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Routine Funding in the NHS in the UK of Medicines Authorised Between 2011 and 2016 via the European Centralised Procedure

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EXECUTIVE SUMMARY

Introduction

Most of the appraisals conducted in Great Britain by the National Institute for Health and Care Excellence (NICE), All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) involve innovative medicines which are authorised in the European Union (EU) via the centralised procedure[1] coordinated by the European Medicines Agency (EMA). The granting of a marketing authorisation is usually followed by a health technology appraisal (HTA) evaluation aimed at deciding whether or not these new products will be routinely funded and can be accessed by patients in the NHS. The primary objective of our study was to analyse the HTA recommendations for centrally authorised products (CAPs) in England, Wales and Scotland. For that purpose, we analysed publicly available information on appraisals by NICE, AWMSG and SMC and commissioning by NHS England for CAPs which received an initial authorisation (or an extension to the initial indication) between 1 January 2011 and 31 December 2016. We compared the access to CAPs across England, Wales, and Scotland, with a special focus on oncology and orphan medicinal products (OMPs).

Methods

We collected information on the authorisation, appraisal and commissioning of CAPs from the relevant data sources (European Medicines Agency, NICE, AWMSG, SMC and NHS England). Data extraction on the medicinal products included relevant information aiming at comparing coverage of the HTA for the considered CAPs, distribution across therapeutic areas, outcomes of the HTA decisions, and time elapsed between marketing authorisation granted by the European Commission and the publication of the HTA decision. Separate analysis is presented to compare HTA decisions for oncology vs non-oncology products, and for orphan vs non-orphan products. Besides NICE decisions, we analysed coverage in England of NHS England specialised commissioning policies. Further statistical analysis is presented to obtain the degree of agreement between NICE and SMC decisions, and to analyse whether oncology therapeutic class and orphan designation affect the probability of obtaining a positive recommendation by the three HTA agencies.

Results

During the six year period from 2011 to 2016, a total of 713 new authorisations were granted by the EC for CAPs. The EC granted 512 new authorisations (initial or extensions of indications) for 376 medicinal products containing a new active substance. The largest number of products authorised via the centralised procedure were anticancer medicines (63 or 23%). We confirmed that medicines authorised in oncology were most likely to have received an orphan designation compared with the other therapeutic classes.

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[1] The centralised procedure is the EU procedure of authorisation of medicinal products described in Regulation (EC) No 726/2004, as amended.

Between 40% (NICE) and 80% (SMC and AWMSG) of the indications granted for products containing a new active substance were evaluated by the HTA agencies. Oncology products were proportionately more frequently evaluated by the HTA agencies than the products of other classes.

NICE evaluated 42% (216) of the 512 indications (which involved a product containing a new active substance). During the period covered by our study, NICE recommended 85% of the medicinal products that it evaluated. 378 indications (approximately 75%) out of 512 were evaluated by the SMC. Over the period covered by our study, the SMC recommended 67% of the new CAPs which received an authorisation between 2011 and 2016. In Wales, AWMSG conducted 263 evaluations, but did not receive any evidence submission for nearly 50% of CAPs (129 products). Of the remaining 134 appraisals, 123 products (92%) were recommended by the AWMSG (see Table below).

Table E1: Number of products scheduled for HTA evaluations (appraisals or highly specialised technologies evaluations), number of evaluations completed, evidence submissions performed by the companies and number of positive recommendations published by NICE, SMC and AWMSG for the medicines authorised centrally between 2011 and 2016

HTA	Authorised indications	Scheduled evaluations	Evaluations finalised	Evidence submission	Positive recommend ations
NICE	512	216	206	186	154
SMC	512	378	402	N/A	268
AWMSG	512	411	263	134	123

Importantly, our analysis shows that only 70% (88) of the indications for products used in oncology and less than 50% of the indications for OMPs (52 or 46%) were referred to NICE by the Department of Health. A higher proportion of indications were evaluated by the SMC and AWMSG, with 84% (94%, respectively) for oncology products and 68% (82%) for OMPs. Therefore, our study shows that an important number of oncology and OMPs products were not scheduled for an appraisal, especially in England.

Table E2: Number of oncology and orphan medicines authorised centrally between 2011 and 2016 evaluated by NICE, SMC and AWMSG

HTA	Oncology medicines – authorised indications	Oncology medicines – evaluated	Orphan medicines – authorised indications	Orphan medicines – evaluated
NICE	126	88	114	52
SMC	126	106	114	78
AWMSG	126	118	114	93

In England and in Scotland, products used in oncology and OMPs were associated with a lower odds of receiving a positive HTA recommendation compared with non-oncology and products which did not receive an orphan designation in the EU. Our study shows that in England the outcome of the appraisals for orphan medicines depended on the

evaluation process undertaken by the products. All the 4 orphan products evaluated under the HST programme by NICE received positive recommendations. On the other hand, this was the case for only 64% (16/25) of the orphan products appraised under the TA programme.

The longest median times which elapsed between the publication of the EU marketing authorisation and the publication of the final guidance were observed for NICE (the appraisals are conducted for half of the products within 404 days i.e. more than 13 months). The median time between authorisation and decision was 259 days for the SMC (more than 8 months) and 173 days for AWMSG (more than 5 months). We only observed longer median time differences for oncology products evaluated by the SMC (311 days vs 235 days). The evaluations of oncology products by AWMSG require shorter evaluation times compared to the other products. We did not observe any time difference between oncology and non-oncology products evaluated by NICE. These median times were longer for orphan medicinal products (OMP) evaluated by NICE and SMC (551 vs 369 days for non-orphans for NICE, 324 days vs 235 days for SMC).We did not observe any time difference between orphan and non-orphan medicines evaluated by AWMSG. Overall, the appraisal of medicines in the UK requires a substantial amount of time after the granting of the marketing authorisation. More importantly, these figures show that the evaluation of orphan or oncology medicines is not consistently prioritised by HTA agencies in the UK (see Table below).

Table E3: Median evaluation times for all medicines, oncology and orphan medicines authorised centrally between 2011 and 2016 evaluated by NICE, SMC and AWMSG

HTA	Median evaluation time (all products)	Median evaluation time (oncology medicines)	Median evaluation time (orphan medicines)
NICE	404 days (1 year 1 month)	404 days (1 year 1 month)	551 days (1 year 6 months)
SMC	259 days (8 months 18 days)	311 days (10 months 10 days)	324 days (10 months 24 days)
AWMSG	173 days (5 months 23 days)	133 days (4 months 13 days)	161 days (5 months 11 days)

Finally, we found little agreement in the outcomes of the evaluations completed by AWMSG, NICE and SMC for the products which underwent evaluations by these agencies.

61 products included in our analysis were directly funded by NHS England specialised commissioning. The most important class is the anti-infectives for systemic use, they represent 44% (27) of the products funded via this mechanism. Most of these products are antiretrovirals. Overall, taking into consideration the number of products referred to NICE, the outcomes of the evaluations, the number of products directly commissioned by NHS England and made available via the Cancer Drugs Fund, we estimated that 233 (or 45%) of the 512 new authorisations granted during the period of our study were not appraised and therefore, that the products authorised in these 233 indications were either accessible via other funding mechanisms (e.g. recommended for use in NICE clinical guidelines) or not routinely funded by the NHS.

