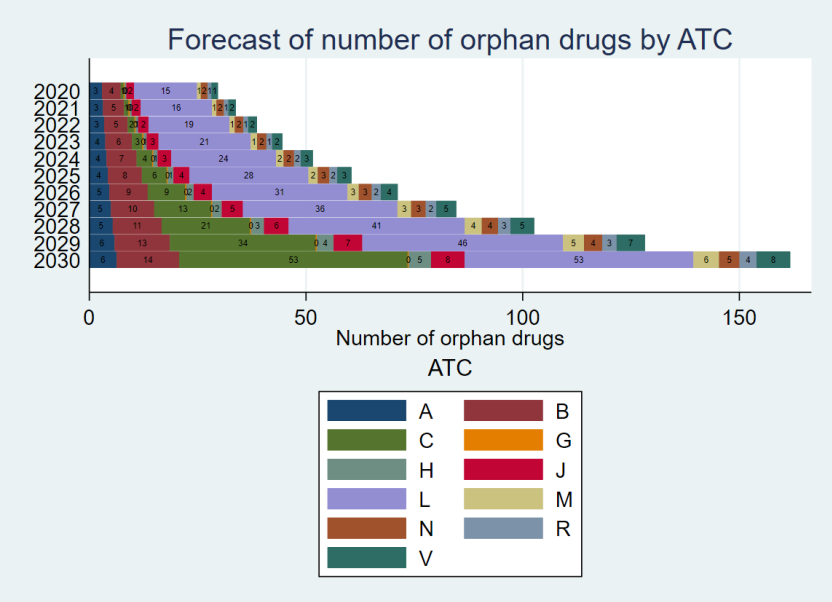


Figure 29. Forecasted orphan designated products to be launched between 2020 and 2030 by ATC. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). Diagnostic agents (ATC class T), P-parasitology and S-sensory organs could not be forecasted due to the very low level of market launches due to low volumes in the products launched in this ATC.

Figure 30 shows the forecast from 2020 to 2030 by ATC for non-orphan products. It shows that 3088 non-orphan products can be expected to be launched between 2020 and 2030. Three ATCs will absorb more than 60% of total innovation, these are ATCs A-Alimentary tract and metabolism, D-Dermatologicals and L-Antineoplastic and immunomodulating agents (with 13%, 20%, 27% of total forecasted innovation respectively). ATCs H-Systemic hormonal preparations, excluding sex hormones, P-Parasitology and S-Sensory organs are those where the least innovation can be expected in the next ten years (0.91%, 0.44% and 1.6% of total forecasted innovation respectively).

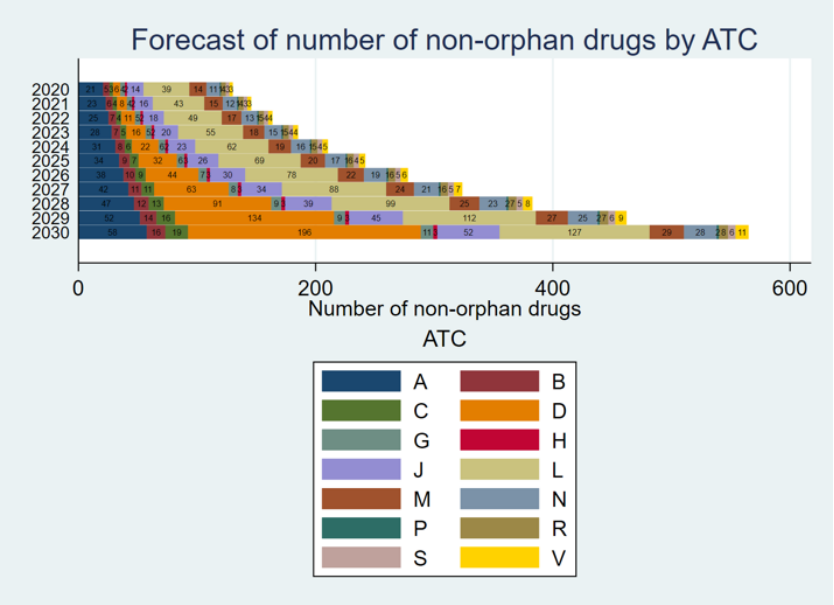


Figure 30. Forecast for number of non-orphan products to be launched between 2020 and 2030 by ATC. A = Alimentary tract and metabolism, B = Blood and blood forming organs, C = Cardiovascular system, G = Genito-urinary system and sex hormones, H = Systemic hormonal preparations, excluding sex hormones, J = General anti-infectives systemic, L = Antineoplastic and immunomodulating agents, M = Musculo-skeletal system, N = Nervous system, P = Parasitology, R = Respiratory system, S = Sensory organs, V = Various (EphMRA, 2020). Please note that forecasts could not be made for diagnostic agents (ATC class T) due to the reduced number of launches for this ATC.

2.3.4 Key Messages

- Based on the historical data and in the absence of any policy changes, between 675 and 807 orphan designated products, and between 2485 and 3088 non-orphan products, can be expected to be launched between 2020 and 2030.
- Most new orphan designated products will target cancer, cardiovascular disease, endocrine and metabolic disorders and musculoskeletal disorders, while most new non-orphan products will target cancer (28%), musculoskeletal (15%) and infectious diseases (11%).
- Almost no new orphan designated products expected to target ophthalmological, genitourinary, dermatological, gastrointestinal, respiratory and CNS disorders

3. Inequalities

The analyses in section 2.2. reveals heterogeneity in R&D activity and market launches across the different disease areas and ATCs. These differences may be justified by differences in need across the different disease areas but may also be driven by other considerations beyond need such as prospects for profitability, inherent difficulty of innovation and higher risk of investment in certain disease areas. While differences in R&D efforts across disease areas that reflect differential needs would warrant, a distribution of efforts across disease areas that does not reflect need generates inequalities in R&D and market launch activity that may reflect in inequalities in health outcomes in the population. In this section we measure the direction and magnitude of such inequalities. In particular, we run two types of analyses. In the first we compare inequalities in R&D activity and market launches across parent categories. In the second analyses we measure the level and direction of inequalities for each patent disease separately. Both analyses consider data from 1980-2019 and two distinct periods – pre-2000 and post-2000 - reflecting the period prior and post European Orphan Medicinal Product Regulation.

3.1 Data

We build a unique dataset merging R&D activity across all disease areas matched to prevalence data. To do so we merge to the dataset described in section 2.1.3 the prevalence data from the Orphanet epidemiological disease database (Orphanet, 2019b).

For any rare disease indications in the IQVIA indication hierarchy, we mapped the indication to the ORPHA code in Orphanet. In addition, any free text in the IQVIA Pipeline Intelligence dataset that described a rare disease indication for a product was similarly mapped to the relevant ORPHA code. We did this for across all products in the pipeline intelligence dataset to obtain a comprehensive overview of innovation and market launch for rare diseases (regardless of orphan drug status of individual products).

As described in section 2.1.3, we are left with a database where all possible observations relating to rare diseases are flagged, and where possible, these events are assigned to the relevant ORPHA code. For the few rare disease observations in the Pipeline Data not already assigned a code, we manually search synonyms using a disease dictionary and search for the relevant ORPHA code. The Orphanet classification is organised according to three hierarchical levels: *group of disorders*, *disorder*, and *subtype of disorder*, that determine the level of precision. The *disorder* level is the main typological level for reporting and identifies unique clinical rare diseases. We therefore aim to match each rare disease observation at the *disorder* level. However, due to the nature of the Pipeline Intelligence dataset and the sometimes-broad level of the IQVIA indications, in some cases it is only possible to match observations at the *group of disorders* level.

To allow for analysis by medical speciality, we match each rare disease observation to a parent category, as defined by Orphanet. While a *disorder* may correspond to multiple medical specialities to which it is relevant, Orphanet have assigned each *disorder* to one prioritised medical speciality, known as the 'preferential parent' (Orphanet 2019c). We thereby assign each rare disease observation within the dataset to its preferential parent according to the ORPHA code. Where possible, we manually assign parents to the rare disease observations for which either i) the matched ORPHA code is at the *group of disorders* level (by matching to the parent which most disorders within the group are paired to) and ii) for which we have not managed to map to an ORPHA code (using the indication and any other detail provided by IQVIA).

The epidemiological disease database contains data on prevalence and incidence of rare diseases, based on the international scientific literature, and expert opinion. This data was used to estimate prevalence at the *disorder* level and calculate aggregated prevalence for rare disease parent categories. Using the same steps as Nuegang Wakap et al. (2020), to avoid duplicate counts we considered only data at the *disorder* level (unique clinical rare diseases) and 'point prevalence' was chosen as the epidemiological indicator for analysis. The original Orphanet data are recorded as either numerical values or as predefined ranges when numerical values are not available, and are available at the level of worldwide, European, or individual country prevalence estimates; each disorder may have several values for different geographic regions. As per Nuegang Wakap et al. (2020), a subset of the data was selected to ensure homogeneity as follows: i) disorders were excluded if a point prevalence could not be calculated, including all rare cancers, infectious diseases, and poisonings which are described by incidence; ii) one-point prevalence per disorder was included in preference of worldwide then European values. If no aggregate point prevalence estimates were available, an average of the European country estimates was used, or finally, the USA figure was used if no other data were available; iii) disorders with a mean prevalence exceeding 5/10,000 were excluded. We obtain a minimum and maximum estimate of the point prevalence per 100,000 for each disorder, treating data differently based on whether the prevalence was i) a numerical value, ii) a predefined class range, or iii) based on case and family reports. For those with a numerical value, the minimum and maximum were set as equal to the value. For those with a prevalence range, the minimum was defined as the lowest value within the range and the maximum was the highest value within the range. For class <1/1,000,000, the maximum were assigned as 1/1,000,000 and the minimum was designated as the known lowest prevalence for any *disorder* within the same preferential parent category; here we depart from Nuegang Wakap et al. as it is important for our analysis that we are able to rank *disorders* according to prevalence and assigning a value of 1/1,000,000 for both the minimum and maximum (as they do), artificially ranks these disorders identified by classes at the top end of the burden. For disorders characterised by case and family reports, the minimum value was indirectly calculated as the sum of the case reports divided by the 2019 global population; to ensure family size was accounted for, the maximum value was set repeating the analysis using ten cases per family.

Note that prevalence estimates are not available for all disorders, and while it is difficult to reasonably infer prevalence estimates for these disorders, as a robustness check, we attempt to characterise the additional prevalence burden. For each *disorder* which meets the criteria laid out (i.e., is a rare disease in Europe & can be characterised by point prevalence) and is not assigned a point prevalence estimate, we impute a prevalence range for the disorder. We assign these disorders with a prevalence range that is equal to the most common Orphanet defined prevalence range within that parent category that appears in the existing data – this was almost exclusively

the lowest class range of <1/1,000,000. We then build sensitivity minimum and maximum boundaries according the methods above.

The resulting prevalence dataset includes all *disorders* defined by Orphanet, each matched to their preferential parent, and each with four prevalence estimates: i) the minimum and maximum boundaries where *disorders* without a prevalence estimate in the epidemiological dataset are marked as missing; and ii) the minimum and maximum boundaries including imputed prevalence estimates for the *disorders* with no available data.

