Orphanet Report Series

Orphan Drugs collection

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Medicinal products for rare diseases in Europe*

** European Community marketing authorisation under the centralised procedure*

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Medicinal products for rare diseases in Europe*

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Medicinal products for rare diseases in Europe*

Methodology

The objective of this report is to describe key characteristics of medicinal products that have been granted a centralised marketing authorisation (MA) (granted by the European Medicines Agency - EMA) in rare diseases, with or without orphan designation, at the date indicated in the report.

Orphan medicinal products in Europe are defined by medicinal products that have been granted a European Orphan Designation (according to the Regulation (EC) No 141/2000), and then that have been granted a European Marketing Authorisation and - if applicable - a positive evaluation of significant benefit.

Orphan designation is a regulatory procedure established by a law introduced by the European Union to encourage the pharmaceutical industry and biotechnology companies to develop medicines intended to diagnose, prevent or treat a rare disease: this is the purpose of the Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[1]. The purpose of this regulation was to establish a community procedure for the designation of orphan medicinal products and to encourage their research, development and marketing through various incentives[1,2].

This is a regulatory procedure allowing the designation of a medicinal product with therapeutic potential for the treatment of a rare disease, before its first administration in humans or during its clinical development.

Medicinal products with an orphan designation without MA are not yet approved and available for commercialisation.

Furthermore, obtaining a European MA does not mean that the drug is available in all member states. They may not yet be available in Europe or may only be available in specific European countries at the date of this report. Indeed, the accessibility in the countries may depend on the strategy of the pharmaceutical company, the national administrative/regulatory delays, and the decision of reimbursement taken by the national health authorities.

The rare diseases concerned by the medicinal products described in this report are defined in accordance with European legislation defining a prevalence threshold of less than 5 patients per 10,000 people in the general European population[1] and are based on the Orphanet nomenclature.

Part 1

In this report, we propose a quantitative and qualitative analysis of orphan drugs in Europe registered in the Orphanet database. The list of orphan drugs in Europe registered in the Orphanet database (with orphan designation and European Marketing Authorisation) is established by crossing the register of health products with an orphan designation (Community Register of orphan medicinal products) with the register of medicinal products with a marketing authorisation (Union Register of medicinal products for human use). The EMA register lists all medicinal products with marketing authorisation, not just orphan medicinal products. Both registers are available on the website of the European Commission's Directorate-General for Health and Food Safety (DG SANTE). The analysis presented in this report is based on the information displayed in these registers, supplemented, and registered in the Orphanet database.

Part 2

We also propose in this report a quantitative and qualitative analysis of the medicinal products registered in the Orphanet database with a centralised European MA approved for one or more rare disease indication(s) but which have not been granted a European orphan designation or for which the orphan designation has expired or has been withdrawn. These medicinal products may or may not have been granted an orphan designation in another region of the

world. The list of medicinal products that have obtained a centralised European MA for one or more rare disease indication(s) without orphan designation is established by crossing the list of products that have obtained a MA from DG SANTE (Union Register of medicinal products for human use) and the Orphanet list of rare diseases. The analysis presented in this report is based on the information displayed on this register, supplemented and registered in the Orphanet database.

To obtain the detailed list of orphan medicinal products or medicinal products without orphan designation having at least one indication in a rare disease, in Europe, we invite you to visit the website https://www.orphadata.com/ which offers in particular a catalogue of expert resources including data collected and registered in the Orphanet database concerning drugs for rare diseases.

Additional information on each drug, such as active substance description, regulatory status in Europe, indication, OPRHAcodes/names of the concerned rare diseases, grant dates, orphan designation and MA identification numbers, and orphan designation sponsor/MA holder can be obtained from the "Inventory of Orphan Drugs" tab on https://www.orpha.net, from the catalog of expert resources on the above-mentioned website https://www.orphadata.com/ or from the EMA (European Medicines Agency) website http://www.ema.europa.eu.

Data are also available on designated orphan medicinal products in the United States at www.orphanet.fr and https://www.orphadata.com/.

Official and up to date information about orphan medicinal products is available in the Community Register of orphan medicinal products for human use: Union Register of medicinal products - Public health - European Commission (europa.eu)

[1]EUR-Lex. Regulation (CE) n° 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products . EUR-Lex - 32000R0141 - EN - EUR-Lex (europa.eu). Accessed in May 2024.
[2]Ministrère de la Santé et de la Prévention. Les médicaments orphelins. Les médicaments orphelins (sante.gouv.fr). Accessed in May 2024.

European Community marketing authorisation under the centralised procedure

PART 1

Orphan medicinal products in Europe with European orphan designation and European marketing authorisation*

**European Community marketing authorisation under the centralised procedure*

Number of medicinal products

Total number of orphan medicinal products, i.e. drugs with a MA with orphan designation at the end of February 2023: **184** (figure 1). Figure 1 below shows the evolution of the granting of MAs with orphan designation over time (in years).