It is also important to note that 25 OMPs are among the 61 CAPs directly commissioned by NHS England. Therefore, the findings of our study on the appraisal of orphan drugs need to be put into perspective with the fact that a large number of orphan drugs do not undergo any NICE evaluation. Our study shows despite the fact that the NHS has put several mechanisms to grant access to orphan drugs in England, only approx. 60% of the orphan drugs authorised during the period of our study were accessible to patients in England.

Since October 2016, 8 CAPs were recommended for interim commissioning in NHS Wales, of these, 2 products were recommended in non-authorised indications.

We could not evaluate the access to the medicines included in our study via individual funding requests in England, Wales and Scotland which is an important limitation of our study. Therefore, we did not estimate the number of products not referred to NICE or not evaluated by the AWMSG or SMC which not routinely funded by the NHS in these countries but which are available under other funding mechanisms. For that reason, it is difficult to compare the access to the products across the three countries. However, our results suggest an important heterogeneity in access across England, Wales and Scotland.

Conclusions

Our study shows that a substantial number of products which received an EU authorisation between 2011 and 2016 were not evaluated by the HTA bodies in Great Britain. In most of these cases, we did not investigate whether these products were funded by the NHS in the devolved nations. In England and in Scotland, products used in oncology and OMPs were associated with a lower odds of receiving a positive HTA recommendation compared with non-oncology and products which did not receive an orphan designation in the EU. The median evaluation times for orphan medicines were longer than for the other products. We show that there is both variation across agencies and variation across therapeutic classes in terms of adoption decisions and access across the three countries.

Our study demonstrates that there is some important heterogeneity in the access in the NHS to new medicines authorised across the UK. This heterogeneity involves the number of products evaluated for routine funding in the NHS, the time to publication of the recommendations for baseline commissioning and, for given products, a heterogeneity of access across the devolved nations. The evaluations of oncology and orphan medicines (intended to treat rare, life-threatening or disabling conditions) are inconsistently prioritised. Therefore, our study suggests that one of the primary aims of the European centralised procedure – that of facilitating timely and consistent access to innovative medicines – was partially achieved in the UK.

1. BACKGROUND AND OBJECTIVES

Most of the appraisals conducted in the United Kingdom[2] by the National Institute for Health and Care Excellence (NICE), the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) involve innovative medicines which are authorised in the European Union (EU) via the centralised procedure[3] coordinated by the European Medicines Agency (EMA). The granting of a United Kingdom (UK) marketing authorisation is usually followed by a health technology appraisal (HTA) aimed at informing decisions as to whether or not these new products will be routinely funded for patient access in the NHS.

The primary objective of the study was to assess the access in the UK to new medicines recently authorised via the centralised procedure with a particularly focus on oncology and orphan medicines. We conducted an analysis (descriptive and statistical) of the outcomes of the HTA evaluations conducted in the UK by NICE, the AWMSG and the SMC for the centrally authorised products (CAPs) which recently received an authorisation (initial authorisation or an extension of indication) by the European Commission (EC) (via the EMA). We selected the authorisations granted over the past 6 year, i.e. between 1 January 2011 and 31 December 2016. This time period of 6-years covers appraisals conducted with the most recent appraisals methods (NICE, 2013). Generics, similar biological medicinal products, hybrids, informed consent applications, and vaccines are excluded from the analysis of HTA decisions.

The report is organised as follows. Section 2 describes the methods of the analysis and data collection. Section 3 presents the results for the distribution of CAPs and the HTA decisions made by the three HTA agencies. Section 4 presents the comparative analysis of decisions made by the three HTA agencies. Section 5 describes the distribution of products routinely funded in England even though they do not have a positive decision by NICE. Section 6 concludes with a summary.

2. METHODS AND DATA SOURCES

The analysis utilises the OHE Medicines Tracker. The medicines tracker is a relational database developed at the Office of Health Economics containing detailed information on: (1) the properties of the CAPs, (2) the EU marketing authorisation and (3) the HTA evaluations by NICE, SMC, and AWSMG. The database also includes the extensions of indications granted since 1 January 2011.

The Medicines Tracker includes information concerning the availability of medicinal products in England (specialised commissioning by NHS England or availability in the Cancer Drugs Fund).

The information relating to the CAPs was downloaded or obtained from the human medicines section of the EMA website (http://www.ema.europa.eu/).

The products which have received a commission decision for an initial marketing authorisation or for an extension of indication have been identified in the Committee for

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[2] There is no health technology appraisal in Northern Ireland which implements the NICE recommendations.

[3] The centralised procedure is the EU procedure of authorisation of medicinal products described in Regulation (EC) No 726/2004, as amended.

Human Medicinal Products (CHMP) highlights published by the EMA. We obtained the date of the commission decision (the date of the marketing authorisation in the European Public Assessment Report (EPAR) and the Procedural steps taken and scientific information after authorisation). In that respect, the information collected from the EPAR includes the dates of the CHMP opinion, EC decision and orphan designation, when applicable[4].

The time period considered in this study covers CAPs authorised between 1 January 2011 and 31 December 2016 (initial or extension of indication) and HTA decisions on these CAPs, ongoing and completed until the end of April 2017. This includes the stand-alone marketing authorisation applications, the generics, hybrid, informed consent and applications for similar biological medicinal products. Similarly to the application type presented in analyses conducted by the EMA on the newly authorised products (EMA, 2016), we conducted separate analyses on the products containing a new active substance (in opposition to medicines which contain copies of existing products which are usually authorised under the generic, informed consent, hybrid or similar biological medicinal products legal bases). In the report, the analyses conducted on two different sets of products are respectively referred to as covering "all products" or only "new active substances". We have subsequently conducted our analyses on the CAPs undergoing HTA evaluations on the medicines containing new active substances.

We also undertook analyses using the WHO Anatomical Therapeutic Chemical (ATC) classification of medicines[5]; The ATC L category is very heterogeneous from a clinical point of view. Therefore for the purpose of our analysis, we separated the products belonging to the ATC L category (antineoplastics and immunomodulators) into two sub-categories: we manually selected the medicines used in oncology indications from the immune-modulatory products used in other non-oncology conditions (we performed this selection on the basis of the initial authorised indication). Therefore, the products under the category "oncology" refer to the products classified under the level L of the ATC classification used specifically in oncology indications. The products classified by us as products used in immune disorders include the other non-oncology products classified under the ATC L category. These products are labelled as "immunomodulating agents". Orphan designation is also considered and a separate analysis is presented for OMPs.

With respect to the EC authorisation process, we conducted a descriptive analysis of CAPs whose applications received positive opinions by the CHMP for two subsets of products: (1) Applications for initial evaluations (initial authorisations), or (2) Applications for extension of therapeutic indication (extension of indication).

With respect to the HTA evaluation, medicinal products such as generics or hybrids are usually not evaluated by HTA bodies and are therefore not evaluated by HTA agencies. Therefore, we restricted the analysis of HTA evaluations to authorisations granted to the

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[4] The information collected on the CAPs includes: the invented name of the product, the international non-proprietary name (INN), the name of the substance (salt, ester, etc.), the name of the marketing authorisation holder, the EMA product reference number and the information concerning an orphan designation, biosimilar or generic status, marketing authorisation under conditional or exceptional circumstances, and WHO ATC classification code level 5. The therapeutic indication includes information indicating whether the authorisation was granted for an initial or in a variation application for an extension of indication and the date of the EC decision (date of the authorisation).