For the inequalities analysis we are also interested in calculating prevalence by parent. To do so we obtain minimum and maximum boundaries of global point prevalence by parent Orphanet category. We do this by summing the *disorder* level prevalence estimates by parent category. We calculate these point prevalence estimates for parent categories that are i) suitable to be estimated using point prevalence (i.e., excluding the neoplastic, infectious diseases, and toxic effect parent categories) and ii) that are relevant to this study assessing pharmacological R&D. For the latter, we exclude parent categories relating to rare surgical disease and are left with 23/30 Orphanet parent categories (Table 7).

DISEASE CATEGORIES
Rare bone disease
Rare cardiac disease
Rare circulatory system disease
Rare developmental defect during embryogenesis
Rare disorder potentially indicated for transplant or complication after transplantation
Rare endocrine disease
Rare gastroenterologic disease
Rare genetic disease
Rare gynaecologic or obstetric disease
Rare hematologic disease
Rare hepatic disease
Rare immune disease
Rare inborn errors of metabolism
Rare infertility
Rare neurologic disease
Rare odontologic disease
Rare ophthalmic disorder
Rare otorhinolaryngologic disease
Rare renal disease
Rare respiratory disease
Rare skin disease
Rare systemic or rheumatologic disease
Rare urogenital disease

Table 7. Parent disease categories.

We carry two types of analyses: i) across parent categories and ii) within parent category. The prevalence datasets as described above are merged to the master Pipeline data at both levels so that each observation has two sets of prevalence estimates (i) aggregated at the parent level and ii) unique at the disorder level. The final database contains 95,558 observations that can be used at the parent level and 77,896 (82%) observations at the *disorder* level. The reason for the discordance is that, as described above: i) some observations in our dataset are identifiable only at the *group of disorders* level, and so can be assigned a parent but not a *disorder*, and ii) some observations have no ORPHA code, but the parent can be identified using the IQVIA indication. For those event observations showing in IQVIA with a broad indication (i.e., not at disorder level) we assessed whether the same product with an event flagging a *group of disorders* had further events in the Pipeline data presenting a more disaggregated *disorder*. If that happened and the identified *disorder* was nested within the identified *group of disorders* we have attributed that *disorder* to the original event. For the cases where that was not feasible and in the disorder level analysis we proceeded in two ways: i) first excluded those observations we could not match to a disorder; ii) as a second approach expanded to include every possible *disorder* that is included under the *group of disorders* within the Orphanet hierarchy. The expanded dataset includes 356,851 observations at the parent level and 354,915 (99%) observations at the disorder level. The baseline analyses use the expanded dataset, but we also run it by considering the data resulting from i) as a robustness check.

Analysis at Parent level

We start with a sample of 95,558 observations in the rare disease events data relating to parent disease categories we can include in the analysis. Events before 1980 are excluded (7 observations). For each product-country-indication we include only the first time an event is observed i.e., duplicate events for the same product-country-indication are excluded (indication captures either the orpha code where available or the narrow indication presented in the Pipeline data where a orpha name is not available). We then classify all events into three stages – early, late and marketed. For description of these events see section 3.1. We drop all observations that are not classified into one of the three stages. This leads to a sample size of 53,482 observations. We then count total R&D activity per parent disease across all years for each R&D stage, i.e., R&D activity is summed across years to produce a total count of R&D activity for each parent disease for each stage. This data is then merged with the prevalence data on parent diseases. The data is then collapsed at the parent disease level. Given that there are three diseases parent categories for which there is prevalence but historically no R&D activity or market launches in the Pipeline data we further generate these observations attributing a value of zero for early, late and marketed stages. The final parent disease level dataset contains 23 parent diseases with information on prevalence and R&D activity for early, late and marketed stages from 1980 to 2019. When we perform the analysis before and after year 2000, we use the same procedure to calculate the total R&D activity per parent disease per R&D stage from 1980 to 1999 and then from 2000 to 2019.

Analysis within parent disease level

Using the expanded dataset as explained above, the staring data contains 354,915 observations in the rare disease events data within the included parent categories. Events before 1980 are excluded (10 observations). For each product-country-orpha code we include only the first time an event is observed i.e., duplicate events for the same product-country-orpha code are excluded. We then classify all events into three stages – early, late and marketed. For description of these events see section 3.1. We drop all observations that are not classified into one of the three

stages. This leads to a sample size of 219,066 observations. We then count total R&D activity per orpha code over all years for each R&D stage, i.e., R&D activity is summed across years to produce a total count of R&D activity for each disorder for each stage. These data are then merged with the prevalence data. For a total 3564 disorders for which there exists prevalence data there is no R&D or market launch activity in the Pipeline data we attribute zero value to the early, late and marketed variables. Observations with missing prevalence data are excluded. The data is then collapsed at the disorder level so that we end up with a dataset at disorder level for 3,725 unique disorders nested within 23 parent disease categories with information on prevalence, total R&D activity and total market launches over the entire period of the data, i.e., 1980 and 2019. When we perform the analysis before and after year 2000, we use the same procedure to calculate the total R&D activity per disorder per R&D stage from 1980 to 1999 and then from 2000 to 2019.

3.2 Methods

Inequalities R&D for the different diseases are measured by means of concentration curves (CCs) and indices (CIs). The concentration curves plot the cumulative share of one variable ranked by the medical need – i.e., diseases ranked by prevalence, the incidence and the survival rates - against the cumulative share of the number/weighted number/magnitude of R&D activity and market launches targeting the given diseases to provide a graphic representation of the distribution of R&D activity and market launches. If each disease were to benefit from a volume of R&D activity/market launches in proportion to the associated medical need as proxied by their epidemiological variables, the concentration curve would be on the 45^{o} diagonal line, coinciding with the line of equality.

Inequality is therefore represented as the distance of concentration curve from the equality line. If the concentration curve lies below the line of equality, there is an inequality favouring high-incidence and/or high-prevalence diseases that we call *pro-occurrence* inequality, whereas if concentration curves lie above the line of equality, activity will be concentrated on lower-occurrence disorders, which we label *low-occurrence* inequality. Similarly, if concentration curves drawn according to the relative survival rates lie below the line of equality, research disproportionately favours those disorders with a high survival, whereas if they lie above the line of equality, research disproportionately concentrates on those disorders with a lower survival rate.

Although the concentration curves offer a graphic representation of the direction of the inequality, they do not allow ascertaining its magnitude. Therefore, for each distribution we compute a standard concentration index which measures twice the area between the concentration curve and the line of equality. There are a family of concentration indices and the choice of concentration index is dependent on the characteristics of the outcome variable as well as normative judgements on the measurement of inequality (O'Donnell et al., 2016). As the number of clinical trials and market launches for each disease is not upper bounded and the measurement scale is fixed, the standard concentration index is an appropriate measure of the divergence from the line of equality. The concentration index is therefore defined as:

$$CI = 1 - 2\int_0^1 C_x dx \qquad (1)$$

where C_x is the concentration curve. It can also be calculated as:

$$\frac{1}{n}.\sum_{i=1}^{n}\left(\frac{T_i}{\bar{T}_i} - (2E_i - 1)\right) \qquad (2)$$

where T_i is the outcome variable for which inequality is measured (the number of R&D events/market launches for disease *i*), while E_i is the fractional rank of the ordering variable (prevalence, incidence or survival rate for disease *i*). The concentration index ranges between -1, maximum *low-occurrence inequality* in the case of concentration curves defined according to the prevalence, that is the research is concentrated on lower occurrence diseases, to 1, maximum *pro-occurrence inequality*, that is research is concentrated on the most common diseases. As the index measures relative inequality, it is invariant to equi-proportional changes in the variable of interest (R&D activity and market launches) and can be an appropriate measure even when concentration curves coincide, thus the inequality assessment cannot be done by visual inspection of the curves.

3.3 Results

3.3.1 Across Parent Categories

Figure 31 presents the concentration curves of early- and late-stage R&D and market launches across parent rare disease groups ranked by prevalence. For all stages there is inequality with activity disproportionately concentrated in high-prevalence parent groups.

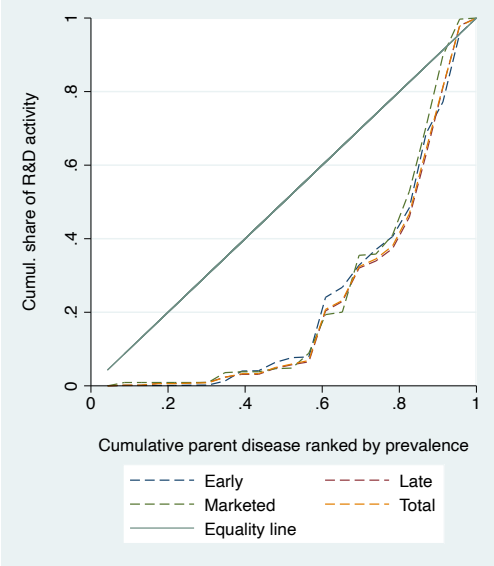


Figure 31. R&D Concentration curve for rare cancers

The level of inequality is statistically significant and similar magnitude across the different stages of the process as observed by the concentration indices in Table 8.

		N	CI	P-value
1980-2019	Early	23	0.536***	0.0004
	Late	23	0.553***	0.0003
	Marketed	23	0.522***	0.0012
	Total	23	0.549***	0.0003
Pre-2000	Early	23	0.576***	0.0096
	Late	23	0.593***	0.0017
	Marketed	23	0.410**	0.0444
	Total	23	0.556***	0.002
Post-2000	Early	23	0.528***	0.0004
	Late	23	0.551***	0.0003
	Marketed	23	0.550***	0.0014
	Total	23	0.548***	0.0002

Table 8. Concentration Indices (CI) for the distribution or Early-, Lata-Stage R&D Activity and Market Launches. Note: *** p-value<0.001, ** p-value<0.05, * p-value<0.1.

In Figure 32 and Table 8 we decompose the analysis considering two distinct periods that capture the years pre- and post- European Orphan Medicinal Product Regulation. While the level of inequality does not exhibit significant changes before and after the regulation, for marketed there has been an increase of the inequality level. The concentration curve analysis is confirmed by the concentration indices presented in Table 8 where we can see that for market launches the CI increases from 0.410 (p-value<0.05) for the pre-2000 period to 0.55 (p-value<0.001) in the post-2000 period.

Notably several rare parent categories have zero R&D and/or market launch activity. There is no early- and late-stage R&D activity nor market launches in our data between 1980 and 2019 for genetic diseases, infertility diseases and odontologic disease over the entire period of the analyses. There is no early R&D activity, and no market launches for rare circulatory disease over the entire period. Finally, there are no market launches over the entire period for gynaecologic or obstetric disease.