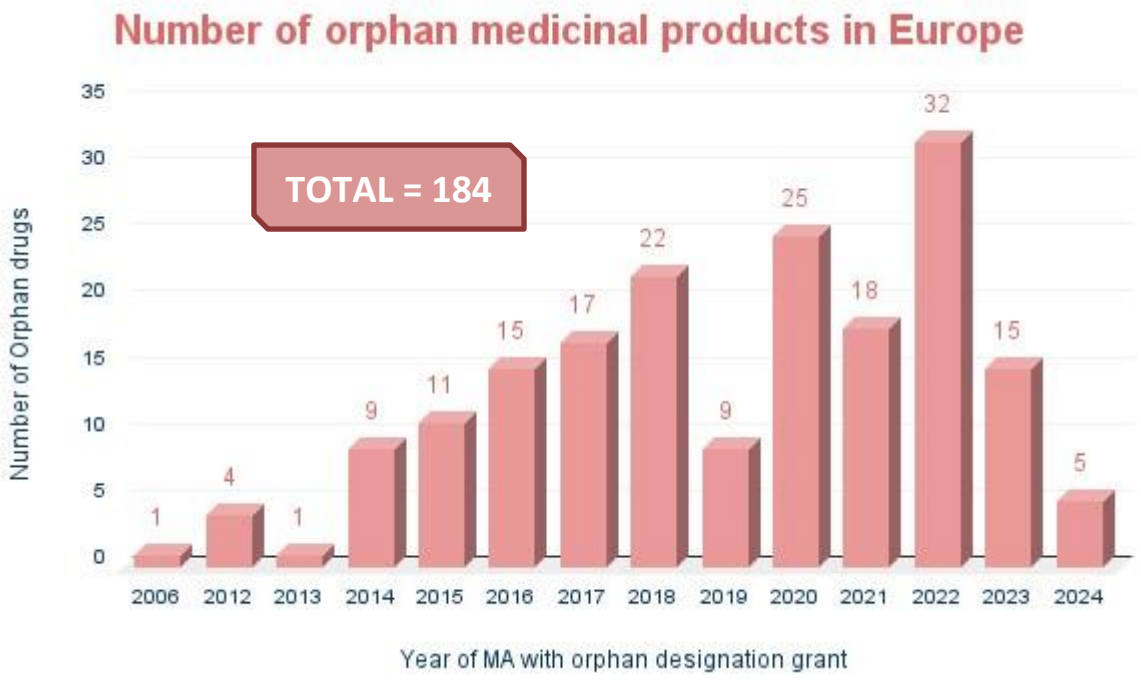

Figure 1: Number of orphan medicinal products in Europe

Description of medicinal products

Production type

47,8% Biotechnology

52,2% Chemistry

Product type

10,3% Gene therapy

1,6% Cell therapy

88,1% Others

*Other types of therapy: immunotherapies, biotherapies, targeted therapies, chemical drugs, blood derived products, etc…

Distribution of medicinal products by ATC class

Figure 2 shows the distribution of orphan medicinal products according to the ATC classification system. This is the Anatomical Therapeutic Chemical (ATC) Classification System, which classifies drugs according to the organ or system on which they act and their mode of action. This classification system is maintained by the World Health Organization (WHO)[3].

According to the analysis of the Orphanet database, the 3 most represented pharmacotherapeutic groups of orphan medicinal products are (percentage of all orphan drugs) :

1. Antineoplastic and immunomodulating agents (42,9%).
2. Alimentary tract and metabolism medicinal products (16,3%).
3. Nervous system medicinal products (7,6%).

The least represented being: dermatologicals (1.1%), cardiovascular system medicinal products (1.1%), antiparasitic products, insecticides and repellents (0.5%), genito-urinary system and sex hormones medicinal products (0%).