[5] The WHO ATC 2017 classification is available on the WHO collaborating centre for drug statistics methodology at the following URL: https://www.whocc.no/atc_ddd_index/

medicines containing a new active substance. Vaccines, generics, informed consent, biosimilar and hybrid applications were excluded from the analyses.[6] The HTA information was collected from the websites from the three HTA agencies (AWMSG, NICE and SMC).[7,8]

The first three headline decision outcomes are common to the three HTA agencies. However, the three HTA bodies handle the absence of evidence submission by manufacturers in a very different way. In the absence of evidence submission, SMC does "not recommended" the use of the technology in Scotland. In contrast, NICE and AWMSG will generally terminate the appraisal and issue a recommendation stating that they were "unable to recommend" the technology. This difference was reflected in our data entry and therefore in our analyses.

We classified the decision outcomes as follows: "Recommended" when the product was recommended in accordance with the indication included in the marketing authorisation; "Optimised" when the recommended use of the product was restricted compared with the marketing authorisation (e.g. subpopulation of patients, stopping rules, etc.); "Not recommended" when the technology was not recommended for baseline commissioning in the NHS; "Other" describes instances where NICE and AWMSG were "unable to recommend" the funding of the technology since the manufacturer did not submit any evidence, these appraisals were terminated by NICE. Lastly, this group includes a possible outcome of NICE decisions labelled as "recommended in research". Given the AWMSG recommendations are superseded by NICE recommendations when NICE issues a recommendation on the same technology, we focused on the decisions made by AWMSG not subsequently replaced by any NICE guidance.

We analysed the time which elapsed between the granting of the marketing authorisation by the EC and the recommendations issued by the 3 HTA bodies using a time to event analysis. We have produced Kaplan-Meier curves which compare the times from the authorisation to the publication of the final HTA recommendation for different classes or types of medicines (e.g. cancer vs non-cancer medicines or orphan vs non-orphan medicines) (Collett, 2014). In order to minimise any underestimate the access to medicines across the devolved nations (England, Wales and Scotland), the time period of HTA evaluations covers until the end April 2017.[9] For scheduled HTA evaluations with a forthcoming publication date known or unknown, we have considered that the appraisal was "ongoing". We have right-censored the ongoing appraisals with the date of conduct of our analysis (23 May 2017), as it is usually performed in this type of analysis (Collett, 2014).

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[6] Vaccines are excluded as they are reviewed by the Joint Committee for Vaccination and Immunisation (JCVI).

[7] All Wales Medicines Strategy Group http://www.awmsg.org/, NICE (National Institute for Health and Care Excellence) https://www.nice.org.uk/ and Scottish Medicines Consortium. https://www.scottishmedicines.org.uk/ [Accessed on 30 April 2017].

[8] The information collected include: the HTA decision date (date of publication of the final recommendation for NICE and SMC and date of Ministerial ratification for AWMSG); Programme type for NICE guidance: Technology Appraisal (TA) or Highly Specialised Technologies (HST). All HTA evaluations of SMC and AWMSG are TAs; HTA reference number (resubmissions of a new evidence dossier for CAPs previously evaluated by SMC maintain the same HTA reference number) and the HTA recommendation.

[9] Effectively the latest dates in which appraisals were published by the three HTA were 26th April 2017 for NICE, 8th May 2017 for SMC, and 3rd April for AWMSG.

The results are presented for each of the three HTA agencies, including a descriptive analysis of the distribution of HTA evaluations by ATC classification and by outcome. The descriptive analysis also considers HTA decisions for anticancer products and OMPs. A further statistical analysis provides insight on the time elapsed between EU marketing authorisations and the publication of HTA recommendations.

More detailed analyses compare HTA decisions among the three HTA agencies. These analyses include an estimation of the agreement among NICE and SMC regarding headline decision outcomes, and estimation of the odds ratios of receiving a positive decision outcome associated to two characteristics of the CAP: orphan designation and anticancer for the three HTA agencies. In line with the recommendations published by the HTA bodies, non-submissions were excluded in the logistic regressions as "unable to recommend" outcomes for NICE and AWMSG, these appraisals were included in the appraisal outcomes for the SMC as they are classified as negative decisions by the consortium. We have estimated the odds ratios using two different approaches. We directly computed the unadjusted odds ratios and we also fitted a logistic regression model using the HTA, orphan and oncology status as explanatory variables. We have first fitted a full saturated model including all these variables and the interaction terms and we subsequently removed the non-significant explanatory variables from the initial model to obtain the final parameters estimates. The AWMSG was used as a reference in our model. We considered the OR to be significantly different from 1 when the upper bound of the 95% CI was below 1 (or the lower bound above it). The OR were computed by taking the exponential of the coefficient estimates of the logistic regressions (for more detailed explanation on the interpretation of the parameters of the model and the derivation of the OR see Agresti, 2013).

3. RESULTS

3.1. Central marketing authorisations

During the six year period from 1 January 2011 to 31 December 2016, a total of 713 new authorisations were granted by the EC for CAPs. The EC has granted 512 new authorisations (initial or extension) for the medicines containing a new active substance. Of the remaining 201 authorisations, 173 applications were for generics, hybrid or similar biological, and informed consent applications and 28 applications were for vaccines.

Table 1 and Figure 1 show the distribution of each type of authorisation or specific types of products (OMPs and anticancer) granted by the EC by year for all the CAPs (i.e. 713 authorisations). The breakdown of the number of authorisations for new substances is presented according to the authorisation type (initial authorisation or extension of indication). For authorisations of medicines based on copies of previously authorised new substances and vaccines, the breakdown is presented by type of legal basis. The table and figure also provide an annual breakdown of the 117 authorisations granted to OMPs; of these 114 are new active substances.

Table 1. Number of authorisations per category and year (all medicines)

Year	Vaccines and copies of existing substances				New active substances		Total
	Generics	Biosimilars	Other legal status	Vaccines	Initial Authorisa-tions	Extensions of indications	
2011	23	1	4	3	41	28	100
2012	22	0	14	6	33	34	109
2013	15	4	7	11	46	38	121
2014	6	3	13	2	50	33	107
2015	22	0	7	2	62	49	142
2016	19	3	13	4	45	53	137
Total	107	11	55	28	277	235	713

On average, 119 authorisations (initial and extensions of indications) were granted every year for all types of products and 85 for the products containing a new active substance. The year with the largest number of new authorisations was 2015 with 142 authorisations (all products) and 111 authorisations (new active substances).