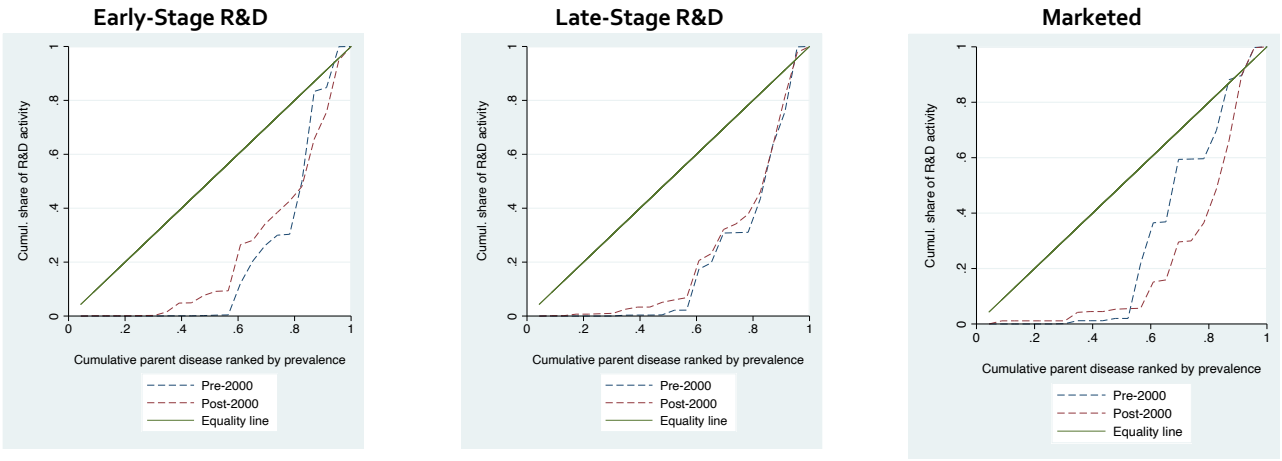
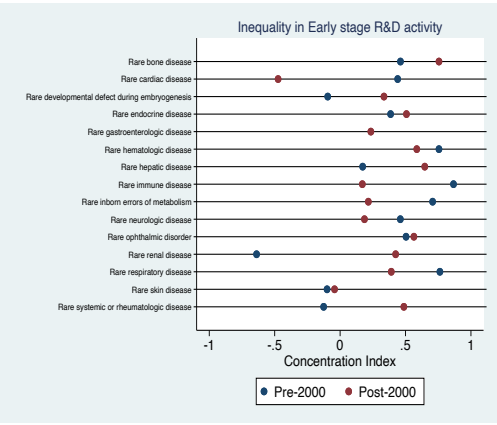


Figure 32. R&D Activity Concentration curve for rare cancers, in pre-2000 and 2000-2019

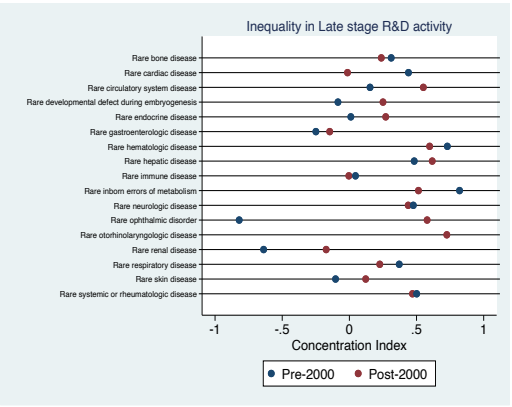
3.3.2 By Parent

We then assessed inequalities for each parent category separately, pre- and post- 2000. Figure 33 and Tables 9-11 present the CIs. Inequalities vary significantly across parent categories, over time and across the different stages of the R&D process.

Early-Stage R&D



Late-Stage R&D



Market Launch

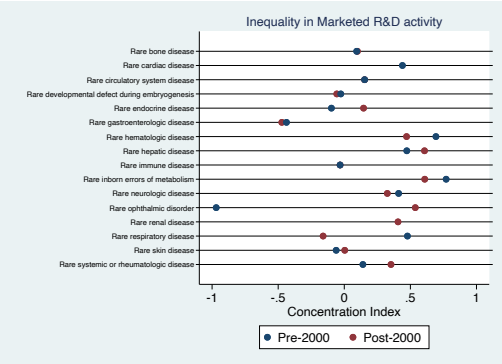


Figure 33. Concentration Indices by activity type pre-2000 and 2000-2019. Note: some parent categories exhibit no or very few R&D activity and/or market launches in some years. For those the CI corresponding to those years is not computed.

	Early-Stage R&D Activity			
	1980-1999		2000-2019	
Parent name	CI	p-value	CI	p-value
Rare bone disease	0.461	0.1646	0.756**	0.0297
Rare cardiac disease	0.440	0.4567	-0.474*	0.0926
Rare developmental defect during embryogenesis	-0.095	0.5677	0.335***	0.0014
Rare endocrine disease	0.386	0.3893	0.507**	0.0192
Rare gastroenterologic disease			0.235	0.4239
Rare hematologic disease	0.756**	0.0233	0.586***	0.0010
Rare hepatic disease	0.172	0.7709	0.647**	0.0436
Rare immune disease	0.867***	0.0081	0.170*	0.0555
Rare inborn errors of metabolism	0.707*	0.062	0.216**	0.0181
Rare neurologic disease	0.460***	0.001	0.186***	0.0014
Rare ophthalmic disorder	0.504*	0.0587	0.564**	0.0115
Rare renal disease	-0.638	0.273	0.425	0.1252
Rare otorhinolaryngologic disease			0.642**	0.0889
Rare respiratory disease	0.763*	0.0515	0.391	0.1565
Rare skin disease	-0.100	0.572	-0.042	0.7589
Rare systemic or rheumatologic disease	-0.126	0.7873	0.487***	0.0001

Table 9. Concentration Indices for the distribution of Early-Stage R&D pre-2000 and 2000-2019. Note: some rare parent categories exhibit no or very few early-stage R&D activity in some years and/or have missing prevalence. For those the CIs are not computed. *** p-value<0.001, ** p-value<0.05, * p-value<0.1.

For early-stage R&D pre-2000 several disease categories exhibited pro-high prevalence inequality in the distribution of early stage R&D activity, these are namely hematologic disease, immune disease, inborn errors of metabolism, neurologic disease, ophthalmic disorders and respiratory disease. For most of these disease groups inequality has remained pro-high prevalence but has reduced after the implementation of the European Orphan Medicinal Product Regulation as observed by the lower (positive and significant) CIs (Table 9, Figure 33). Exceptions in this group are for ophthalmic disorders where the level of pro-occurrence inequality has remained at the same level and for respiratory disease where post-2000 there are no inequalities with activity being distributed in proportion to prevalence. The level of inequality has increased for rare bone disease, rare hepatic disease, rare developmental defect during embryogenesis, rare endocrine disease, and rare systemic or rheumatologic disease.

All these disease categories exhibit no inequality pre-2000 but have positive CIs statistically different from zero indicating pro-occurrence inequality post-2000 (Table 9).

Early stage R&D is distributed proportionally to prevalence over the entire period of analyses for rare gastroenterologic, renal and skin disease. Finally, for cardiac disease early stage R&D activity is found to be distributed in proportion to prevalence pre-2000 but post-2000 (Table 9, Figure 33). The distribution of activity exhibits pro low occurrence inequality with cardiac disorders with lower prevalence receiving disproportionately more activity (albeit the CI being only significant at 10%) (Table 9, Figure 33).

	Late-Stage R&D Activity			
	1980-1999		**2000-2019**	
Parent name	CI	p-value	CI	p-value
Rare bone disease	0.311***	0.0096	0.238	0.1725
Rare cardiac disease	0.440	0.4567	-0.014	0.9588
Rare circulatory system disease	0.154	0.8022	0.551	0.1543
Rare developmental defect during embryogenesis	-0.085	0.5053	0.250***	0.0001
Rare endocrine disease	0.011	0.9552	0.271**	0.024
Rare gastroenterologic disease	-0.249	0.2081	-0.146	0.3208
Rare hematologic disease	0.729**	0.0183	0.597***	0.0024
Rare hepatic disease	0.483	0.4123	0.617**	0.019
Rare immune disease	0.045	0.141	-0.004	0.8809
Rare inborn errors of metabolism	0.820*	0.0842	0.514***	0.0000
Rare neurologic disease	0.476**	0.0421	0.438***	0.0000
Rare ophthalmic disorder	-0.820	0.1165	0.579**	0.0134
Rare otorhinolaryngologic disease			0.725	0.0637
Rare renal disease	-0.638	0.273	-0.173	0.6060
Rare respiratory disease	0.371	0.3052	0.226	0.2561
Rare skin disease	-0.103	0.5497	0.122	0.1816
Rare systemic or rheumatologic disease	0.501**	0.0213	0.470***	0.0000

Table 10. Concentration Indices for the distribution of Early-Stage R&D pre-2000 and 2000-2019. Note: some parent categories exhibit no or very few late stage R&D activity in some years and/or have missing prevalence. For those the CIs are not computed. *** p-value<0.001, ** p-value<0.05, * p-value<0.1.

For late-stage R&D and pre-2000 the disease categories that exhibited pro-high prevalence inequality in the distribution of R&D activity, are, in order of level of inequality, inborn errors of the metabolism, hematologic disease, rare systemic or rheumatologic disease, neurological disease and bone disease (Table 10, Figure 33). For the remainder disease categories late stage R&D activity was distributed in proportion to need. The level of inequality has decreased for all these disease groups post-2000 although only marginally for neurologic disease and systemic or rheumatologic disease. For bone disease post-2000 late stage R&D activity is distributed in proportion to need (Table 10, Figure 33). Inequality has increased post-2000 for rare developmental defect during embryogenesis, rare endocrine disease, rare hepatic disease, and rare ophthalmic disorder that exhibited no inequality pre-2000 but pro-occurrence inequality after the implementation of the European Orphan Medicinal Product Regulation (Table 10, Figure 33).

Late stage R&D is distributed proportionally to prevalence over the entire period of analyses for rare cardiac disease, circulatory system disease, gastroenterologic disease, immune disease, otorhinolaryngologic disease, renal, respiratory and skin disease (Table 9, Figure 33).

	Market Launch			
	1980-1999		2000-2019	
Parent name	CI	p-value	CI	p-value
Rare bone disease	0.094	0.6645	0.099	0.6344
Rare cardiac disease	0.440	0.4567		
Rare circulatory system disease	0.154	0.8022	0.154	0.8022
Rare developmental defect during embryogenesis	-0.026	0.8503	-0.057	0.645
Rare endocrine disease	-0.097	0.6656	0.146	0.4082
Rare gastroenterologic disease	-0.437**	0.0219	-0.472**	0.0158
Rare hematologic disease	0.693**	0.0346	0.471**	0.01
Rare hepatic disease	0.473	0.1527	0.607**	0.0452
Rare immune disease	-0.032**	0.0363	-0.032**	0.0855
Rare inborn errors of metabolism	0.770	0.1349	0.609***	0.0001
Rare neurologic disease	0.411**	0.0456	0.326**	0.0105
Rare ophthalmic disorder	-0.969*	0.0934	0.537*	0.073
Rare renal disease			0.406	0.1376
Rare respiratory disease	0.478	0.2177	-0.160	0.5169
Rare skin disease	-0.061	0.68	0.004	0.9856
Rare systemic or rheumatologic disease	0.141	0.2724	0.353**	0.0173

Table 11. Concentration Indices for the distribution of market launches pre-2000 and 2000-2019. Note: some parent categories exhibit no or very few market launches in some years and/or have missing prevalence. For those the CIs are not computed. *** p-value<0.001, ** p-value<0.05, * p-value<0.1.