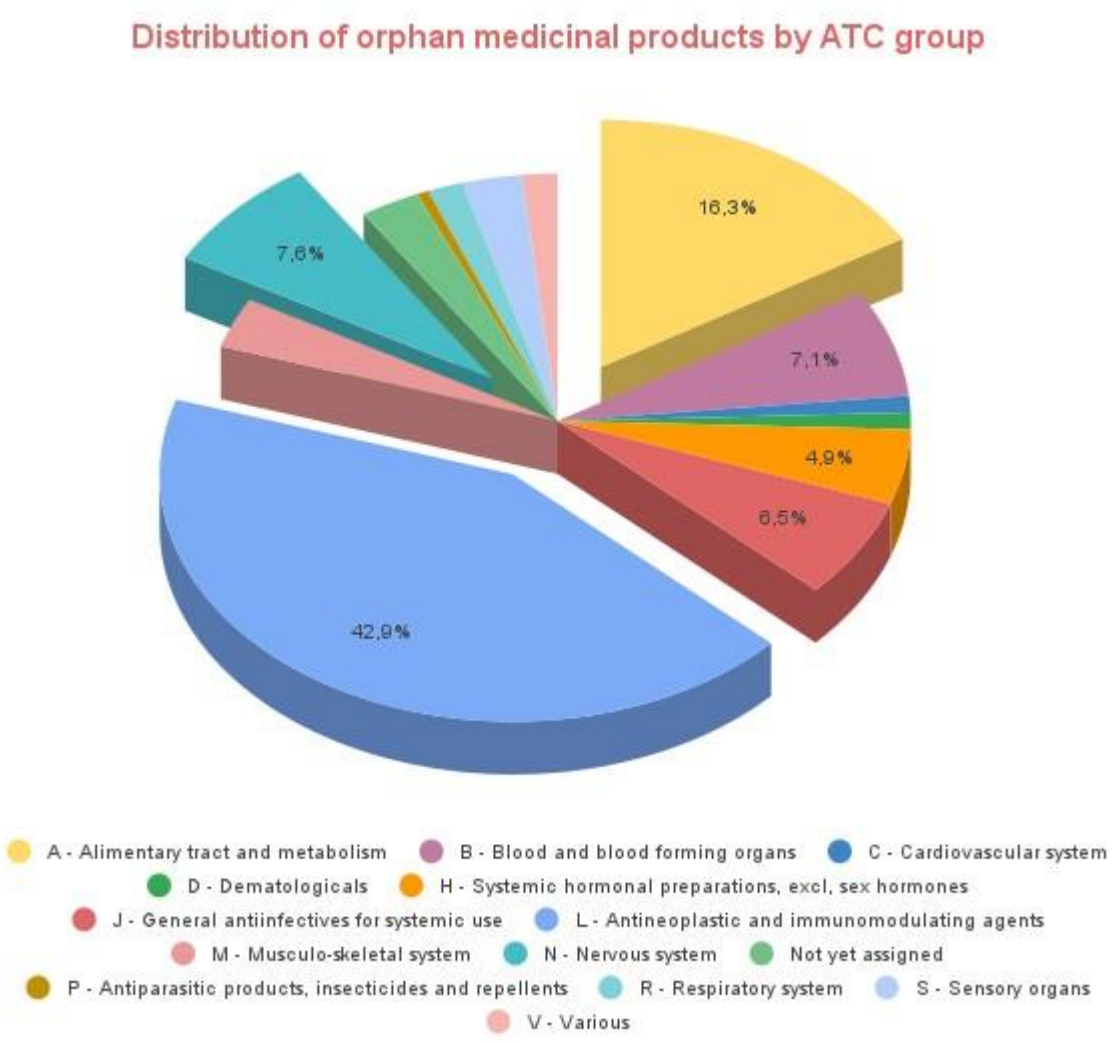

Figure 2: Distribution of orphan medicinal products by ATC class

[3]European Medicines Agency. ATC code. https://www.ema.europa.eu/en/glossary/atc-code. Accessed in May 2024.

Classification by marketing authorisation holder

Number of MA holders with orphan designation = **94 pharmaceutical companies.**

Figure 3 describes the MA holders with at least 5 orphan medicinal products.

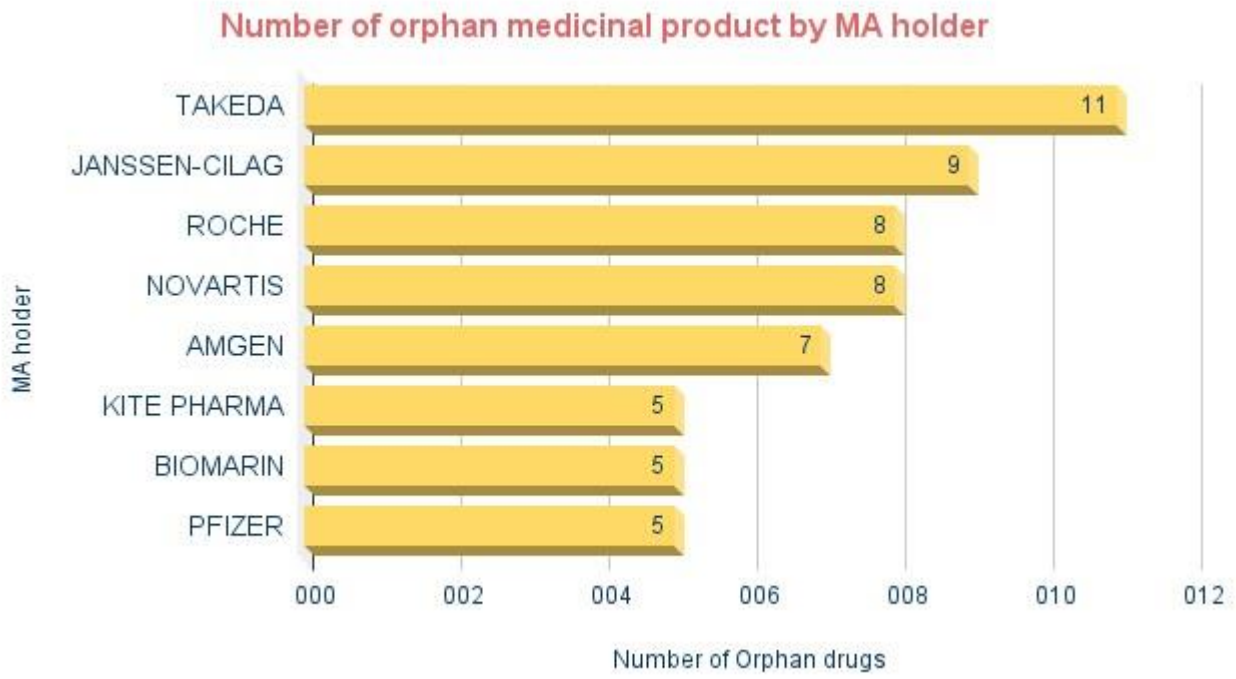

Figure 3: Number of Orphan medicinal products by MA holder (with ≥ 5 orphan medicinal products)

Therapeutic indications

The number of indications for all orphan medicinal products is 246 covering 163 rare diseases/groups of rare diseases representing a total of 307 rare disorders: **4.84% of rare disorders benefit from an orphan medicinal product in Europe** (total number of rare disorders in the Orphanet database in January 2024 = 6346).