Figure 1. Number of authorisations (initial and extensions) granted per year between 2011 and 2016 according to the type of product and according to the legal basis
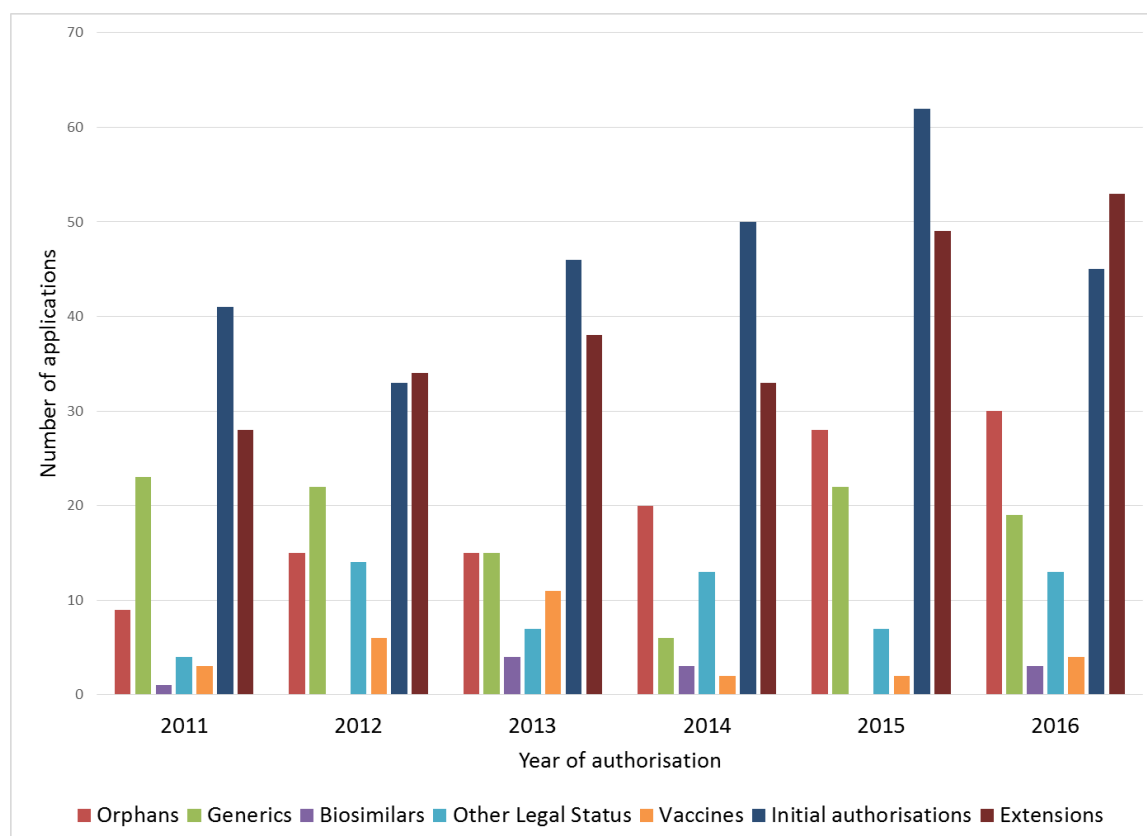
Figures 2 to 7 display the distribution of the authorisations according to the ATC of all the products (new active substances and copies of existing products). Products of the ATC L class are presented separately as oncology and immunomodulating agents. Figure 2 displays the distribution of the authorisations granted to all medicines. Figure 3

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provides the ATC distribution of the 448 initial authorisations for all medicines. Figure 4 shows the ATC distribution for 265 extensions of indications.

Figure 2. ATC class of the products which were granted an authorisation (initial and extensions, all products), between 2011-2016 (n=713) (products of the ATC L class are presented separately as oncology and immunomodulating agents)
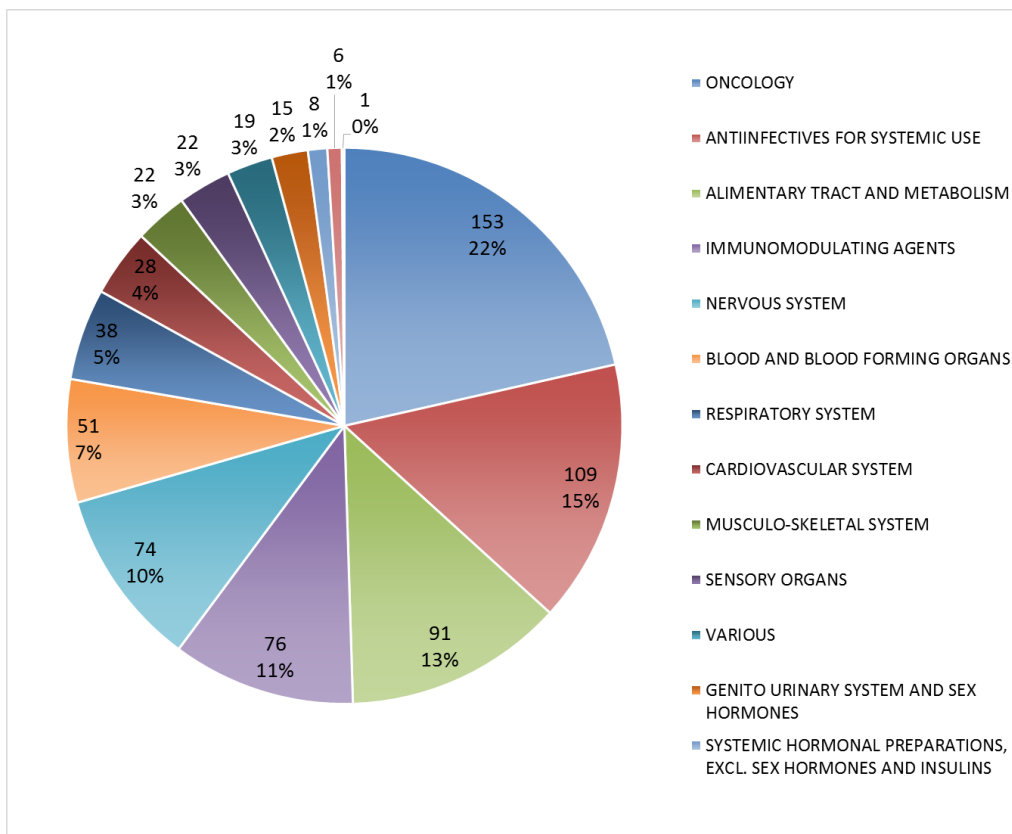
A quarter of new authorisations refer to products used in oncology. In total, 153 authorisations were granted to products indicated in oncology including 90 initial authorisations (Figures 2 and 3). Anti-infectives for systemic use, and alimentary tract and metabolism products are the next two most frequent therapeutic classes represented in all authorisations (Figure 2). Products used in conditions affecting the nervous system is the second class of products represented in the initial marketing authorisations (Figure 3). Our analysis shows that the granting of extensions of indications varies according to the therapeutic class of products (Figure 4). Whereas, products used in oncology have their indications frequently extended to other types of cancers, this happens less frequently for products used in other therapeutic areas (e.g. products used in neurology). Products used in respiratory disorders are often included in generic applications.