Concentration indices for market launches (Table 11, Figure 33) show that these are distributed in proportion to need for several disease groups over the entire period, namely: rare bone disease, cardiac disease, circulatory system disease, developmental defects during embryogenesis, endocrine disease, renal disease, respiratory disease, and rare skin disease.

Inequality has increased for systemic or rheumatologic disease, inborn errors of metabolism and hepatic disease for which activity was distributed in proportion to need pre-2000 but post-2000 becomes disproportionately concentrated towards high prevalence diseases. For certain disease groups the direction of inequality has remained

stable over time, albeit of, marginally, lower magnitude. Namely, for hematologic and neurologic disease over the entire period there is inequality pro-occurrence with a disproportionate level of market launches concentrated towards high prevalence disease. Instead for gastroenterologic disease and rare immune disease pre- and post-2000 market launches are disproportionately concentrated towards low prevalence diseases, and the level of low-occurrence inequality has remained fairly stable over time. An interesting finding relates to market launches for ophthalmic disorders that exhibit low-occurrence inequality pre-2000 but pro-occurrence inequality post-2000, albeit CIs being only significant at 10% in both periods (Table 11, Figure 33).

4. R&D Inequalities for Cancer

Cancer is the second leading cause of death globally accounting for more than 8.7 million deaths and particularly endemic in rich countries (Fitzmaurice et al., 2017). Rare cancers represent about 22% of all cancers diagnosed worldwide (Pillai and Jayasree, 2017).

To address this need, substantial investment has been directed towards the development of oncological therapies (Scannell et al., 2012; Pammolli et al., 2011). Anticancer therapies have been shown to be amongst the most profitable research and development (R&D) investments; representing more than 30% of the total new launches in the last decade and forecasted to contribute to increases in the industry's revenues of almost 50% between 2017 and 2022 (Iervolino and Urquhart, 2018). The increase in market launches of such high-cost therapies has been at the centre of the debate on whether the associated health benefits are commensurate to the high levels of expenditure required to fund access to these therapies and the opportunity cost of investing in such treatments rather than alternative therapeutically areas and/or disease areas (Claxton et al., 2015; Belloni et al., 2016; Exarchakou et al., 2018; Paris et al., 2017).

Ceteris paribus, with larger market sizes, common cancers exhibit higher prospects of profitability than rare cancers. Furthermore, according to Wong et al. (2019), rare cancers have a lower rate of probability of success (POS) on a clinical trial than common ones. While the authors estimated the POS to be 3.4% for overall oncology research, it is merely 1.2% in the case of rare cancers. POS could be lower in rare cancers research because of their intrinsic nature: heterogeneity between the small number of patients hinders the understanding of the disease's natural history and epidemiology, and hence the definition of specific diagnostic criteria which make research complex (Auvin et al., 2018; Nestler-Parr et al., 2018). Higher risk associated with complexity of research and low market profitability also creates incentives for firms to abandon the development of therapies targeting rare- cancers and repurpose them to other therapeutic indications with higher financial prospects (Pushpakom et al., 2019).

The question which arises then is what effect these differences have on the availability of treatment for rare cancer patients. The disproportionate incentives for the development of new therapies targeting rare cancers can give rise to inequalities in innovation targeting malignancies with substantial public health implications. According to Gatta et al. (2011), the European five-year relative survival rate is, on average, far worse for rare cancers (47%) than for more common ones (65%). Yet, there is lack of understanding of how research on new anticancer drugs is aligned to unmet medical need. In this paper, we analyse the distribution of anticancer R&D in terms of medical need across types of cancer, including rare cancers. To do this, we construct a unique global database of clinical trials between 1996 and 2016, across 227 different cancer types and match each type of cancer with epidemiological data to proxy need, namely prevalence, incidence, and survival rates.

We assess inequalities in pharmaceutical innovation and investment for rare and non-rare cancers. To do so we leverage on a unique dataset and use concentration curves and concentration indices to : i) measure and assess the evolution over time of inequalities in R&D activity, for rare and non-rare cancers ii) measure trial activity inequalities for each stage of clinical trials, for rare and non-rare cancers iii) measure inequalities in R&D investment (proxied by costs and trial duration) for rare and non-rare cancers. We do so by using three proxies for unmet need, namely, prevalence, incidence and survival rates.

4.1 Data

We build a unique dataset that links clinical trials targeting rare and non-rare cancers with epidemiological data per type of cancer and over time. We do so by merging data from three different sources: i) the Clinicaltrial.gov database that provides registry data on the number of clinical trials targeting each type of (rare and non-rare) cancer between 1996 and 2016; ii) Orphanet that provides data on clinical trials targeting rare cancers between 1996 and 2016; iii) Rarecarenet.eu that provides epidemiological data on prevalence, incidence, one-year and five-year survival rates for year 2007, per cancer type.

Clinicaltrials.gov is a publicly available database provided by the U.S. National Library of Medicine at the National Institute of Health (NIH), containing privately and publicly funded clinical trials around the world since 1970. It allows us to collate the number of clinical trials for 20 non-rare cancer types. In order to do so, we use medical subject headings (MeSH) to characterize clinical trials by types of cancer in terms of their site of origin. Commonly, one MeSH term corresponds to more than one type of cancer, given that one clinical trial might target several cancer types simultaneously. We consider all multiple cancer types targeted by each clinical trial.

Using this information, we construct two datasets with a total of 31,081 observations: one dataset that yearly counts the number of clinical trials targeting each cancer type assigning equal weights to all observations – henceforth labelled as non-rare clinical trial dataset (NRD) - and a second dataset with similar number of observations weighting observations according to the number of cancer types targeted by each trial - henceforth labelled the non-rare weighted clinical trial dataset (NRWD). The NRWD allows us to perform the analysis correcting for possible over-representation of trials with many cancer types associated. Figure 34 shows each step of the dataset construction.

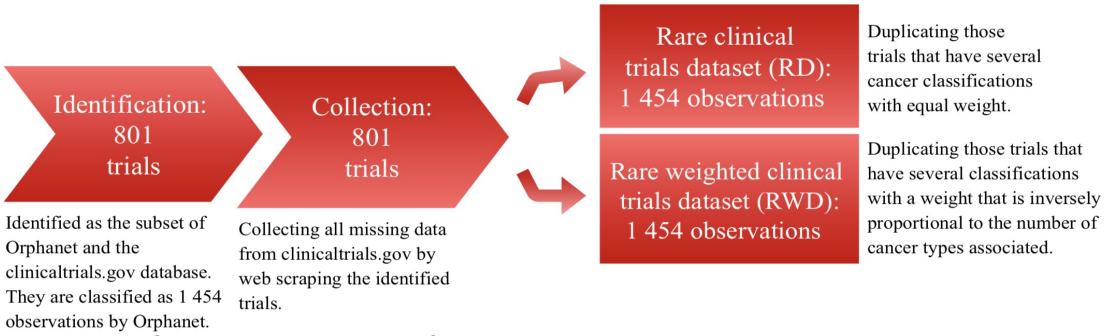


Figure 34: Process of database construction for rare cancer clinical trials

For rare cancers we also collect the number of clinical trials from clinicaltrials.gov. As in Bell and Smith (2014), we identify clinical trials targeting rare cancers if at least one submitted MeSH ID annotation in the conditions indicated is found. Trials primarily targeting non-rare cancer types, with a possible application to a rare cancer, will tend to report all possible applications, even though research is dominantly non-rare cancer targeted. This may lead to an overestimation of the number of rare cancer trials. Therefore, to identify clinical trials truly targeting rare cancers, we use Orphanet database. Orphanet provides information on clinical trials between 1996 and 2016, classified into rare types of cancer by clinical experts. We consider only those clinical trials registered on clinicaltrials.gov that target rare cancers according to Orphanet, amounting to a total of 801 clinical trials (1454 observations) for rare cancers between 2000 and 2016.

Naturally, the question arises as to whether we lose information by using only a subset of the Orphanet's database. We argue that for consistency, we need to limit our data to clinicaltrials.gov, as having only one source in the case of the non-rare cancers but several in case of rare cancers might bias our analyses. Furthermore, as already mentioned, we assume that cancer types are uncorrelated with the proportion of clinical trials registered. We call one observation a trial addressing one cancer type; therefore, we construct two rare cancer clinical trials dataset according to the way we assign weights to each observation. We refer to rare cancer clinical trials data (RD) as the dataset of those observations with equal weights, and to rare weighted clinical trials data (RWD) the dataset with weights that are inversely proportional to the number of entries of the trial in the dataset. The process of dataset construction for rare cancers is presented in Figure 35.

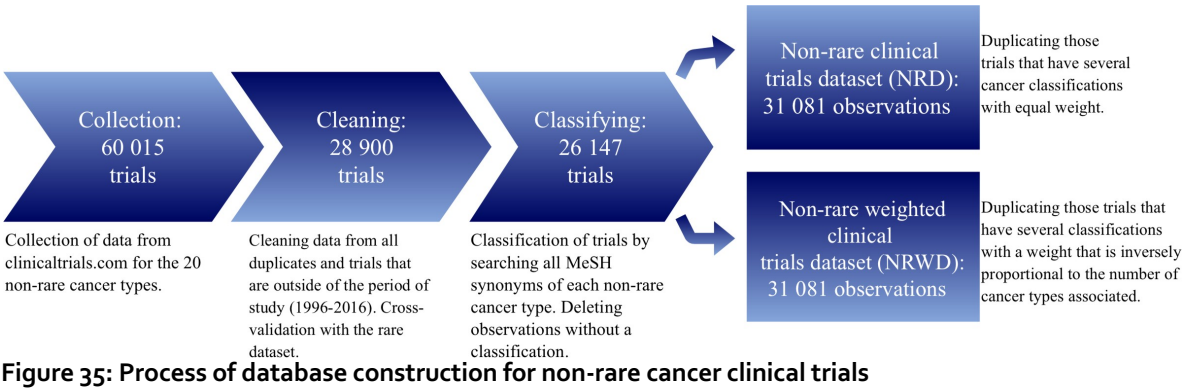


Figure 35: Process of database construction for non-rare cancer clinical trials

Besides analysing inequalities in innovation measured by trial activity we also assess inequalities in R&D investment proxied by the number of enrolled patients per year and the duration of clinical trials. Albeit being an imperfect measure of total R&D efforts (Joe Martinez, 2016), trials duration and costs are a significant part of overall expenditure in R&D. The number of patients enrolled in trials and trial durations are only considered for Phase 2 clinical trials, with already completed enrolment. We consider Phase 2 clinical trials as they recruit patients more uniformly. Many oncological drugs are accessing the market without a Phase 1 and/or a Phase 3 because of ethical considerations (Wright et al., 2002; Agrawal & Emanuel, 2003). Next, we measure the duration of the trial as the number of days that occur between the date the trial was firstly posted and its completion date. For the 4,479 non-rare and 352 rare Phase 2 clinical trials, the average duration of rare cancer trials with already completed enrolment is slightly longer (4.5 years) than that of non-rare cancer trials (3.9 years), while the average enrolment is higher for rare (178.1) than for non-rare cancer (104.8) trials (p-value < 0.002).