Table 1. Rare diseases or groups of rare diseases for which there is more than one approved orphan medicinal product.

Rare disease/group of rare diseases	Number of Orphan drugs (>1)
Multiple myeloma	12
Diffuse large B-cell lymphoma	8
Acute myeloid leukemia	7
Precursor B-cell acute lymphoblastic leukemia	7
Follicular lymphoma	5
Classic Hodgkin lymphoma	3
Complication after organ transplantation	3
Complications after hematopoietic stem cell transplantation	3
Cystic fibrosis	3
Cytomegalovirus disease in patients with impaired cell mediated immunity deemed at risk	3
Hereditary ATTR amyloidosis	3
Myasthenia gravis	3
Non-acquired isolated growth hormone deficiency	3
Tuberculosis	3
Acromegaly	2
Anaplastic large cell lymphoma	2
Argininemia	2
Autoimmune hypoparathyroidism	2
Autoimmune polyendocrinopathy type 1	2
Beta-thalassemia	2
Cholangiocarcinoma	2
Dravet syndrome	2
Duchenne muscular dystrophy	2
Endogenous Cushing syndrome	2
Essential thrombocythemia	2
Fabry disease	2
Familial isolated hypoparathyroidism	2
Gastroenteropancreatic neuroendocrine neoplasm	2
Gastrointestinal stromal tumor	2
Glial tumor	2
Immune-mediated thrombotic thrombocytopenic purpura	2
Lennox-Gastaut syndrome	2
Malignant epithelial tumor of ovary	2
Malignant tumor of fallopian tubes	2

Moderate hemophilia B	2
Neuromyelitis optica spectrum disorder	2
Polycythemia vera	2
Primary myelofibrosis	2
Primary peritoneal carcinoma	2
Proximal spinal muscular atrophy	2
Secondary hypoparathyroidism due to impaired parathormon secretion	2
Severe hemophilia B	2
Sickle cell anemia	2
Systemic mastocytosis with associated hematologic neoplasm	2
Tuberous sclerosis complex	2

The medical specialties presented in Figure 4 hereafter represent the highest levels of the Orphanet classification of rare diseases or groups of rare disease for which orphan medicinal products are indicated. It should be noted that in the Orphanet classification, many diseases or groups of rare diseases can be assigned to several medical specialties (due to the multidimensional nature of rare diseases) but only the preferred specialty (determined according to the main specialty of the physicians diagnosing and managing the concerned disease in accordance with the Orphanet procedure Linearization rules for Orphanet classifications) is presented in this figure (a drug is therefore counted only once if all its indications correspond to the same preferential specialty).