Figure 3. ATC class of the products which received an initial marketing authorisation (all products), 2011-2016 (n=448)
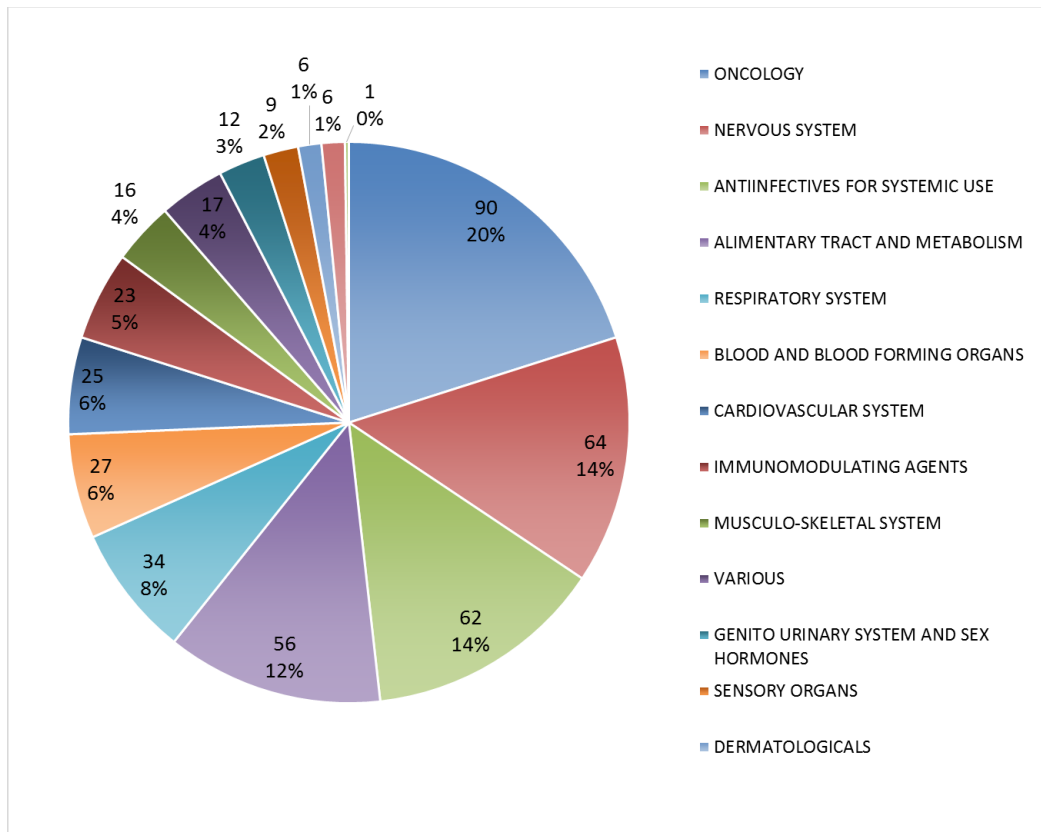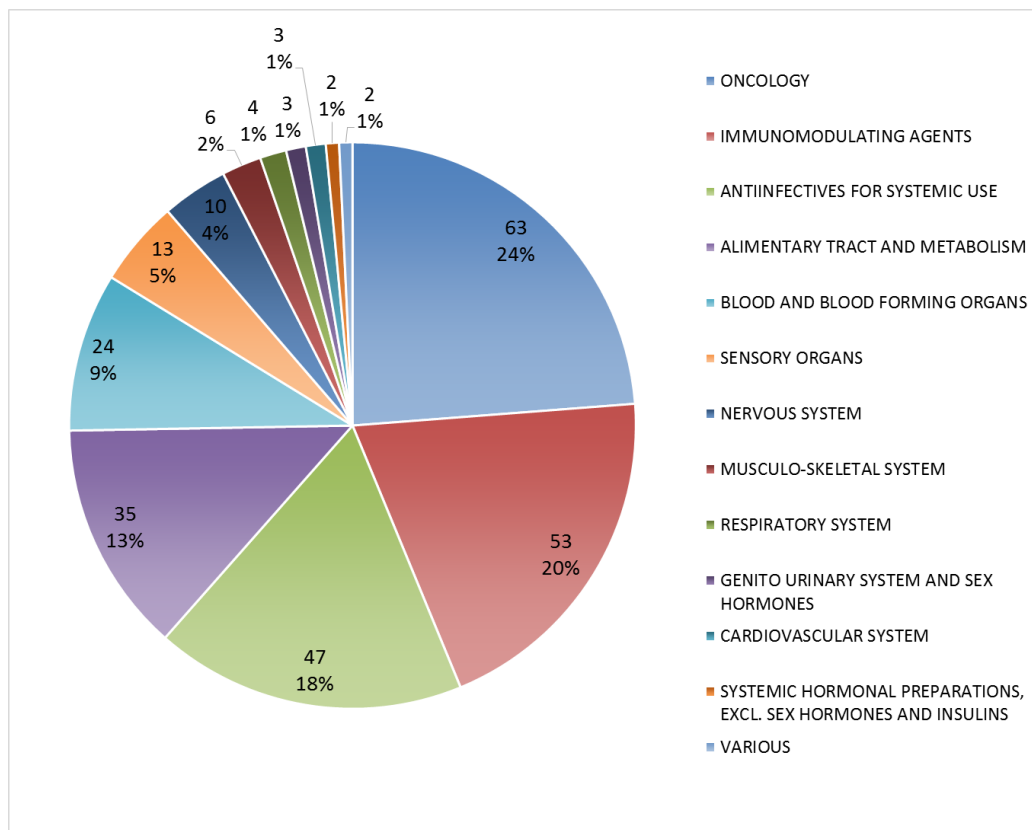

Pie chart values:
- ONCOLOGY: 90, 20%
- NERVOUS SYSTEM: 64, 14%
- ANTIINFECTIVES FOR SYSTEMIC USE: 62, 14%
- ALIMENTARY TRACT AND METABOLISM: 56, 12%
- RESPIRATORY SYSTEM: 34, 8%
- BLOOD AND BLOOD FORMING ORGANS: 27, 6%
- CARDIOVASCULAR SYSTEM: 25, 6%
- IMMUNOMODULATING AGENTS: 23, 5%
- MUSCULO-SKELETAL SYSTEM: 16, 4%
- VARIOUS: 17, 4%
- GENITO URINARY SYSTEM AND SEX HORMONES: 12, 3%
- SENSORY ORGANS: 9, 2%
- DERMATOLOGICALS: 6, 1%
- 6, 1%
- 1, 0%

Figure 4. ATC class of the products which received an extension of indication (all products), 2011-2016 (n=265)

Pie chart values:
- ONCOLOGY: 63, 24%
- IMMUNOMODULATING AGENTS: 53, 20%
- ANTIINFECTIVES FOR SYSTEMIC USE: 47, 18%
- ALIMENTARY TRACT AND METABOLISM: 35, 13%
- BLOOD AND BLOOD FORMING ORGANS: 24, 9%
- SENSORY ORGANS: 13, 5%
- NERVOUS SYSTEM: 10, 4%
- MUSCULO-SKELETAL SYSTEM: 6, 2%
- RESPIRATORY SYSTEM: 4, 1%
- GENITO URINARY SYSTEM AND SEX HORMONES: 3, 1%
- CARDIOVASCULAR SYSTEM: 3, 1%
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS: 2, 1%
- VARIOUS: 2, 1%

The EC has granted 512 new authorisations (initial or extension) for the medicines containing a new active substance. The 512 initial and extensions of indications were granted to 376 different medicinal products. Just under half of the 512 authorisations were for extensions of indications (46%), and the number of extensions per year has been steadily increasing since 2011. In 2016, the number of extensions was greater than the number of initial marketing authorisations (53 vs 45). We focused our analysis of the HTA decisions on these 512 authorisations.

Figures 5 and 6 display the distribution of the 512 products containing a new active substance according to their ATC class for the initial authorisations (277) (Figure 5) and the extensions of indications (235) (Figure 6). Lastly, Figure 7 presents the distribution of ATC class for the 114 OMPs (excluding 2 hybrid applications and 1 vaccine).