Finally, to measure need, we use estimates of European crude, age specific incidence, 15-year prevalence and 1 and 5-year age-adjusted relative survival rates for cancers obtained from the rarecarenet.eu. Their data is drawn from the EUROCARE-5 study, the largest, European collaboration of research efforts to provide information on the epidemiology of rare cancers. They provide estimates of the prevalence, incidence and rate of survival based on data obtained from 92 Cancer Registries, in 22 European countries, including more than 21 million cancer diagnosis until 2007. The list of rare tumours is hierarchically structured in three layers based on the ICD-O morphology and topography.

Therefore, the final dataset contains each cancer's epidemiological data matched with the number of clinical trials/weighted clinical trials targeting the given type of cancer, divided by year/period/phase. The question arises whether using epidemiological data estimated at a given point in time while clinical trials are collected for the whole period of time could bias our analysis. While this is a hypothetical limitation of the analyses due to data unavailability, it is unlikely to bias our analyses given that the ranking of cancers in terms of epidemiological variables is likely to remain constant over time. As the concentration curves and indices measure relative inequality, they are invariant to equi-proportional changes in the variables.

Given that the classification of rare cancers clinical trials differs between Orphanet and EUROCARE-5 study (which uses ICD-O morphology and defines 194 rare cancers) we harmonize the two by matching manually the Orphanet classification onto the EUROCARE classification. The accuracy of the harmonization of the two classifications is then verified by an expert specialized in genetics.

The final dataset consists of 32,535 observations, with 31,081 observations for non-rare cancers and 1,454 for rare ones. One trial may target several cancers and thus count as several observations. Considering a trial only once, we get 26,948 clinical trials observations: 801 trials targeting rare cancers and 26,147 targeting non-rare cancers. Considering only enrolment-completed trials to avoid trials where enrolling is occurring or has not started yet, we find that rare disease trials enrol fewer participants on average (183 for rare cancers compared to 294,7 respectively for non- rare cancers, with p-value < 0.001).

4.2 Methods

We leverage the methods described in section 3.2 to run several analyses: i) inequalities of clinical trials, R&D efforts and survival rates for rare and non-rare cancers ii) evolution of inequalities over time iii) inequalities by R&D phase comparing early with late stage trials.

We also look at the evolution of inequalities over time and compare inequalities in the period pre- and post- orphan drug European legislation, by comparing the period 1996-2000 with 2012-2016. While ideally, we would compare the period pre 2000 with post 2000 unfortunately, we find no prior 2000 observations in the clinicaltrial.gov database included in the Orphanet database. Therefore, we only measure inequalities in 2012-2016 for the post legislation period.

4.3 Results

CIs for cancer types

Firstly, we look at the distribution of clinical trials per cancer type. Figure 36 shows the cumulative percentage of cancers ranked by the number of trials on the X axis, and the cumulative percentage of trials on the Y axis, separately for rare and non-rare cancers. Results show that almost 60% of rare cancers have no corresponding clinical trials between 2000 and 2016, the research being concentrated on only a few types of cancer. Indeed, more than 90% of rare cancer studies address a mere 20% of rare cancer types.

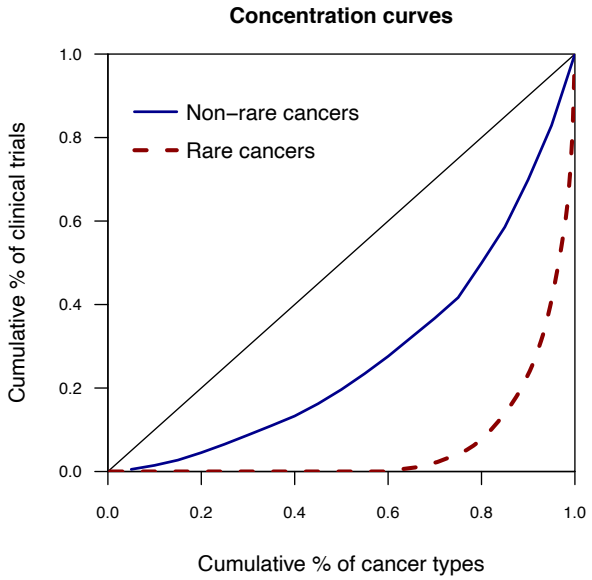


Figure 36: Concentration curves for cancer types. Note: The curves plot the cumulative percentage of the number of clinical trials against the cumulative percentage of cancer types.

R&D seems to be distributed unequally in the case of non-rare cancers also, as more than 40% of the clinical trials focus on only 20% of non-rare cancers.

To be able to measure the scale of the inequality, we compute the concentration index for both rare (CI = 0.885, p-value = 0.0000) and non-rare cancers (CI = 0.45, p-value = 0.0000) and we find that both inequalities are significant.

Table 12 shows the number of clinical trials and weighted clinical trials for non-rare cancers. More than 40% of non-rare clinical trials target only three types of cancer: breast cancer, leukemia and tracheal, and bronchus and lung cancer. Table 12 shows the number of clinical trials for the 20 most researched rare cancers. 19% of all rare cancer studies target one type of cancer, the acute myeloid leukemia, while the 20 most researched types account for 75% of all rare cancer studies

Non-Rare Cancers	No. of trials	No. of weighted trials	% of non-rare trials	% of non-rare weighted trials
Lip, oral and larynx cancer	169	125	0.52%	0.48%
Thyroid cancer	296	266	0.95%	1.02%
Uterine cancer	393	307	1.26%	1.17%
Non-melanoma skin cancer	554	358	1.78%	1.37%
Bladder cancer	630	501	2.03%	1.92%
Chronic lymphoid leukemia	683	311	2.20%	1.19%
Malignant skin melanoma	695	472	2.24%	1.81%
Esophageal cancer	719	506	2.31%	1.93%
Kidney cancer	1058	854	3.40%	3.27%
Stomach cancer	914	704	2.94%	2.69%
Non-Hodgkin lymphoma	1189	956	3.83%	3.66%
Liver cancer	1283	1096	4.13%	4.19%
Pancreatic cancer	1420	1218	4.57%	4.66%
Ovarian cancer	1421	1138	4.57%	4.35%
Brain and nervous system cancer	1533	1310	4.93%	5.01%
Colon and rectum cancer	2570	2175	8.27%	8.32%
Prostate cancer	2687	2491	8.65%	9.53%
Leukemia	3529	2974	11.35%	11.37%
Tracheal, bronchus, and lung cancer	4031	3559	12.97%	13.61%
Breast cancer	5314	4827	17.10%	18.46%
Total	*31081*	*26147*	*100%*	*100%*

Rare Cancers	No. of trials	No. of weighted trials	% of rare trials	% of rare weighted trials
Other myeloproliferative neoplasms	18	8	1.24%	1.00%
Neuroblastoma and ganglio-neuroblastoma	20	4	1.38%	0.50%
Astrocytic tumors of CNS	21	3	1.44%	0.87%
T cutaneous lymphoma	23	7	1.58%	0.87%
Rhabdomyosarcoma	25	2	1.72%	0.25%
Hepatocellular carcinoma of liver and IBT	29	10	1.99%	1.25%
Hodgkin lymphoma classical	32	7	2.20%	0.87%

Diffuse B lymphoma	33	4	2.27%	0.50%
Endocrine carcinoma of pancreas & digestive system	36	11	2.48%	1.37%
Mantle cell lymphoma	41	10	2.82%	1.25%
Precursor B/T lymphoblastic leukemia/lymphoma	42	14	2.89%	1.75%
Salivary gland type tumors of head and neck	42	11	2.89%	1.37%
Follicular B lymphoma	47	14	3.23%	1.75%
Malignant/immature teratomas of ovary	50	14	3.44%	1.75%
Chronic myeloid leukemia	53	20	3.65%	2.50%
Other T cell lymphomas and NK cell neoplasms	66	20	4.54%	2.50%
Plasmacytoma/multiple myeloma	101	30	6.95%	3.75%
Soft tissue sarcoma of head and neck	133	25	9.18%	3.12%
Acute myeloid leukemia	269	139	18.50%	17.35%
Total	*1454*	*801*	*75.93%*	*44.94%*

Table 12: Number of clinical trials and weighted clinical trials of non-rare cancers and rare cancers types, between 2000 and 2016. Note: The Total refers to the number of observations in the non-rare clinical trials dataset and not the sum of the number of clinical trials of the 20 cancer types shown. Similarly, the % calculated as hematological and solid tumors are calculated according to the sum of all clinical trials and not only to the sum of the shown trials.

Inequalities on the number of trials for different cancer types

Although we observe inequality in the distribution of the number of clinical trials for the treatment of rare and non-rare cancers, this difference might be explained by the varying level of prevalence and incidence of the different types of cancers.

Figure 37 shows the concentration curves for the stock of clinical trials with cancers ranked by prevalence and incidence for rare and non-rare cancers separately. Table 13 presents the associated concentration indices.

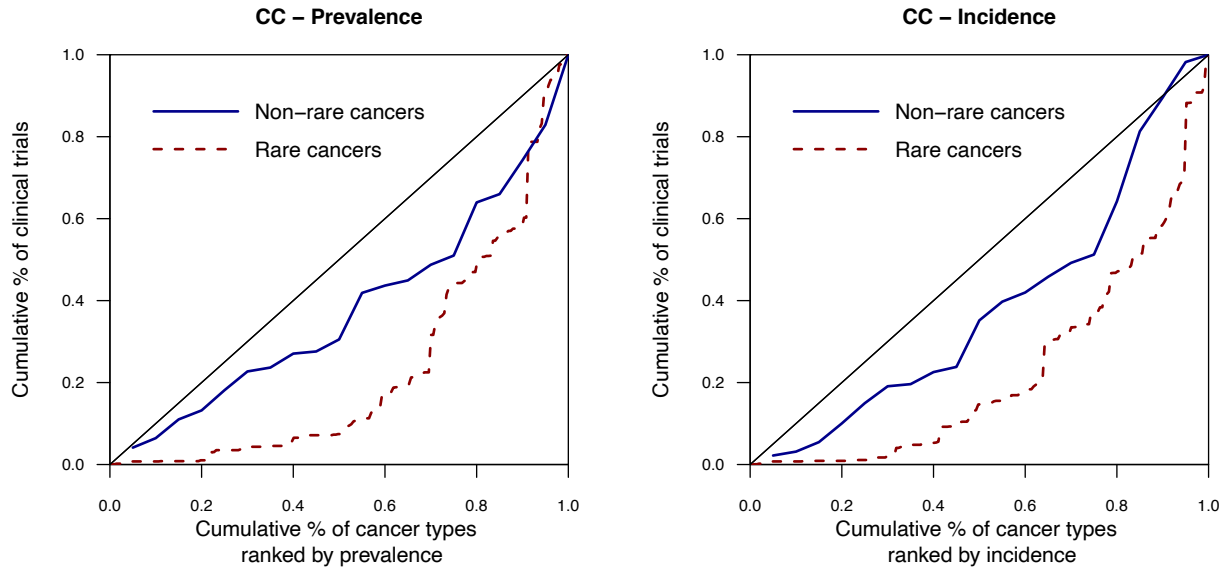


Figure 37: Concentration curves for prevalence and incidence. Note: The curves plot the cumulative percentage of clinical trials against the cumulative percentage of the given epidemiological variables.