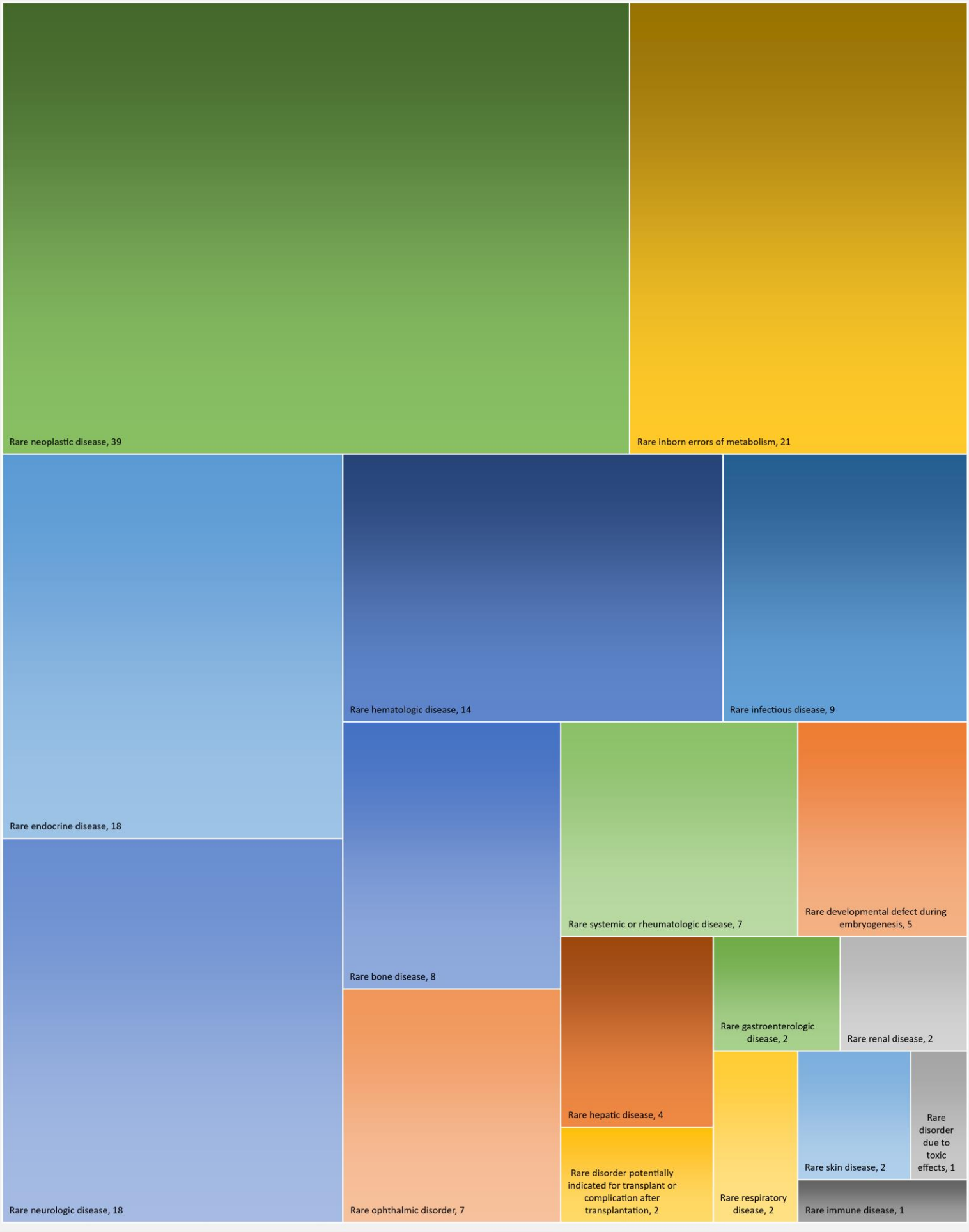

Figure 4: Distribution of rare diseases/groups of rare diseases preferred medical specialties covered by orphan medicinal products (n=162 rare diseases/groups of rare diseases)*

**One disease excluded from the analysis as it is non-rare but registered in the database because associated with an orphan designation*

PART 2

Medicinal products with European marketing authorisation for rare disease without orphan designation*

**European Community marketing authorisation under the centralised procedure*

Number of medicinal products

Total number of medicinal products approved in rare disease without orphan designation at the end of April 2024: **410** (figure 5). Figure 5 below shows the evolution of the granting of MAs without orphan designation over time (in years).

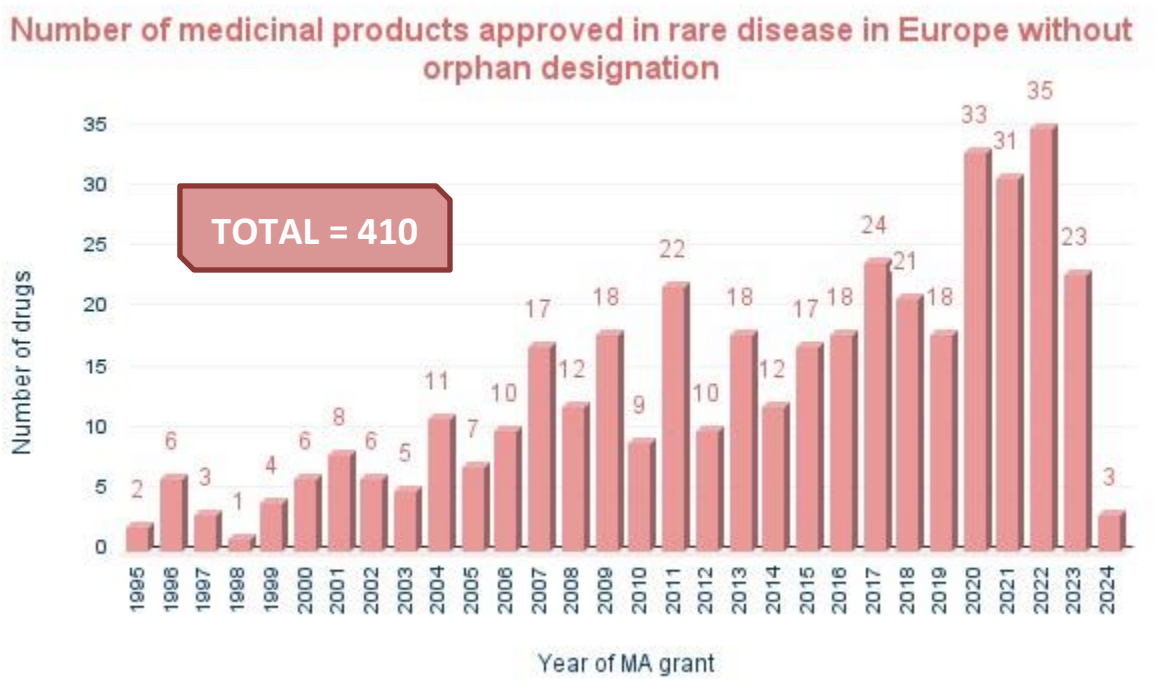

Figure 5: Number of medicinal products approved in rare disease in Europe without orphan designation

Description of medicinal products

Production type

40,0% Biotechnology

60,0% Chemistry

Product type

0% Gene/cell therapy

2% Blood-derived

98% Others

*Other types of therapy: immunotherapies, biotherapies, targeted therapies, chemical drugs, etc…

Distribution of medicinal products by ATC class

Figure 6 shows the distribution of medicinal products approved for rare disease in Europe without orphan deisgnation according to the ATC classification system. This is the Anatomical Therapeutic Chemical (ATC) Classification System, which classifies drugs according to the organ or system on which they act and their mode of action. This classification system is maintained by the World Health Organization (WHO)[3].