Most anticancer products authorised via the centralised procedure over the period of the study were products which contained a new active substance. 126 authorisations were granted to medicines containing a new active substance including 63 initial authorisations and 63 extensions of indications (see Table 2, Figures 5 and 6). It is noteworthy that all 63 extensions of indications for oncology products are for new active substances and accounted for nearly a quarter of the extensions of indications (Figure 4).The rest of the oncology products shown in Figure 2 correspond to 25 generics and 2 products authorised under another legal basis (e.g. informed consent). The annual number of authorisations for anticancer products has more than doubled from 13 authorisations in 2001 to 38 in 2016, with more rapid increase in authorisations for extensions of indications (see Table 2). This increase is probably explained by the implementation of the Regulation (EC) No 141/2000 on orphan medicinal products in 2000 and by the extension of the mandatory scope in 2004 in Regulation (EC) No 726/2004 by which all marketing authorisations for orphan medicines and products used in oncology in the EU should be authorised according to the centralised procedure. As a result of these legal changes and the creation of incentives for the development of orphan drugs, there is a large overlap between the oncology and orphan medicines. 37% of anticancer products received an orphan designation. Similarly, out of 114 OMPs, 47 products were indicated in oncology, representing 41% of the orphan drugs.

The annual number of authorisations for OMPs has increased threefold over the period covered by the study, 9 authorisations were granted to OMPs in 2011 and 29 in 2016. Most of the increase is explained by the increase of authorisations granted in 2012, 2014, and 2015, while there was a decrease in the number of authorisations to OMPs granted in 2013 (see Table 2).

Table 2. Number of authorisations granted to anticancer and orphan medicines between 2011 and2016 (the figures refer to the products containing a new active substance)

Year	Oncology products				Orphan medicinal products		
	Initial authori-sations	Extension of indication	Total	Of which are OMPs	Initial authorisations	Extension of indication	Total
2011	7	6	13	2	5	4	9
2012	9	6	15	6	11	4	15
2013	11	9	20	6	6	7	13
2014	9	7	16	9	14	6	20
2015	12	12	24	9	20	8	28
2016	15	23	38	15	14	15	29
Total	63	63	126	47	70	44	114

Figure 5. ATC class of the products containing a new active substance which received an initial marketing authorisation, 2011-2016 (n=277)
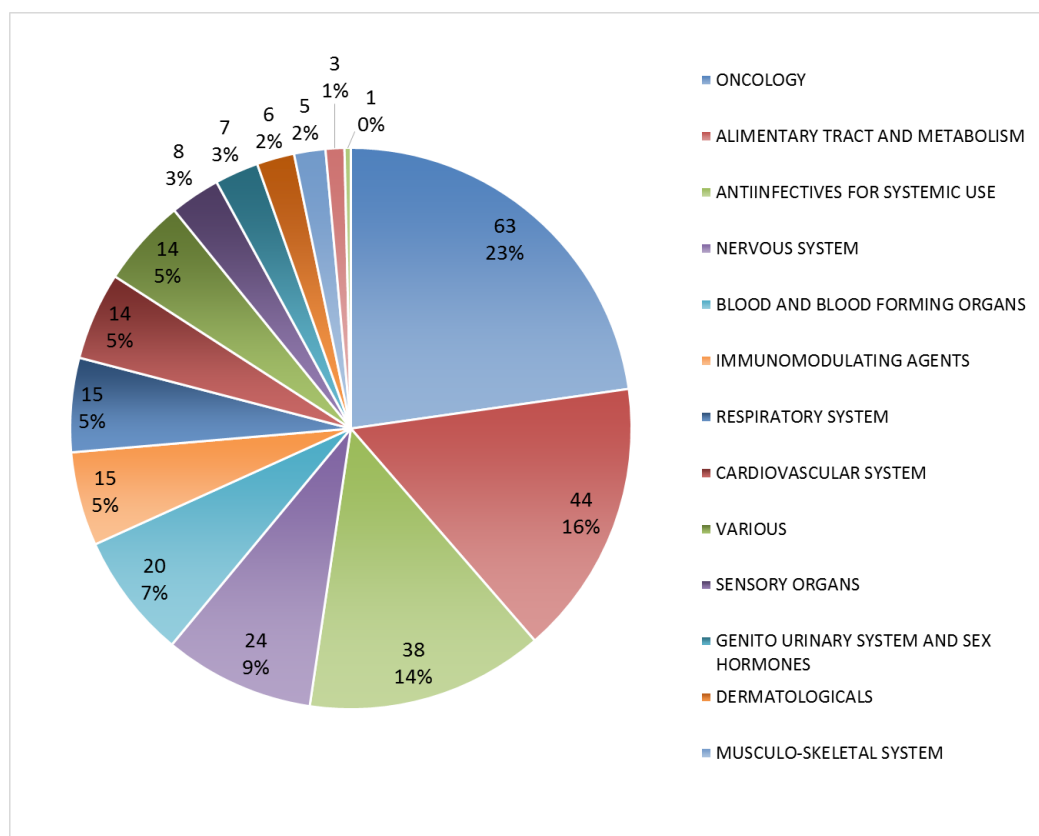
Figure 6. ATC class of the products containing a new active substance which were granted an extension of indication, 2011-2016 (n=235)
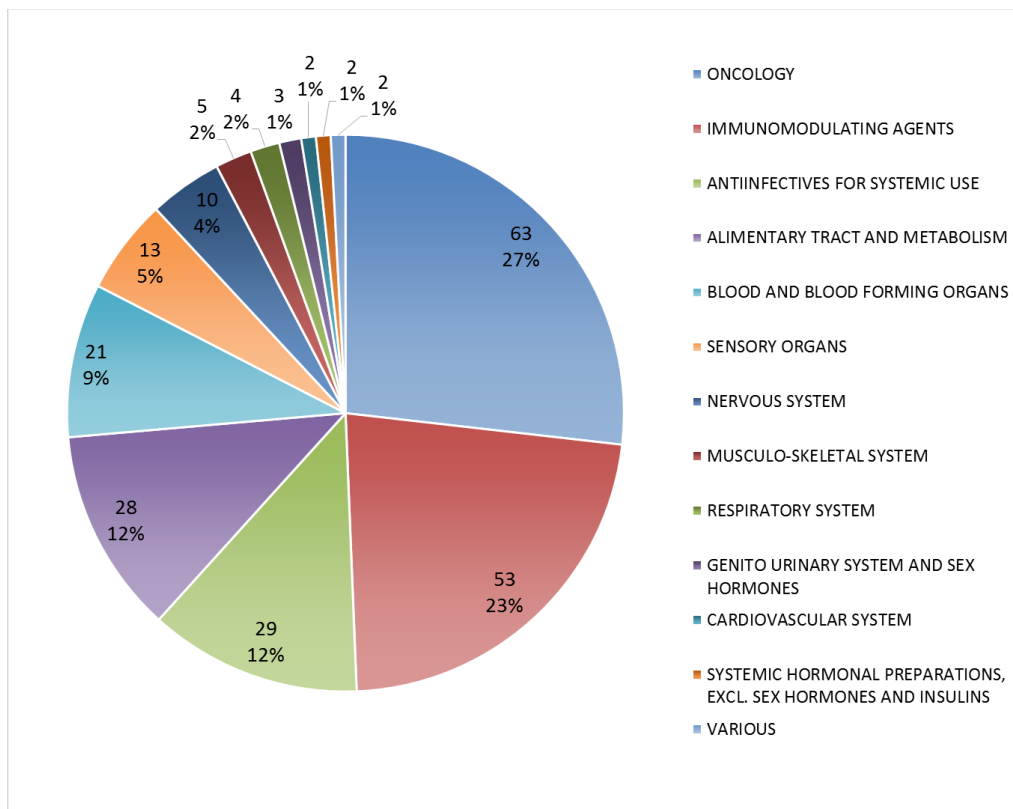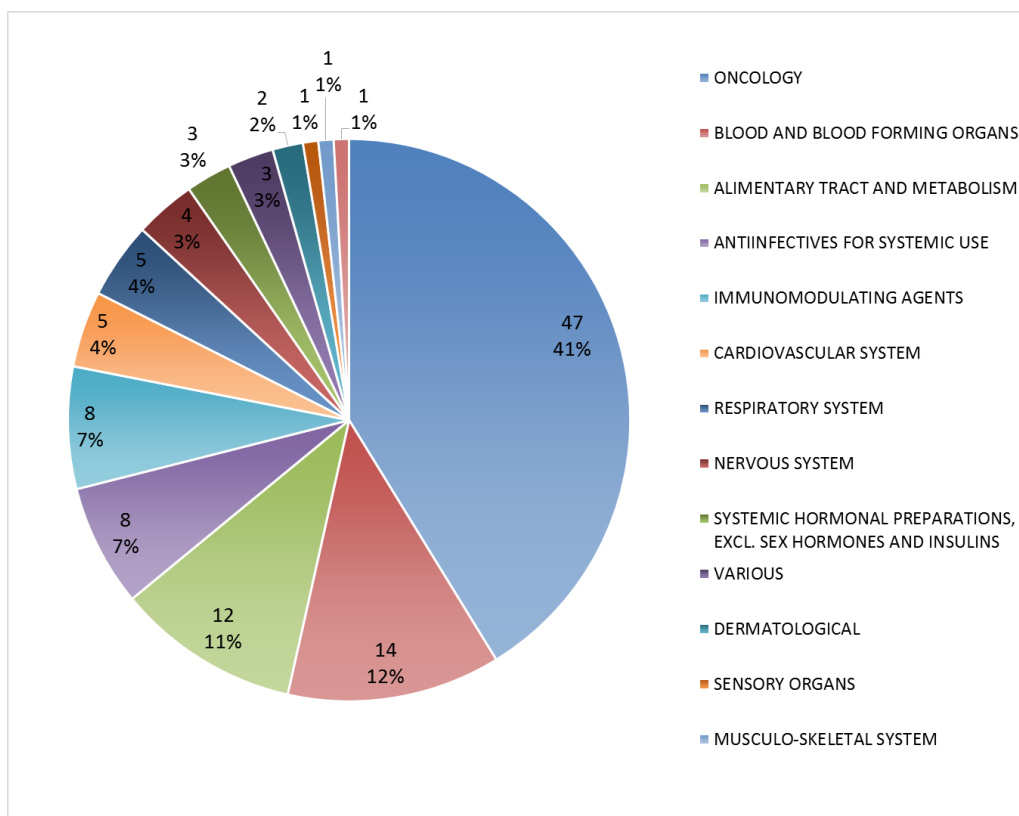