	Metric	Number of cancer types	Prevalence	Incidence	1-year survival	5-year survival
Rare cancer trials	CI	0.869	0.539	0.544	-0.066	-0.039
	Standard error	0.106	0.131	0.131	0.137	0.137
	p-value	0.000*	0.001*	0.000*	0.63	0.772
Non-rare cancer trials	CI	0.442	0.248	0.233	-0.022	-0.051
	Standard error	0.117	0.102	0.104	0.118	0.117
	p-value	0.000*	0.026*	0.039*	0.8544	0.669

Table 13: Concentration indices computed according to the number of cancer types, the prevalence, the incidence and the survival rates. All values are calculated using the rare and non-rare clinical trial datasets.

First, both rare and non-rare cancer clinical trials show a *pro-high-occurrence* inequality, as trials are disproportionately concentrated on higher prevalence malignancies. However, this inequality is greater for rare cancers (CI = 0.53, p-value = 0.0001) than for non-rare cancers (CI = 0.25, p-value = 0.026). The concentration curves using incidence as cancer ranking variable, confirm the former results: inequality is greater for rare cancers (CI = 0.54, p-value= 0.000), than for non-rare cancers (CI = 0.23, p-value = 0.038), revealing that rare cancer clinical trials are more disproportionately concentrated on higher occurrence types than non-rare ones.

As described in the data section, a trial might target multiple cancers and therefore our analyses are at cancer-trial level, with each trial targeting on average 1.8 and 1.18 cancer types respectively for rare and non- rare cancers in the NRD and RD. To ensure that duplicated entries with equal weights do not distort our analysis, we compute the concentration curves for robustness for the weighted clinical trials datasets (NRWD and RWD, Figure 38).

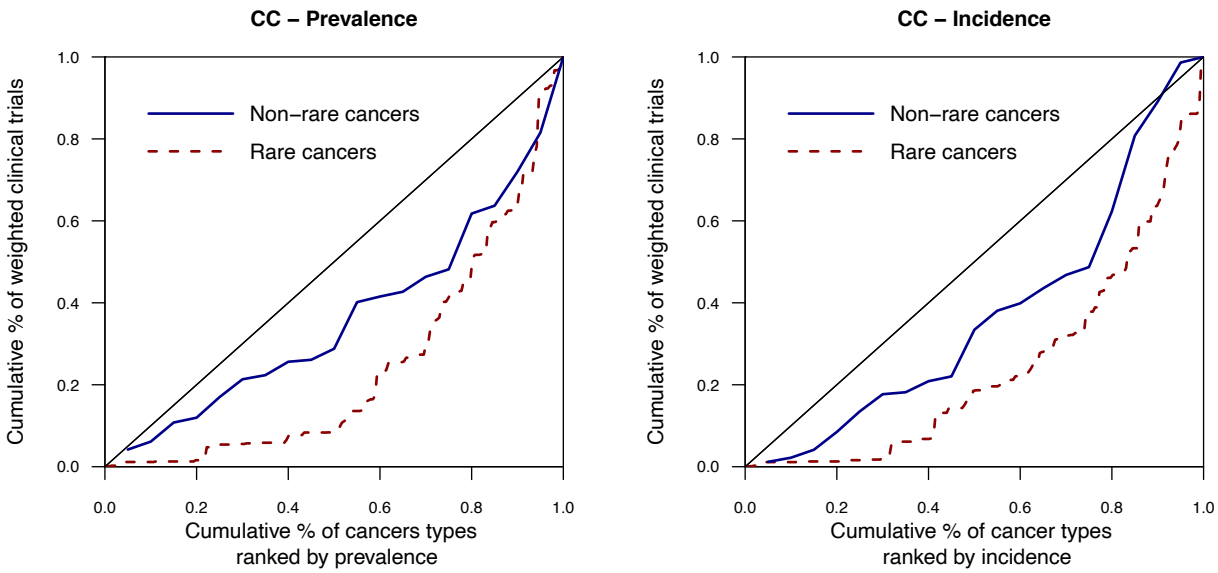


Figure 38: Concentration curves for rare and non-rare cancers separately according to the prevalence and incidence.

We see weighted clinical trials data (NRWD and RWD) presents almost identical results as the clinical trial data (NRD and RD), showing that assigning an equal weight or an inversely proportional weight to the number of entries for each observation does not change qualitatively our results. Rare cancer clinical trials present a greater level of *pro-high-occurrence* inequality (CI= 0.54, p-value = 0.0000 when incidence is the ranking variable; and CI=0.51, p-value = 0.000 when prevalence is the ranking variable) than trials for non-rare cancers (CI = 0.26, p-value = 0.03 when incidence is the ranking variable; and CI = 0.27, p-value = 0.022 when prevalence is the ranking variable).

Altogether, lower occurrence cancers are less researched, and this inequality is greater for rare cancers than non-rare cancers, as the former have very few, if any clinical trials between 2000 and 2016. These results suggest that research tends to be disproportionately focused on cancer areas with higher market size, suggesting a potential strategic investment by the industry in areas that can generate higher financial returns on investment, thus help to recoup the invested funds.

Inequalities of clinical trials over time

Figure 39 shows the yearly concentration indices for the distribution of clinical trials with cancer types ranked by the prevalence and incidence for both rare and non-rare cancers separately.

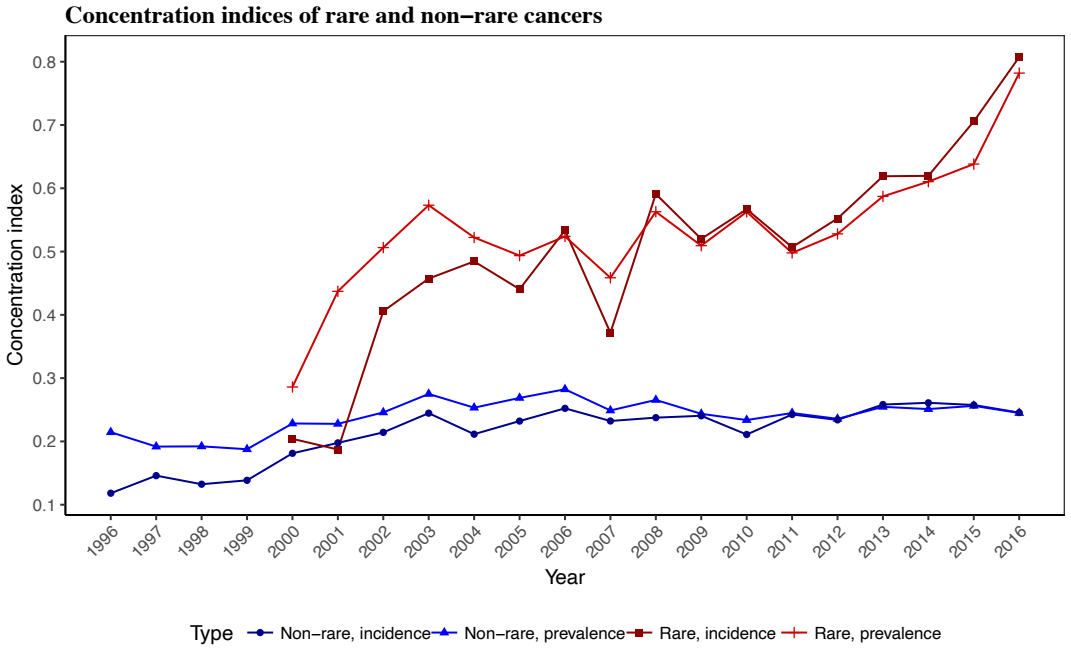


Figure 39: Concentration indices over time, calculated for rare and non-rare cancers separately, both for prevalence and incidence.

Firstly, there is a *pro-occurrence inequality* each year of the study for rare cancers as all CI-s are positive and significant, while the non-rare cancer trials have smaller (around 0.25) and often non-significant indices. Moreover, the magnitude of the inequality seems to be increasing over time for rare cancers, whereas it remains constant for non-rare cancers over the period of the study.

The next question which arises is whether EU legislation is at risk of generating more inequality within the rare cancer types, in its attempt at reducing the overall inequality between the rare and non-rare subtypes. While EU legislation promoting orphan disease research seems to have led to more clinical trials for rare diseases, it remains crucial to analyze whether this affects all orphan diseases or only a subset.

We now compare levels of inequality pre- and post- orphan drug European legislation by comparing the periods 1996-2000 with 2012-2016.

Figure 40 shows the concentration curves according to the incidence and prevalence of the rare and non-rare clinical trials for two periods, 1996-2000 and 2012-2016[8]. Using incidence as need proxy, surprisingly, we find that

[8] Therefore, all data is provided by clinicaltrials.gov except the data for rare cancers between 1996-2000, that are provided by Orphanet.

inequality is greater for the recent period, measured by the concentration indices (CI = 0.62, p-value = 0.000 for rare cancers for the period between 2012 and 2016, while CI = 0.22, p-value = 0.19 between 1996 and 2000), moreover they are statistically different (p-value = 0.000 for a t-test with unequal variances). Results for non-rare cancers suggest that the curve is non-statistically different from the equality line between 1996 and 2000 (CI = 0.15, p-value = 0.176), while inequality increases and becomes statistically significant for the period of 2012-2016 (CI = 0.252, p-value = 0.03). The CIs calculated for 1996-2000 and 2012-2016 are statistically different (p-value = 0.004). Similar findings are found when prevalence is used as proxy for need. Therefore, results suggest that, even though the number of rare cancer clinical trials has increased substantially, so did the inequality among rare cancer trials, indicating that we should carefully analyze the distribution of research within subgroups when evaluating a policy.

