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Review

Designation of orphan conditions in Europe: regulatory observations and considerations after implementation of regulation 141/2000

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Abstract

Introduction: In the first 18 years of the implementation of the orphan medicinal products regulation, it has been noted that every year a steady number of orphan designations refer to new conditions, not designated previously. This is important because it offers documented evidence that research and development is ongoing for many areas of rare diseases. These newly designated rare conditions reflect drug development opportunities in areas of limited regulatory knowledge. Authors carried out a literature search via pubmed and Google as well as refering to previous articles they have been involved in as authors.

Areas covered: The aim of this paper is to review the outcomes associated with new rare conditions designation by the COMP. With over 2000 designations made since its creation data specific to conditions designation collected by the European Medicines Agency (EMA) after each monthly plenary session is presented here. The data is observational and has been grouped into therapeutic criteria based on ATC codes.

Expert opinion: Regulators should continue to engage in constructive dialogue with stakeholders so that the regulatory requirements are less of a hurdle and more of an opportunity to speed up drug development in areas of unmet medical need. The designation of new conditions further supports the utility, need and meaning of the orphan regulation as a catalyst of drug development.

Key words

Orphan designation, regulatory, condition, clustering, drug development

Article Highlights box

• Many rare diseases exist in the world and many are still to be identified and better defined.

• Since the implementation of the orphan medicinal products regulation, every year a steady number of orphan designations refer to new conditions, not designated before.

• Orphan designation helps understand the gathering of science to meet the aims of the regulation.

• The documented evidence that research is ongoing for many rare diseases through orphan designation and these newly defined rare conditions reflect drug development opportunities in areas of limited regulatory knowledge.

• The designation of new conditions further supports the utility, need and meaning of the orphan regulation as a catalyst of drug development.

1. Introduction

There is no universal definition for a rare disease/condition but rather definitions used in legislation in different parts of the world to incentivise drug development for diseases which have a prevalence below a given threshold.(1,7) Each year the COMP designates a varying number of rare conditions which have not been previously assessed at the stage of an initial designation.(8) An initial orphan designation is the first step in the orphan designation process to unlock the incentives associated with protocol assistance and fee reductions and offers the promise of a 10 years Market exclusivity should the product successfully obtain a licence.(7) Designation submissions are discussed at a monthly plenary where the COMP, discusses and recommends granting or not a submission which has been assessed prior to the plenary meeting. (8)

At the end of each monthly plenary the COMP publishes the list of positive orphan designations which are available to the public on the EMA website in the section dedicated to Committees under COMP. They can be found in the COMP monthly plenary reports that stretch back to 2007 when the transparency exercise was started. Old data between 2000-2007 is held in the same manner by EMA. The meeting reports always publish tables found at the end, highlighting the active substance, orphan indication (condition), sponsor, COMP opinion date and EC designation date. These positive designations are available to the public and are entered in a database held in the EMA permitting further analysis. The EMA and COMP continuously record and monitor initial designations.(7) The COMP has used this data in previous publications such as European regulation on orphan medicinal products: 10 years of experience and future perspectives, Westermark K et al, Nat Rev Drug Discov 2011 May;10(5):341-9. (5) The orphan conditions are grouped into prespecified therapeutic areas based on ATC codes, and presented to the COMP members for information and comment on an

annual basis. By grouping both previously designated and new conditions into these pre-specified therapeutic areas trends can be seen helping the COMP to become aware of an ever-changing rare diseases research landscape. This helps understand workload but also monitor the emergence of research and development in new conditions as well as subsequent clustering of additional positive designations around a condition. (2,7) At the end of 2018, 524 rare conditions have been designated. Data shows that new conditions continue to expand the total number of orphan conditions seen by the COMP offering some insight into the evolving landscape regarding therapeutic areas of interest for rare diseases over the last 18 years reflecting changes in research and development.

We have conducted a retrospective review of the designation of conditions by the COMP since 2000 and followed the evolution of new conditions and conditions per therapeutic areas. A discussion of the impact of the designation of a new condition and subsequent associated designations in helping the COMP and potentially the wider public understand interest and development trends is offered. It is hoped that future sponsors interested in the designation system will submit new conditions or additional designations thereby raising awareness and encouraging further research and development in neglected areas of drug development. We hope to highlight some of the positive impact new condition designations could have in some neglected rare diseases and how orphan designation helps development.