According to the analysis of the Orphanet database, the 3 most represented pharmacotherapeutic groups of this type of medicinal products are (percentage of all medicinal products approved for rare disease without orphan designation):

1. Antineoplastic and immunomodulating agents (54,6%).
2. General antiinfectives for systemic use (9,5%).
3. Alimentary tract and metabolism medicinal products (9,3%).

The least represented being (0,2% each): antiparasitic products, insecticides and repellents, and dermatologicals.

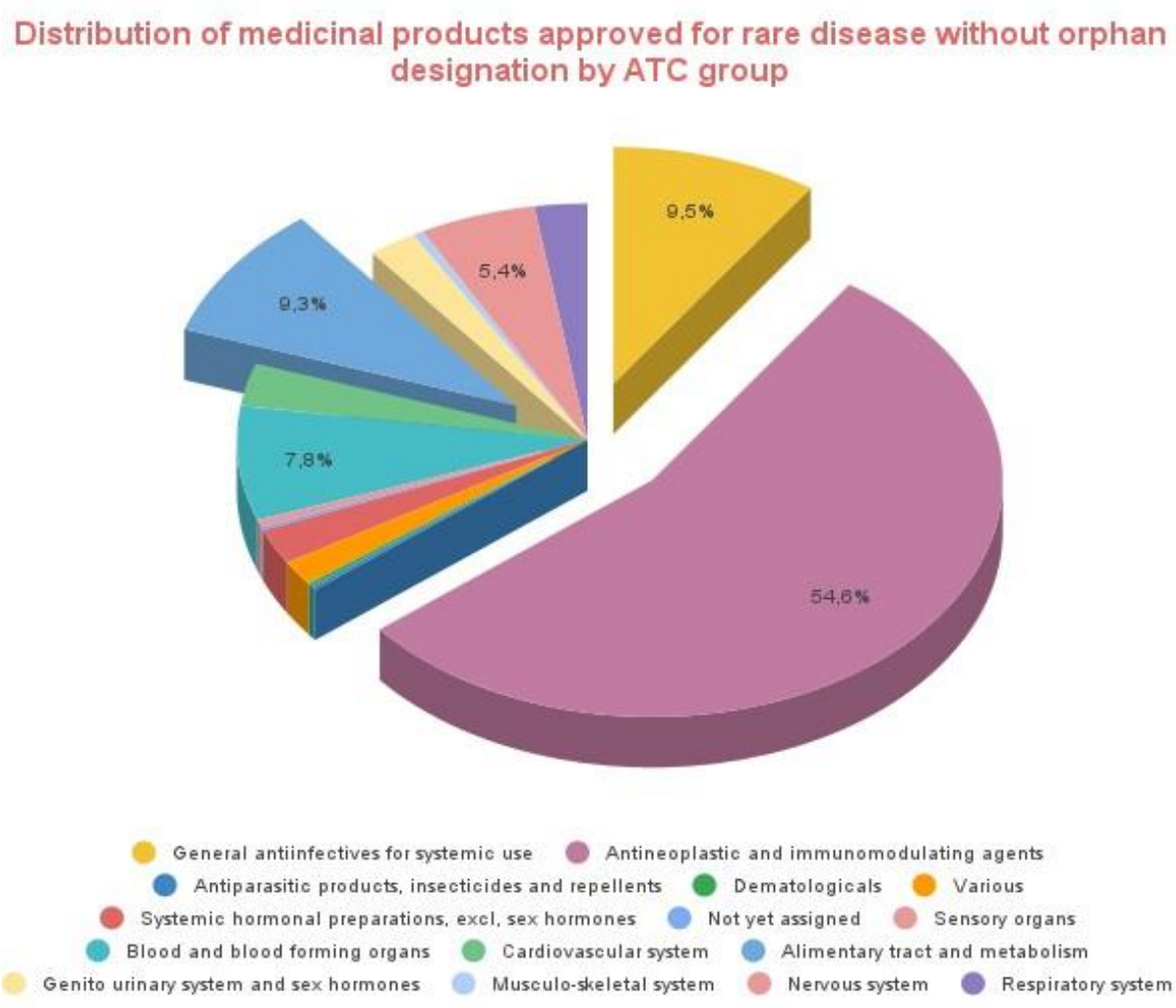

Figure 6: Distribution of medicinal products approved for rare disease without orphan designation by ATC class

[3]European Medicines Agency. ATC code. https://www.ema.europa.eu/en/glossary/atc-code. Accessed in may 2024.

Classification by marketing authorisation holder

Number of MA holders in at least one rare disease without orphan designation = **137 pharmaceutical companies.**

Figure 7 describes the MA holders with at least 5 medicinal products approved in rare disease without orphan designation.