Legend:
- ONCOLOGY
- IMMUNOMODULATING AGENTS
- ANTIINFECTIVES FOR SYSTEMIC USE
- ALIMENTARY TRACT AND METABOLISM
- BLOOD AND BLOOD FORMING ORGANS
- SENSORY ORGANS
- NERVOUS SYSTEM
- MUSCULO-SKELETAL SYSTEM
- RESPIRATORY SYSTEM
- GENITO URINARY SYSTEM AND SEX HORMONES
- CARDIOVASCULAR SYSTEM
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS
- VARIOUS

Figure 7. ATC class of the authorisations (initial and extensions) granted to orphan medicines (products containing a new active substance), 2011-2016 (n=114)

Legend:
- ONCOLOGY
- BLOOD AND BLOOD FORMING ORGANS
- ALIMENTARY TRACT AND METABOLISM
- ANTIINFECTIVES FOR SYSTEMIC USE
- IMMUNOMODULATING AGENTS
- CARDIOVASCULAR SYSTEM
- RESPIRATORY SYSTEM
- NERVOUS SYSTEM
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS
- VARIOUS
- DERMATOLOGICAL
- SENSORY ORGANS
- MUSCULO-SKELETAL SYSTEM

The distribution of OMPs by ATC class as presented in Figure 7 includes all new active substances (70 initial authorisations and 44 extensions of indications). Oncology products also accounted for 41% of the authorisations granted to OMPs, with 22 out of 47 authorisations for extensions of indications. In the case of OMPs, products used in conditions affecting the blood and blood forming organs received more authorisations than medicines used in alimentary tract and metabolism and infectious disorders.

3.2. NICE evaluations

3.2.1. Descriptive analysis of Technology Appraisals

The newly authorised medicines are not systematically referred to NICE by the Department of Health (DH). The DH usually refers the new technologies according to criteria including consideration of the population size, disease severity, resource impact and the value that NICE could add in carrying out a technology appraisal.[10] The application of these selection criteria has resulted in NICE evaluating 42% (216) of the 512 indications (which involved a product containing a new active substance) authorised between 1 January 2011 and 31 December 2016.

NICE has conducted 251 evaluations on the products included in our analysis[11]. These 251 evaluations (TAs and HST) involve 218 of the products which received an authorisation during the period of the study, therefore 43% of the 512 products containing a new active substance were referred to NICE by the Department of Health. 206 evaluations (202 TAs and 4 HSTs) were completed and 45 are still ongoing. 242 evaluations were conducted under a TA and 9 evaluations under the HST programme.[12] 88 out the 126 products used in oncology (70%) and 52 of the 114 OMPs (46%) were referred to NICE by the Department of Health. Medicines which have received an orphan designation in the EU were not systematically evaluated via the NICE HST programme. In fact, the majority of orphan products appraised by NICE have been appraised under the TA programme.

41% of NICE appraisals involved medicines used in oncology (Figure 8). In comparison, results shown in Figures 5 and 6 show that oncology products are proportionately more often referred to NICE than the products of the other classes. In addition, since 126 CAPs were anti-cancer medicines, NICE evaluated approximately 81% of the CAPs indicated in oncology. NICE evaluated 15 out of 21 (71%) of the CAPs used for conditions affecting the sensory organs, including 5 TAs for aflibercept (Eylea) and 4 TAs for ranibizumab (Lucentis). For the other ATC classes NICE evaluations covered fewer CAPs: 36% of blood and blood forming organs, 27% for alimentary tract and metabolism, 22% of anti-infectives for systemic use. NICE did not evaluate any of the 5

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[10] NICE (2014). Guide to the processes of technology appraisal. Process and methods. nice.org.uk/process/pmg19

[11] NICE does not systematically conduct one appraisal for each indication (some indications can be subject of different evaluations), therefore, the number of appraisals conducted by NICE does not exactly match the number of authorisations granted by the European Commission. In addition, some NICE appraisals can involve more than 1 product. This explains the apparent differences present in the results of our study.

[12] Highly specialised technologies (HST) is a type of NICE guidance established in April 2013 to assess orphan drugs which fulfil some criteria (including a prevalence of the disease lower than 1:50 000 – this is a unique definition used in the UK only). The Interim Process and Methods of the HST Programme has been updated to reflect 2017 changes.

products included in systemic hormonal preparations or any of the anti-parasitic medicines.