2. Designated new rare conditions

Rare conditions which the COMP has not previously designated are submitted every year and represent between 18-20% of the positive designations each year. Figure 1 highlights the percentage of new conditions each year in red. Earlier data between 2001 and 2007 reflects the first years of the implementation of the orphan legislation (Figure 1).

New rare condition designation creates the possibility of raising awareness for less well-known or established conditions. With increased awareness comes the hope that other academic research centres or businesses conducting research and development in the newly designated condition may come forward and seek designation. Additionally, it offers a perception of emerging areas of interest for development in rare diseases where previously there were no authorised medicines increasing the knowledge and potentially new medicinal products to treat the condition.

The COMP has been designating rare conditions for almost 20 years. With the support of the EMA, the COMP collects data on conditions after each monthly plenary. These new conditions are added to their corresponding therapeutic area with the subsequent effect of appearing as a change in the

rare disease research landscape over time. Comparing the evolution of positive condition designation by therapeutic grouping offers an interesting insight into research and development across different rare diseases. For the purpose of this publication we have looked at the period spanning between 2009 when the process first produced these grouping to 2018 the last available data release.

Between 2000 and 2009 (Figure 2) almost half of the positive designations were for oncological indications with the next most common grouping being musculosckeletal and nervous system conditions (13%). At the time of the evaluation of conditions a large group, 25% under "Others" was identified highlighting the fact that this group of conditions could not be grouped in any substantial numbers in a given therapeutic area.

As the number of designations increased a follow-up evaluation was conducted in 2014 (Figure 3). It shows an evolution in the therapeutic grouping from 2009. The emergence of groupings in therapeutic areas appears which could be driven by the designation of new conditions. Of note is the drop in the share of oncology was noted from 45% to 36%. New therapeutic areas of interest such as blood and blood forming organs emerged out of "Others" and represented 7% of all designations and those grouped under sensory organs represent 5%. Other therapeutic areas continued to remain stable such as Neurological and musculoskeletal at ~13% share.

A further assessment in 2018 showed a continued drop in oncology conditions albeit more slowly (from 36 to 34%) which has been associated with an overall continued increase in non-oncological conditions. Increases some other more established groupings such as neurological and musculoskeletal (12 to 14%), alimentary tract and metabolism (11 to 12%) and blood and blood-forming organs (7 to 8%) can be noted. A drop was noted in infectious (2 to 1%) and respiratory (6 to 5%) conditions. Somewhat disappointing is the drop-in submissions for infection related conditions which would cover tropical diseases such as malaria and leishmaniosis or rare infections like tularaemia or multidrug resistant tuberculosis. This would support the continuing concern of limited development in the field of infectious diseases noted in the pubic domain. As it is widely publicised that there is a great need for medicines in this therapeutic area it is disappointing to see that the share of designations is declining.

As the designation process matures it appears that more non-oncological rare conditions are being designated over time.

The three pie charts presented (Figure 4) offer a glimpse into the dynamic nature of condition designations over time. Although this has not been analysed using a defined methodology new conditions do not appear to be solely responsible for the variability in the therapeutic categories.

2.1 Clustering following designation of a new condition

An internal analysis by the COMP in 2015 noted that an additional characteristic following a positive orphan condition designation was additional independent designations for that condition which led to clustering or grouping with medicinal products. These products vary in nature being either repurposed or new and in research and development. Examples of the impact of designation on a condition and clustering of subsequent submissions can be seen by simple consultation of the database available in the public domain on the European Medicines Agency website. Pancreatic cancer for example, which was designated since 2000 has had 60 positive designations (as of the 16th August 2019) indicating a high interest and activity for this rare condition. Increased clustering can be interpreted to mean increased public awareness. A similar phenomenon is seen in the high number of designations for example in Duchenne's Muscular Dystrophy (37 designations) or Cystic Fibrosis (59 designations) which have well-established patient organisation networks (as of the 16th August 2019)(10). An indication of the number of sponsors developing medicines for a given condition is noted (many designations are associated with many different sponsors) and gives some indication of the level of interest in development for that condition.

Although a specific analysis of the relationship between an initial designation for a new condition and subsequent submissions for that condition has not been conducted, some observations can be made. The granting of designations for less publicly known conditions by the COMP can also be associated with subsequent designations leading to varying degrees of clustering.