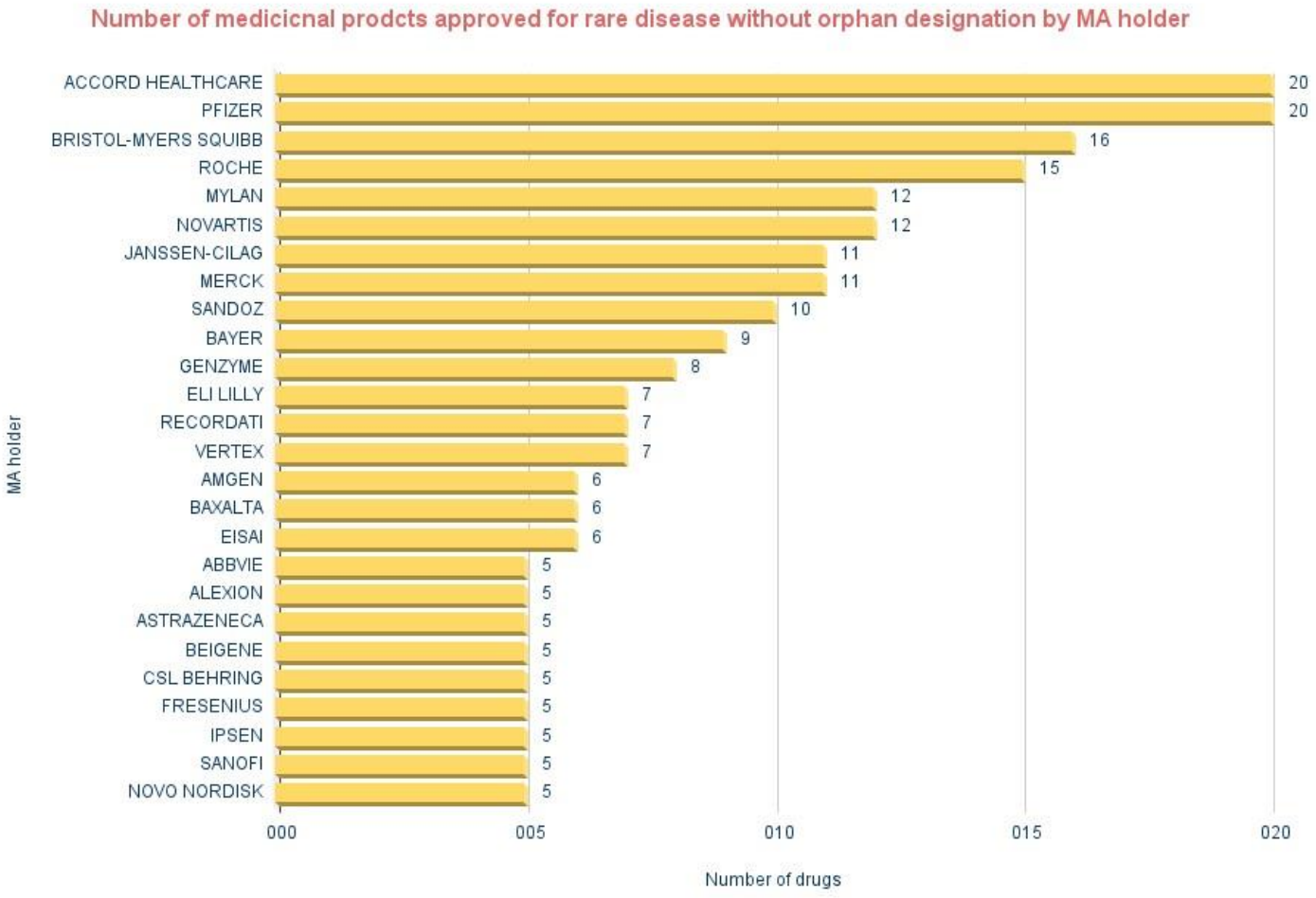

Figure 7: Number of medicinal products approved for rare disease without orphan designation by MA holder (with ≥ 5 medicinal products meeting these criteria)

Therapeutic indications

The number of indications for those medicinal products is 741 covering 260 rare diseases/groups of rare diseases representing a total of 491 rare disorders: **7,84% of rare disorders benefit from a medicinal product approved in Europe for rare disease without orphan designation** (total number of rare disorders in the Orphanet database in February 2023 = 6265).

Table 2. Rare diseases or groups of rare diseases for which there is more than five medicinal product approved for rare disease withour orphan designation.

Rare disease/group of rare diseases	Number of drugs approved for rare disease without orphan designation (>5)
Multiple myeloma	29
Renal cell carcinoma	18
Follicular lymphoma	17
Acute lymphoblastic leukemia	15
Enthesitis-related juvenile idiopathic arthritis	14
B-cell chronic lymphocytic leukemia	13
Cystic fibrosis	13
Polyarticular juvenile idiopathic arthritis	13
Chronic myeloid leukemia	12
Mantle cell lymphoma	12
Pleural mesothelioma	11
Pulmonary arterial hypertension associated with connective tissue disease	10
Adult hepatocellular carcinoma	9
Malignant tumor of fallopian tubes	9
Acute myeloid leukemia	8
Diffuse large B-cell lymphoma	8
Idiopathic/heritable pulmonary arterial hypertension	8
Juvenile myoclonic epilepsy	8
Moderate hemophilia A	8
Non-infectious posterior uveitis	8
Severe hemophilia A	8
Adult idiopathic neutropenia	7
Bleeding disorder in hemophilia A carriers	7
Complications after hematopoietic stem cell transplantation	7
Cyclic neutropenia	7
Idiopathic panuveitis	7
Idiopathic uveal effusion syndrome	7
Intermediate uveitis	7
Non-infectious anterior uveitis	7
Ovarian cancer	7
Severe congenital neutropenia	7
Systemic diseases with panuveitis	7
Vogt-Koyanagi-Harada disease	7
Gaucher disease type 1	6