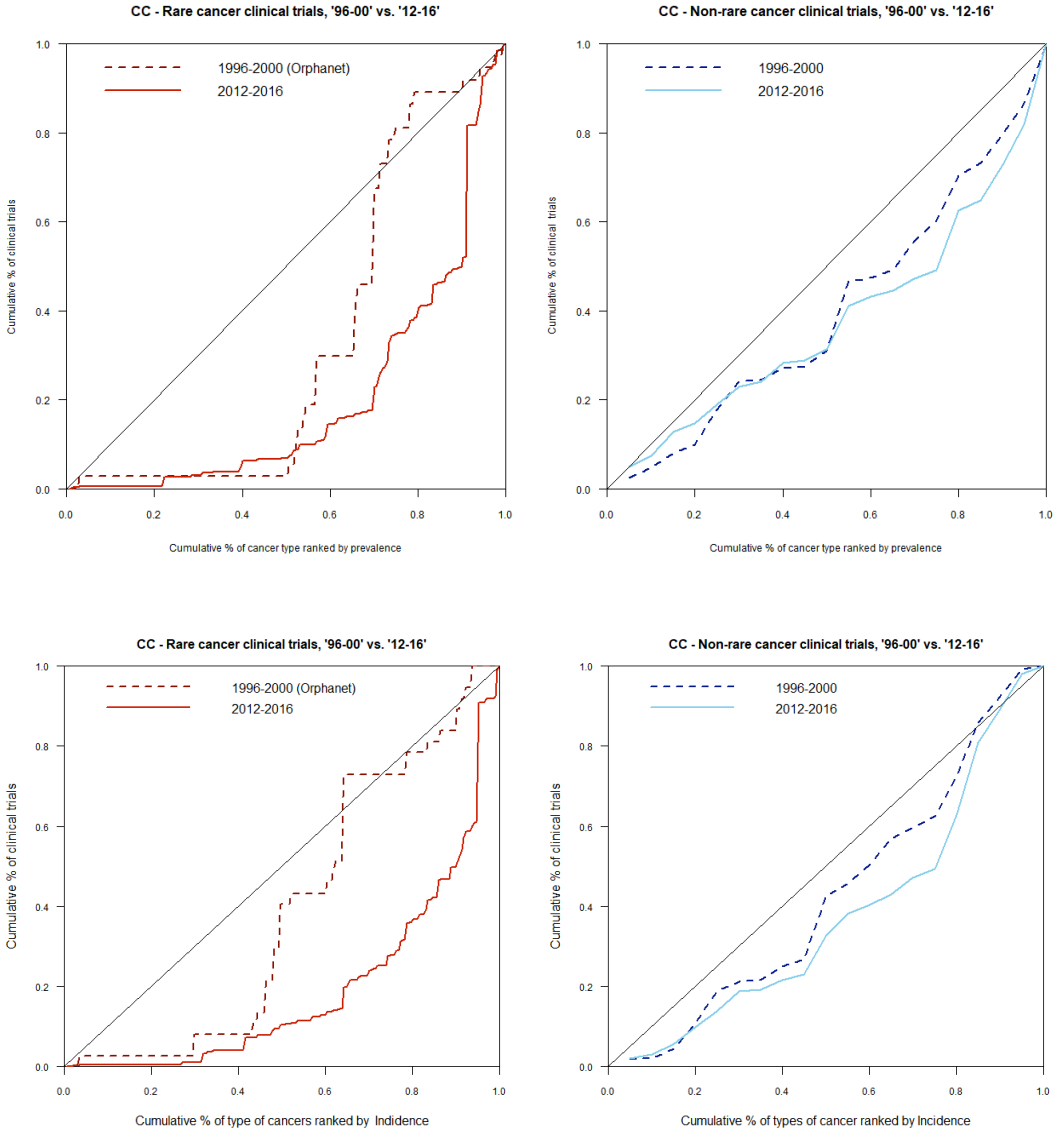


Figure 40: Concentration curves for rare and non-rare cancers separately for the period of 1996-2000 and 2012-2016 according to their incidence and prevalence. Note: The curves plot the cumulative percentage of the number of clinical trials against the cumulative percentage of the incidence. The data of the rare cancer clinical trials for the period 1996-2000 are provided uniquely by Orphanet.

16%, 43% and 41% of rare clinical trials are Phase 1, Phase 2 and Phase 3 respectively, while we find that 28% of non-rare trials are Phase 1, versus 39% and 11% for Phase 2 and Phase 3 trials.[9] Figure 41 shows the concentration curves computed for rare and non-rare clinical trials for each phase for cancers ranked according to incidence. We observe that the inequality seems to be increasing from early to later ones for non- rare cancers but is already high for Phase 1 rare cancer trials.

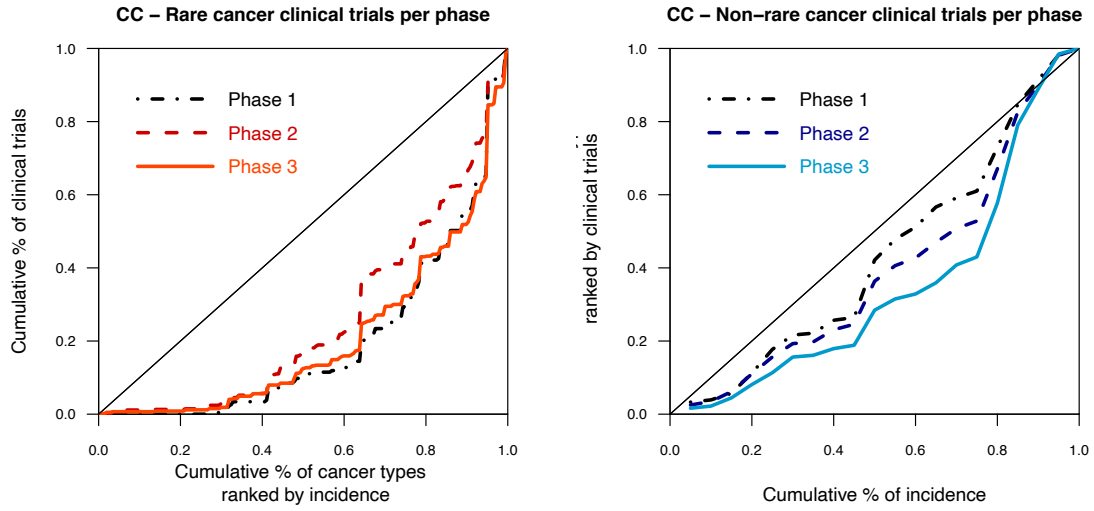


Figure 41: Concentration curves for Phase 1, Phase 2 and Phase 3 trials for rare and non-rare cancers separately. Note: The curves plot the cumulative percentage of the number of clinical trials against the cumulative percentage of incidence.

These results lead to two main conclusions. Firstly, the inequality that we observe in the case of rare cancers is independent of the phase and therefore, the previously observed disparity (according to prevalence and incidence) is not caused by the lower probability of success of very rare cancers, but is already predetermined at early phases, by disproportionately more trials addressing the more common types of rare cancers. Secondly, the inequality we observe in case of non-rare cancers is partially explained by the progression from Phase 1 to Phase 2, and then finally to Phase 3, where higher incidence malignancies seem to perform better. Although the level of pro-occurrence inequality is relatively small and insignificant for Phase 1 trials (CI = 0.147, p-value= 0.171), it is larger

[9] We exclude Phase 4 trials and those trials with the Phase 'not applicable' in this section.

for Phase 2. (CI = 0.216, p-value = 0.048) and even greater for Phase 3 (CI = 0.317, p-value= 0.019). All CI-s computed according to prevalence and incidence are reported in Table 14.

	Metric	Phase 1		Phase 2		Phase 3	
		Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Rare Cancer Trials	CI	0.608	0.588	0.482	0.501	0.587	0.562
	Standard Error	0.16	0.16	0.123	0.123	0.137	0.138
	p-value	0.000	0.000	0.000	0.000	0.000	0.000
	Number of Trials	235		618		590	
		Incidence	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Non-Rare Cancer Trials	CI	0.147	0.157	0.216	0.233	0.317	0.336
	Standard Error	0.103	0.102	0.102	0.1	0.123	0.119
	p-value	0.171	0.143	0.048	0.032	0.019	0.012
	Number of Trials	8707		12067		3566	

Table 14: Concentration indices calculated for Phase 1, Phase 2 and Phase 3 clinical trials according to the incidence and prevalence. All values are calculated using the rare and non-rare clinical trial datasets.

Inequalities in survival rates

In order to assess whether low survival malignancies receive at least as much research attention as high survival ones, we also analyze the distribution of clinical trials according to the 1 and 5-year survival rates. The average 5-year survival rate is lower for rare (48.45%) than non-rare cancers (51.45%) in our data. Figure 42 shows the cumulative percentage of 5-year survival rates for rare and non-rare cancers, plotted against the number of different cancer types ranked by survival rate. Rare and non-rare cancers survival rates present the same level of divergence from the line of equality. We see that 40% of rare and non-rare cancers account for the lowest 10% of 5-year survival, while the highest 40% of cumulative survival is explained by 20% of the cancer types.

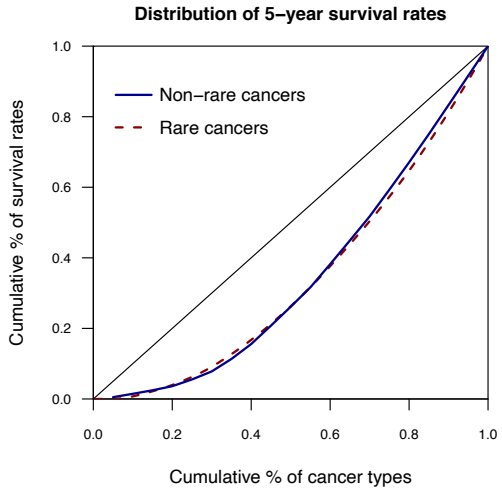


Figure 42: Concentration curves for cancer types. Note: The curves plot the cumulative percentage of the 5-year survival rate against the cumulative percentage of cancer types.

Figure 43 presents the concentration curves for the 1 and 5-year relative survival rates, plotting the distribution of the clinical trials as a function of the cumulative proportion of these variables. These concentration curves are quite close to the line of equality, implying that the distribution of trials across the different types of cancer is proportional to the survival rates. These results are confirmed by the non-significant concentration indices as displayed in Table 13.

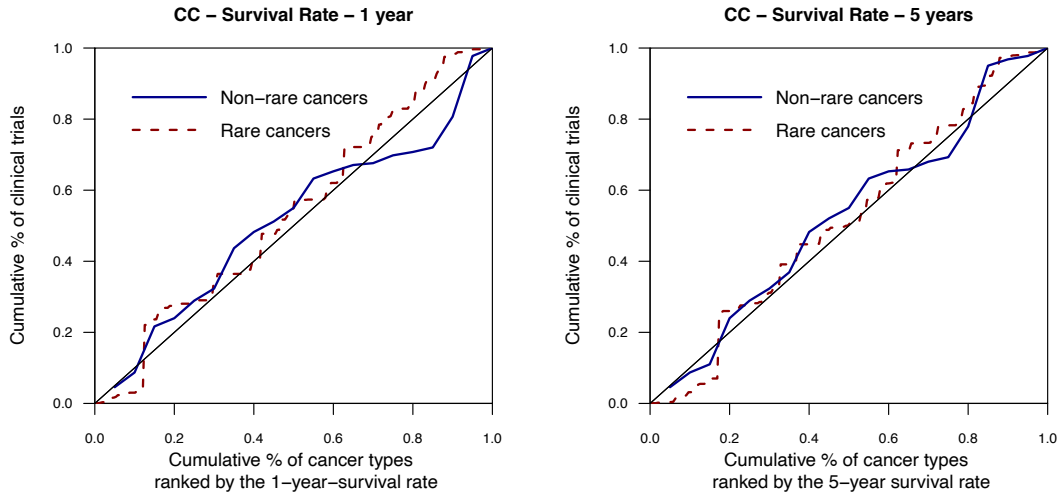


Figure 43: Concentration curves according to 1 and 5-year survival rates. Note: The curves plot the cumulative percentage of the number of clinical trials against the cumulative percentage of survival rates.

While these results could suggest a more equal distribution of innovation across different diseases based on need, survival rates are an imperfect proxy for "medical need" as they fail to capture the number of lives lost due to cancer as well as the impairment in quality of life associated with the disease.

Inequalities in R&D efforts per cancer type

As the number of clinical trials focusing on a given type of cancer does not necessarily reflect the magnitude of research investment dedicated to the malignancy, we also assess a second outcome variable by capturing the cost associated with the trials as proxied by the number of enrolled patients per year and duration of clinical trials.

We, then, compute the concentration curves for the patient/years burden using incidence as the ranking variable (Figure 44). The *pro-occurrence inequality* found previously is confirmed for both types of cancers (CI = 0.563, p-value = 0.0012 for rare and CI = 0.378, p-value = 0.029 for non-rare cancer trials), cancers with higher incidence exhibiting disproportionately more patients and lasting disproportionately longer than cancers with lower incidence. However, the difference between the inequalities observed for rare and non-rare cancers reduces, compared to that found before. These results indicate the importance of estimating the magnitude of the funds invested in research when assessing inequalities in trials' targets.