Several examples of non-oncological conditions offering a greater rate of interest can be extracted from the positive designation data. Under the European Orphan Designation system prevalence is defined as a ration per 10,000. (14) For example, Fragile X Syndrome (prevalence between 2-4 in 10000) a neurological condition which was first designated in 2011 has had 10 subsequent positive designations for other medicines to date. Prader-Willi syndrome another neurological condition first designated in 2012 affects 2 in 10000 in Europe has had 5 additional designations to date and has a product authorised for the indication in 2018. In these cases, designation of these new conditions appears to have been followed by interest and additional designations indicating that the legislation is encouraging development.

Prevalence of a condition does not appear to be the limiting factor regarding clustering for example in Haemophilia B which has a prevalence below 1 in 10,000 (which some would call an ultra-rare condition) has 18 designations (as of the 16th of August 2019). However low Public awareness linked to low prevalence could however be associated with lower submissions and positive opinions. (13)

To illustrate this point, we have highlighted some conditions which have been designated by the COMP for which few additional positive designations have occurred. Adrenoleukodystrophy a metabolic disorder with a prevalence of 0.4 in 10000 in Europe and first designated in 2012 has had 3 more designations to date. Wolfram Syndrome another very rare metabolic condition with a prevalence in Europe estimated to be 0.2 in 10,000 had its initial designation in 2015 and only one additional designation. Aicardi-Goutieres Syndrome (prevalence reported to be 1 in 10,000) where one centre in Europe has submitted two products at the same time for designation in 2015 has had no further submissions. What the limiting factor here is difficult to establish as it can be linked to factors such as limited number of centres working on the condition or limited understanding of the underlying aetiology and pathophysiology or limited patient organisation interaction (12). Although a crude measure designation clustering around a new condition can offer some perception into the interest, awareness and trends regarding medicinal research and development activities associated with the specific condition considered.

2.2 How to view clustering of broad conditions which have been designated by classified subtypes

Although the COMP will often designate a condition under an umbrella term to capture as many subsets of a condition as possible. In some instances, however it has subdivided them according to how they are classified in the public domain. An example are the mucopolysaccharidosis which have been designated by type as described in the literature (Types I, II, III, IV, VI and VII) with each showing clustering of subsequent submissions and positive opinions totalling 34 positive opinions indicating that this is an area of great interest in development. A similar situation exists for mitochondrial disorders where the classification system describes several different disorders such as: mitochondria DNA depletion syndrome, myopathic form, mitochondrial trifunctional protein deficiency, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (2 designations) and mitochondrial neurogastrointestinal encephalopathy (2 designations). (16) There are 7 designations in total retrievable for mitochondrial disorders which are classified theoretically as" various" on the EMA website indicating that there is some interest in developing products in what are very difficult conditions to study and treat.

2.3 Changes to wording of an initial designated condition

In some instances, the COMP may opt to stop clustering by type. Niemann Pick disease which is a metabolic disorder involving three clinical types has been designated 5 times as Niemann-Pick Type

C and more recently 3 times as Niemann-Pick. This would mean a total of 8 designations have clustered around the term Niemann-Pick showing some interest in developing a medicine in this condition. (15) Another condition which became broader recently was spinal muscular atrophy which previously was designated 5q spinal muscular atrophy. The broadening of conditions can be changed into ”umbrella” terms which stay not above 5 in 10,000 can occur with the arrival of new submissions for a previous condition designated such 5q spinal muscular atrophy. In some instances such as the indication of ”treatment in haematopoietic stem cell transplantation the COMP has made a regulatory effort to bring previous smaller conditions such as ”adjunctive treatment in haematopoietic cell transplantation” under this umbrella term. Thus the aim maybe driven by regulatory considerations or due to changes in the classification system such as those seen for haematopoietic malignancies where the WHO published a revised classification system creating a new system which the COMP need to adapt to. Previous designations such as” treatment of hairy cell leukaemia” which were designated before 2008 were subsequently designated as ”Treatment of Chronic Lymphoblastic Leukaemia” since the change. While these kinds of changes do not appear to affect the overall grouping a trend by therapeutic area, the measuring of clustering by condition becomes more fragmented making the overall picture for some conditions difficult to establish. Also, of note is the possibility of a condition changing at the time of submission for marketing authorisation of an orphan designated product. The earlier designation of interstitial cystitis as a distinct condition with a prevalence of not more than 5 in 10000 was revised to bladder pain syndrome following a revision of the classification of these disorders published in 2015. As this occurred during the review for the maintenance of the orphan designation and the prevalence went over 5 in 10000 the applicant could no longer satisfy the criteria for the maintenance of the orphan designation at the time or marketing authorisation and had to withdraw the designation.