Granulomatosis with polyangiitis	6
Immune thrombocytopenia	6
Pulmonary arterial hypertension associated with congenital heart disease	6
Squamous cell carcinoma of the larynx	6
Squamous cell carcinoma of the oropharynx	6

The medical specialties presented in Figure 8 hereafter represent the highest levels of the Orphanet classification of rare diseases or groups of rare diseases for which medicinal products aproved for rare diseases without orphan designation are indicated. It should be noted that in the Orphanet classification, many diseases or groups of rare diseases can be assigned to several medical specialties (due to the multidimensional nature of rare diseases) but only the preferred specialty (determined according to the main specialty of the physicians diagnosing and managing the concerned disease in accordance with the Orphanet procedure Linearization rules for Orphanet classifications) is presented in this figure (a drug is therefore counted only once if all its indications correspond to the same preferential specialty).

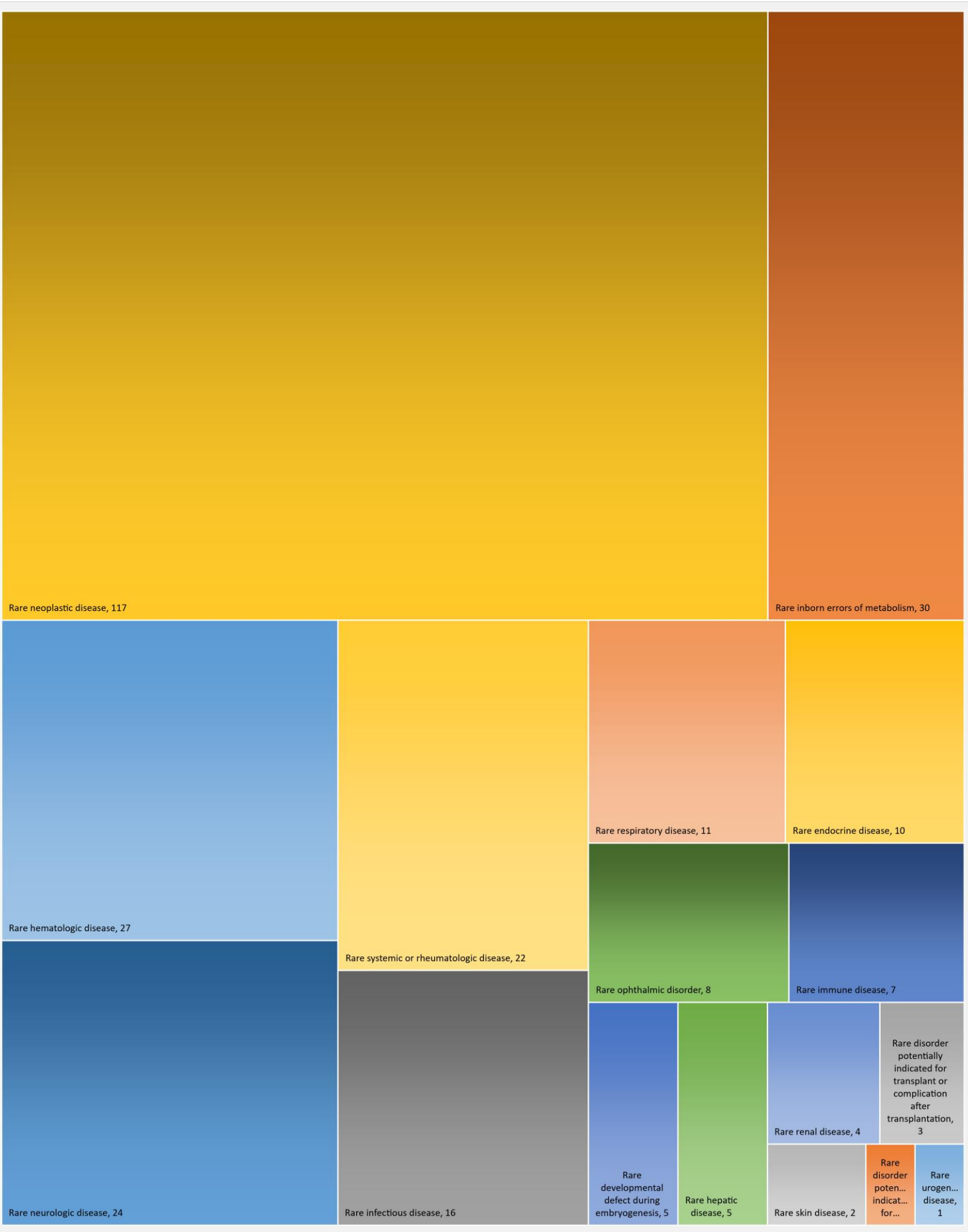

Figure 8: Distribution of rare diseases/groups of rare diseases preferred medical specialties covered by medicinal products approved for rare diseases without orphan designation (n=293 rare diseases/groups of rare diseases)*
**two diseases excluded from the analysis as they are non-rare but registered in the database because associated with former orphan designations*

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