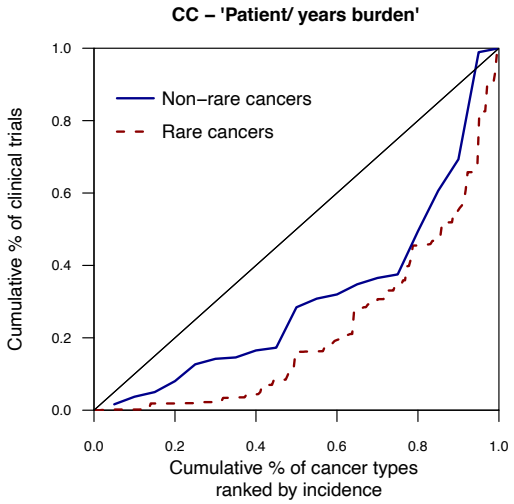


Figure 44: Concentration curves for incidence. Note: The curves plot the cumulative percentage of *patient/years burden* against the cumulative percentage of cancer types.

Key Messages

We analyze the distribution of clinical trials conducted between 1996 and 2016 for drug treatments of rare and non-rare cancers. We find three important differences between the distribution of rare and non-rare cancer trials.

Firstly, we find a higher level of inequality for rare than for non-rare cancer trials that is unexplained by the prevalence and/or the incidence. Indeed, we find that almost 60% of rare cancer types have no corresponding clinical trials in the study period, as trials are concentrated on high prevalence and high incidence rare and non-rare cancers. Then, we assess the distribution of the patients enrolled and the duration of the trials, thereby assessing the distribution of R&D efforts. We confirm our former results, the *pro-occurrence inequality* being higher for rare cancer trials than for non-rare cancer trials. The finding that clinical trials tend to be concentrated on high-occurrence rare and non-rare malignancies, suggests that research is concentrated on those cancers that can deliver higher industry returns in order to recoup the invested funds.

Secondly, we find that inequality has increased substantially between 2000 and 2016 within rare cancers, while staying at about the same level within non-rare cancers over the same period. This result shows that, even though the number of rare cancer clinical trials has increased since 2000, not all rare cancer types benefit equally from this trend. A few cancers, with higher incidence and prevalence tend to disproportionately benefit more rare cancer research, the 20 most funded rare types making up for as much as 75% of all rare cancer observations (RD) and 45% of all rare cancer trials (RWD). Unfortunately, these 20 cancer types only account for around 29% of the prevalence and incidence of rare cancers, leaving the other 71% of cumulative prevalence and/ or incidence with only 25% of rare cancer research. These results underline the importance of assessing the distribution of newly conducted clinical trials when evaluating the orphan drug legislation, and that additional incentives might be needed in order to successfully encourage investment for research for the very rare cancer types.

Thirdly, we find that the inequality is higher for advanced phase non-rare cancer trials than early phase ones, while the disparity observed is already high for Phase 1 rare cancer trials. These results suggest that the inequality we observe in the case of non-rare cancer trials is partially explained by the lower probability of success of low prevalence non- rare cancer trials, whereas it is already pre-determined at early phases for rare cancers.

5. Conclusions

In this report we have assessed historical trends in drug development and market launches, as well as the extent to which there is inequality on how research and market launches is distributed across disease areas and ATCs. Based on historical trends we also forecast the number of orphan drugs that we can expect to be made available in the next decade in the absence of further policy intervention and incentives.

Our findings suggest that for both orphan and non-orphan drugs, certain disease areas exhibit higher proportion of R&D activity and innovation: cancer, endocrine and metabolic disorders, cardiovascular and infectious disease.

Nearly all R&D activity and market launches for orphan designated products occur in the US followed by Europe although the share of global activity for the US declines as one moves from early stage R&D to market launch. Japan assumes an increasing role on activity as we move from early stage R&D to market launch being responsible for 11% of global orphan products market launch. Also, Switzerland role is increasing over the innovation pathway albeit remaining marginal when compared to other regions.

Looking at the evolution over time in R&D activity and market launches we find that across all stages of development (early stage R&D, late stage R&D, and market launch) orphan designated products form an increasing proportion of yearly pharmaceutical innovation, that is more salient in late stages and market launch stage albeit the proportion of orphan (non-orphan) drugs innovation having experienced a decline (increase) in the last couple of years. Early stage global R&D activity is dominated by the US however the US share of early stage activity has increased until 2016 and decreased thereinafter. The US are also the region with the highest share of global late stage R&D activity followed by the EU that has experienced an increase in orphan products R&D activity since around 2000. With regards to market launch activity both the US and the EU account for nearly all orphan products global market launches exhibiting an increasing trend over time since 2000 with the introduction of the Orphan Medicinal Product regulation in the EU.

Based on these trends, we also show that in the absence of any policy changes, between 675 and 807 orphan designated products, and between 2485 and 3088 non-orphan products, can be expected to be launched between 2020 and 2030. Based on these estimates, we will fall about 200 to 400 therapies short of the International Rare Diseases Research Consortium goal of 1000 therapies by 2027 (Austin et al, 2018), so policy changes are actually needed in the short term.

The forecasts highlight that historical trends in the distribution of R&D activity and market launches across disease and ATCs areas will prevail in the absence of further policy and incentives. Most orphan products innovation will be concentrated in cancer, cardiovascular disease, endocrine and metabolic disorders and musculoskeletal disorders. The significantly low levels of innovation on orphan designated products targeting ophthalmological,

genitourinary, dermatological, gastrointestinal, respiratory and CNS disorders will prevail if no incentive frameworks are implemented to foster innovation in these areas.

These trends reflect on inequalities of R&D activity and market launches. Our analyses show that across all rare disease there is inequality pro-occurrence for early- and late-stage R&D and market launches with activity disproportionately concentrated towards the more prevalent diseases.

Looking at each group of diseases though there is heterogeneity in the levels of inequality. Market launches are distributed in proportion to need for several rare disease groups over the entire period, namely: bone disease, cardiac disease, circulatory system disease, developmental defects during embryogenesis, endocrine disease, renal disease, respiratory disease, and skin disease.

However, for other disease areas most recent data shows that there is pro-occurrence inequality (i.e., disproportionate level of market launches concentrated towards high prevalence disease): systemic or rheumatologic disease, inborn errors of metabolism, hepatic disease, hematologic, neurologic disease, and ophthalmic disorders. These disease areas also exhibit pro-occurrence inequality for early and late stage R&D.

In addition, for R&D activity, pro-occurrence inequalities in activity are also observed in rare developmental defect during embryogenesis (for early and late stage activity), rare endocrine disease (for early and late stage activity), respiratory disease (for early stage activity), rare bone disease (for early stage activity) and immune disease (for early stage activity). For most of these disease groups inequality has remained pro-high prevalence but has reduced after the implementation of the European Orphan Medicinal Product Regulation.

Instead for gastroenterologic disease and rare immune disease pre- and post-2000 market launches are disproportionately concentrated towards low prevalence diseases, and the level of low-occurrence inequality has remained fairly stable over time. The distribution of early R&D activity exhibits pro low occurrence inequality with cardiac disorders with lower prevalence receiving disproportionately more activity.

We also assessed the direction and magnitude of inequalities looking at cancer therapeutic innovation. There are four key findings from our analyses. Firstly, clinical trials R&D activity and investments targeting rare cancers are more concentrated on high prevalence/high incidence/high survival-rate malignancies than those targeting non-rare cancers. Very rare cancers have virtually no clinical trials. Secondly, this dispersion inequality increases significantly for rare cancers over the last 20 years but does not change for non-rare cancers. Thirdly, the inequality observed in non-rare cancers is greater in advanced phases of clinical trials (Phase 2 and 3) than in early stages (Phase 1) whereas for rare cancers it is already pre-determined at Phase 1 trials. Lastly, trials targeting rare cancers are more hemopathy-focused than those targeting non-rare cancers.

Taken together our inequalities analyses findings suggest that, even though R&D activity and market launches have increased substantially over the years, so did the inequality in innovation and access to it across the different disease areas, indicating that we should carefully analyze the distribution of research and market launch within subgroups when evaluating policies and incentive frameworks. In light of the identified misalignments of drug development activity and market launches in relation to unmet need our research highlights potential areas to promote equality of access across disease areas. If underlying social preferences are pro-equality, our findings suggest that health systems need better incentives and resource allocation frameworks (both within and across disease groups), for a better alignment between innovation and medical need.

While important our findings should be interpreted in light of the caveats of the analyses, that relate to data availability. While we contribute to the literature by considering activity in different R&D phases and market access, we don't observe R&D expenditure across the innovation pathway and therefore cannot disentangle whether the distribution of innovation is explained by differences in investment across disease areas, or other factors such as differences in the technical complexity and understanding of disease pathogenesis across disease area. For example, evidence suggests that clinical trials that only target rare cancers have a lower success rate than general oncology research trials (Wong, 2017). Lower success rates can be attributed to scientific challenges but also to decreased profitability associated to innovation in associated rare disease markets. Therefore, it could be that inequalities in orphan drug development reflect technical failure of the projects rather than purely industry strategic behavior. Better and more granular data is required to enable a better understanding of the drivers of inequalities that can inform incentive frameworks to foster innovation in areas of need.

In addition, while we considered prevalence, incidence and survival rates in our analysis, they are imperfect measures of unmet need as they do not to capture total disease burden. These metrics also fail to incorporate need that is or can be addressed by other types of care provision beyond therapeutic innovation. Additionally, our data sources are not complete in mapping all R&D activity. While it is highly plausible that trial underreporting affects all disease areas in the same way, we cannot rule out potential bias arising from a potential association of the level of reporting with the development of orphan drugs in specific disease areas.

Quite importantly our analyses are descriptive, and we don't control for the role played by the introduction of policies and regulations nor the dynamics of its effects over time that can impact the projections in these analyses. Therefore, to better understand what key incentive frameworks ought to be implemented to attain the desired levels of innovation in key areas of need further analyses would be required.

Despite these caveats, there are several policy implications suggested by our analyses. The first relates to the current trade-offs between efficiency and equity concerns posed by the current global pharmaceutical R&D model and the potential consequences for the future access and health gains and across populations (Paul et al., 2010; Morton and Kyle, 2012).

Our results show that around 60% of rare cancer types have no corresponding clinical trial activity in the study period. Several other disease areas receive few or very little R&D activity and/or market launches (rare genetic

diseases, infertility and gynaecological diseases, odontologic disease, circulatory disease). Without further data it is not possible to infer on the efficiency implications of this finding, but it certainly raises concerns from an equity standpoint and highlights the need for the need for policies and incentive frameworks to foster innovation in unaddressed areas of need.

Related to this, the second insight call for evaluation of impact of existing incentive mechanisms targeted at promoting innovation in riskier or less profitable areas, such as rare cancer. Our results show that the distribution of the R&D activity and disease burden across several rare diseases did not changed significantly between 2000 and 2016, despite various policy mechanisms in place to foster innovation in rare diseases. This suggests such incentive mechanisms need to be evaluated in light of their potential health and welfare consequences in the short, medium and long run.

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