3. Designation withdrawals

Orphan designation holders have the option to withdraw a designation if it is no longer of commercial interest to hold it or, for example, the product has failed at some stage of development before submission for a marketing authorisation. The reason does not appear in the public domain, so it is difficult to measure development failures by measuring post designation withdrawals from the European Commission Registry.

An indication of some of the difficulties can however be assumed as seen in pancreatic cancer for example where 12 designations have been withdrawn from the registry as of 16 August 2019 of a

total of 49 designations reported since 2001 (around 25% of all positive designations granted). Glioma another difficult area for development has seen 64 designations of which there were 18 withdrawals (around 28% of submissions).

The number of cases which have gone silent due to the orphan designation holder not withdrawing or going into bankruptcy is not included in these considerations.

4. Designated conditions with no authorised products at initial designation followed by a first product obtaining a marketing authorisation

The impact of the marketing of a new medicinal product in a condition which otherwise has had no authorised medicines in Europe has not been studied. The accumulation of applications in some therapeutic areas has been noted which was considered of interest to share. For example, spinal muscular atrophy there has been a total of 13 designations for products in this condition since 2005 to date (of note before 2017 the condition was designated as 5q spinal muscular atrophy). Following the approval of Spinraza the first product for use in this condition in 2017, the COMP has designated a further 4 products for this condition between 2018-2019.(17) Another example of the potential impact of a marketing authorisation of a medicinal product in a condition where no product has previously existed is paroxysmal nocturnal haemoglobinuria. In 2002 paroxysmal nocturnal haemoglobinuria was recognised as a condition by the COMP which led to the designation of eculizumab in 2003 for this condition. Eculizumab received a marketing authorisation for the indication in 2007 and yet the COMP only started to receive additional submission for designation only in 2014 indicating that awareness or impact of a new medicine where there were no medicines previously. This led to another product Ultomiris receiving a licence in 2019.

Idiopathic pulmonary fibrosis which has obtained a total of 20 designations to date, received recognition as a distinct medical entity in 2004 when no authorised medicines existed in Europe for this condition. Between 2004 and 2010 the condition received 8 designations. After 2010 when the first marketing authorisation was obtained for a medicine another 12 designations and one further market authorisation was obtained for another medicinal product in 2015. (18) As can be seen while no hard and fast rule can be linked between creation of awareness of a rare condition due to an initial designation and the first marketing authorisation most examples would indicate that marketing of the first product in a condition in an area where there are no products authorised can lead to further designations. This will also therefore affect the overall metrics regarding the

therapeutic areas where a marketing authorisation for a medicine is obtained as this doesn't seem to slow down further designations.

5. Amendment to a designated condition

The COMP provides sponsors a mechanism by which they can amend a condition to bring a condition which is no longer considered valid into line with changes in science and classification of systems associated with medical entities. This can affect the wording of a condition and the overall prevalence calculation in general however rarely/less frequently the therapeutic area. (3)

Applicants are therefore encouraged to ensure that the condition that they initially obtained a designation for continues to be considered as a distinct medical entity and that classification and/or nomenclature hasn't changed since. In that event that a condition has been changed in the public domain the designation holder should contact the EMA Orphan Office to discuss the need to submit an amendment to the COMP for consideration and assessment if needed. This is of particular importance when the designation holder is submitting for review for the maintenance of an orphan designation at the time of marketing authorisation application as this could have implications for the applicability of the post marketing incentive of a 10 years Market Exclusivity.

6. Conclusion

The COMP has designated 524 distinct rare conditions since the European Orphan Regulation was introduced in 2000 and continues to designate new conditions each year. Over the last 18 years this represented on average 25% of the total of positive designations per year. The recognition of rare conditions through the designation process by the COMP helps visualise the changing dynamics seen in different therapeutic groups as well as potentially increasing awareness so the COMP welcomes and encourages their submission for assessment and designation. It is hoped that this will help foster additional submissions for other medicinal products for the new designated condition thereby creating clustering around the condition and potentially increasing the possibility of obtaining a marketing authorisation for a product where none exists.

7. Expert opinion

It has been stated that 7000 rare diseases exist in the world and many are still to be identified and better defined. It is clear that the starting point of any orphan designation is the definition of the orphan condition and that definition and acceptability is not without challenges sometimes since it needs to fall under the criteria established by the European Orphan Regulation. The COMP has gathered and shared its experience and knowledge in order to best guide sponsors, and this is clear when looking at the amount of published papers over the last 10 years. The biggest challenge remains how to best catalyse the gathering of science to meet the aims of the regulation. In this regard, it's good to look back and see that in the first 18 years of the implementation of the orphan medicinal products regulation, a steady number of orphan designations every year refer to new conditions, not designated in the years before. This is important because it is the documented evidence that research is ongoing for many rare diseases and these newly defined rare conditions reflect drug development opportunities in areas of limited regulatory knowledge. More submissions from academic groups are encouraged as they conduct research in many conditions which are still not designated and significant knowledge is generated by these groups and not immediately captured by industry. The effect of funding programmes like Horizon 2020 on the submissions from academic centres has been noted and indeed in 2015, for example, it was noted that 17 academics had submitted for orphan designation in 2014 as opposed to 4 the year before. Higher awareness of initiatives that exist to help academics should be made such as Outreach which is designed to bring researchers to a Rare Disease or European Reference Networks in rare diseases (such as cystic fibrosis) which are funded by the European Commission. The removal of barriers or hurdles like charging similar fees to academics as non-small to medium enterprises should be encouraged in future legislation. In addition to this, Regulators should continue to engage in constructive dialogue with stakeholders so that the regulatory requirements are less of a hurdle and more of an opportunity to speed up drug development in these areas of unmet medical needs. The designation of new conditions further supports the utility, need and meaning of the orphan regulation as a catalyst of drug development.

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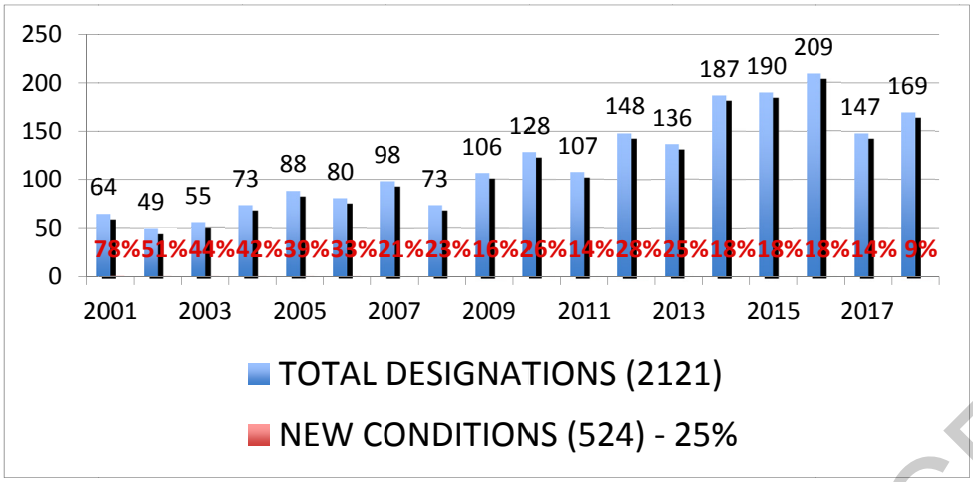

Figure 1. New conditions designated by the COMP (from 2001 to 2018) in comparison to the total designations.

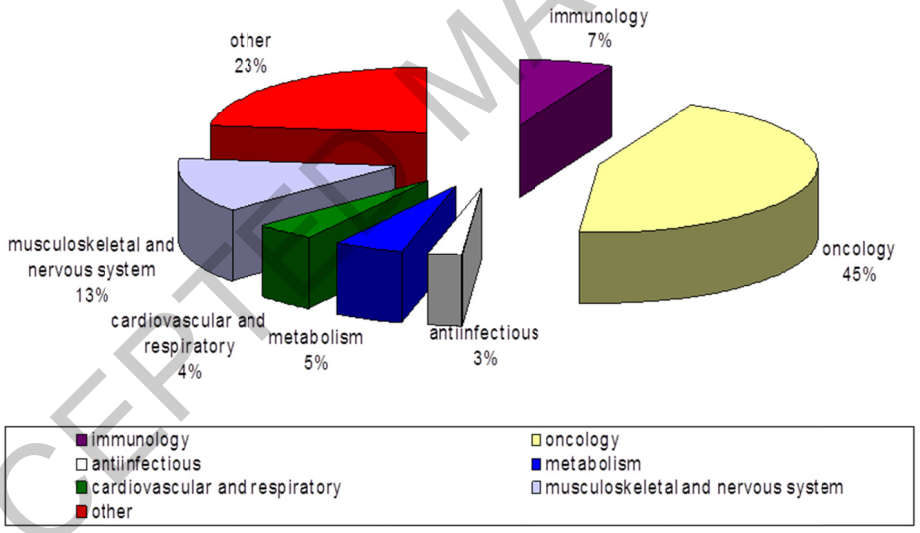

Figure 2. Distribution of Opinions granted by the COMP by therapeutic areas from year 2000 to 2009 (Total opinions = 760) (5,7)

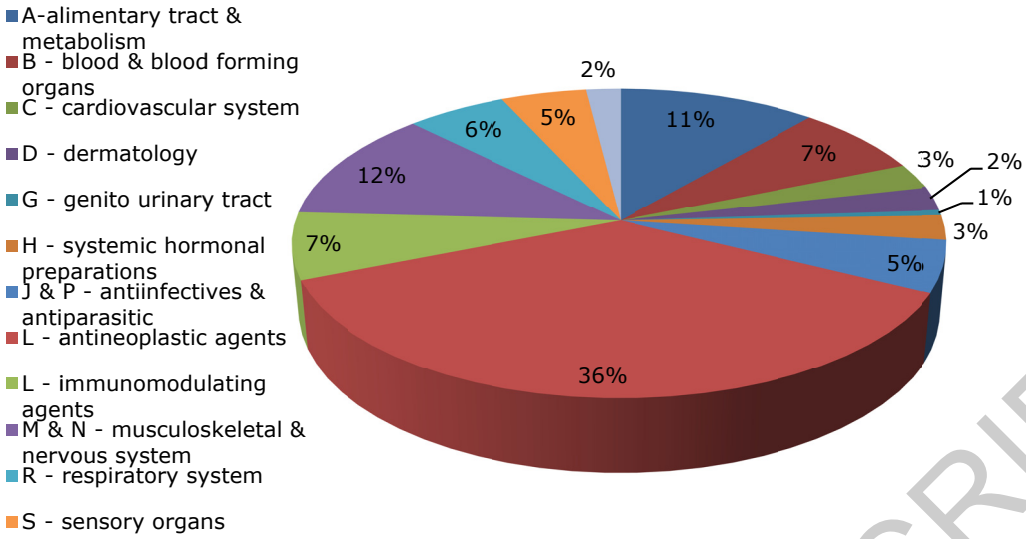

Figure 3. Distribution of Opinions granted by the COMP by therapeutic areas from year 2000 to 2014 (Total opinions = 1430)(8)

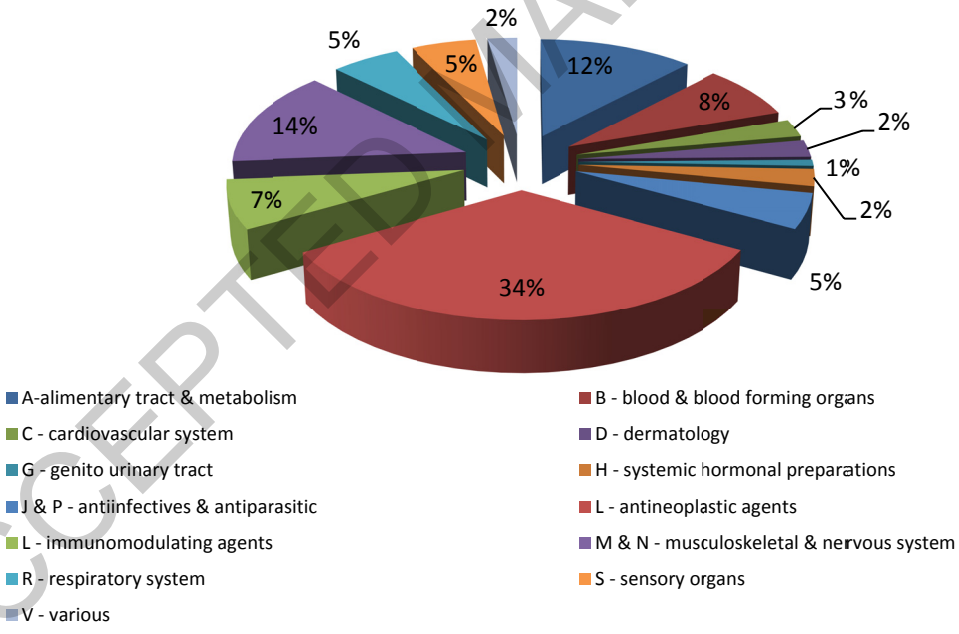

Figure 4. Distribution of Opinions granted by the COMP by therapeutic areas from year 2000 to 2018 (Total opinions = 2134)(9).