Figure 8. ATC class of the centrally authorised products containing a new active substance which underwent a NICE evaluation, 2011-2016
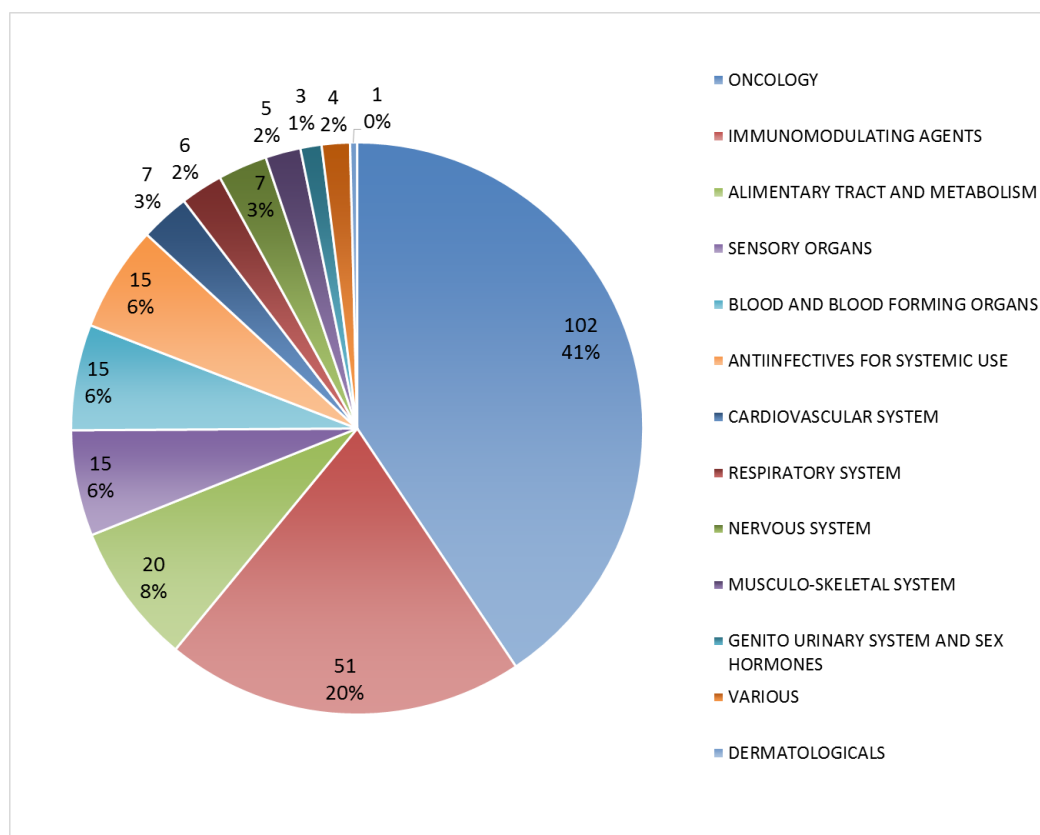
NICE finalised 206 evaluations (202 TA and 4 HST) during the period covered by our study. The distribution of the recommendations outcomes of all products referred to NICE is shown in Figure 9 (1 product was recommended in research[13]). If we take into consideration the products for which manufacturers did not submit any evidence to NICE (22 appraisals), our analyses show that NICE has recommended the use of 154 medicines referred to them (76% of cases). NICE recommended 86% of the medicines referred to the institute where a manufacturer evidence submission was received (180 TA and 4 HST).

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[13] This decision outcome was issued for roflumilast which was recommended in 2012 only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease (COPD).

Figure 9. Outcomes of NICE technology appraisals conducted on centrally authorised products, 2011-2016 (n = 202)
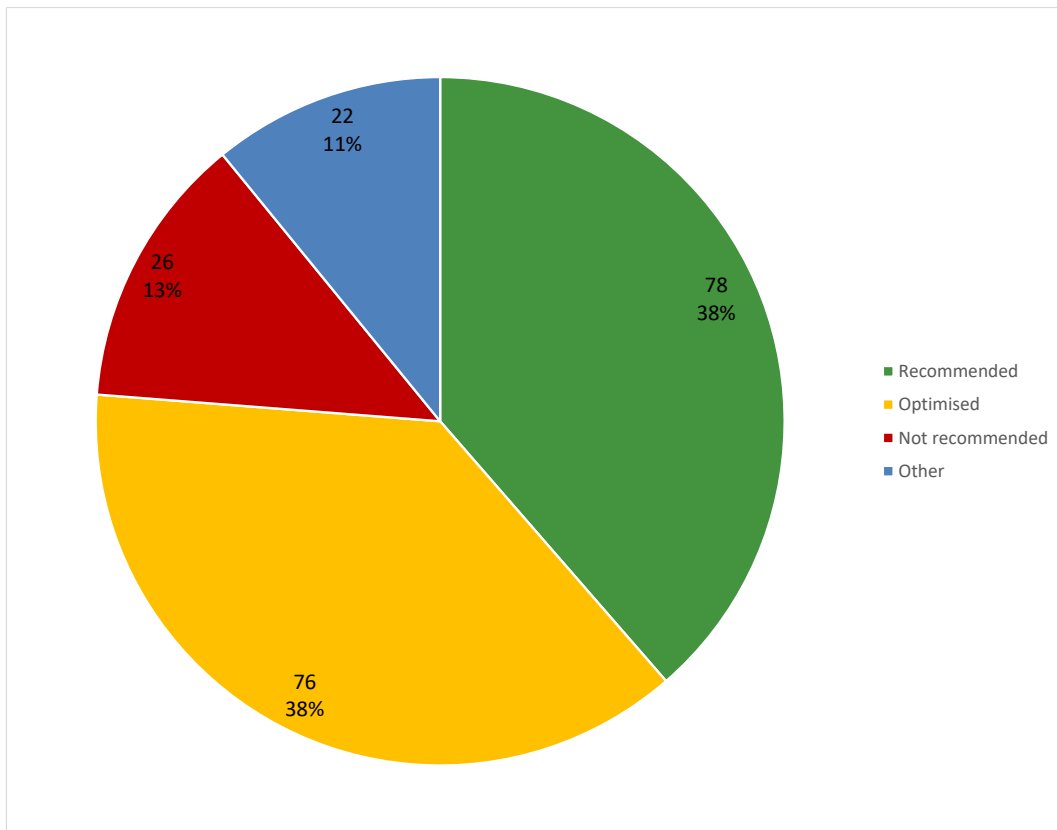
The trend in headline decision outcomes can be seen in Figure 10 which compares decision outcomes by year, including those published between January and April 2017. Firstly, Figure 10 shows the rapid increase in the number of NICE annual evaluations from just 7 TAs in 2011 to 55 TAs in 2015, including 7 products that NICE was "unable to recommend" due to the absence of an evidence submission by the manufacturer. The same number (55) of TAs were completed in 2016, however, without considering the appraisals for which no evidence was submitted by the manufacturer, the number of TAs increased from 48 in 2015 to 54 in 2016. In 2013, NICE did not recommend the routine funding in almost a third of completed appraisals. The proportion of positive decisions has increased since then. Over the last three years of our study (2014-2016), around 14% of medicines subject of NICE appraisals were not recommended.

Figure 10. Outcomes of the NICE technology appraisals conducted on centrally authorised products per year
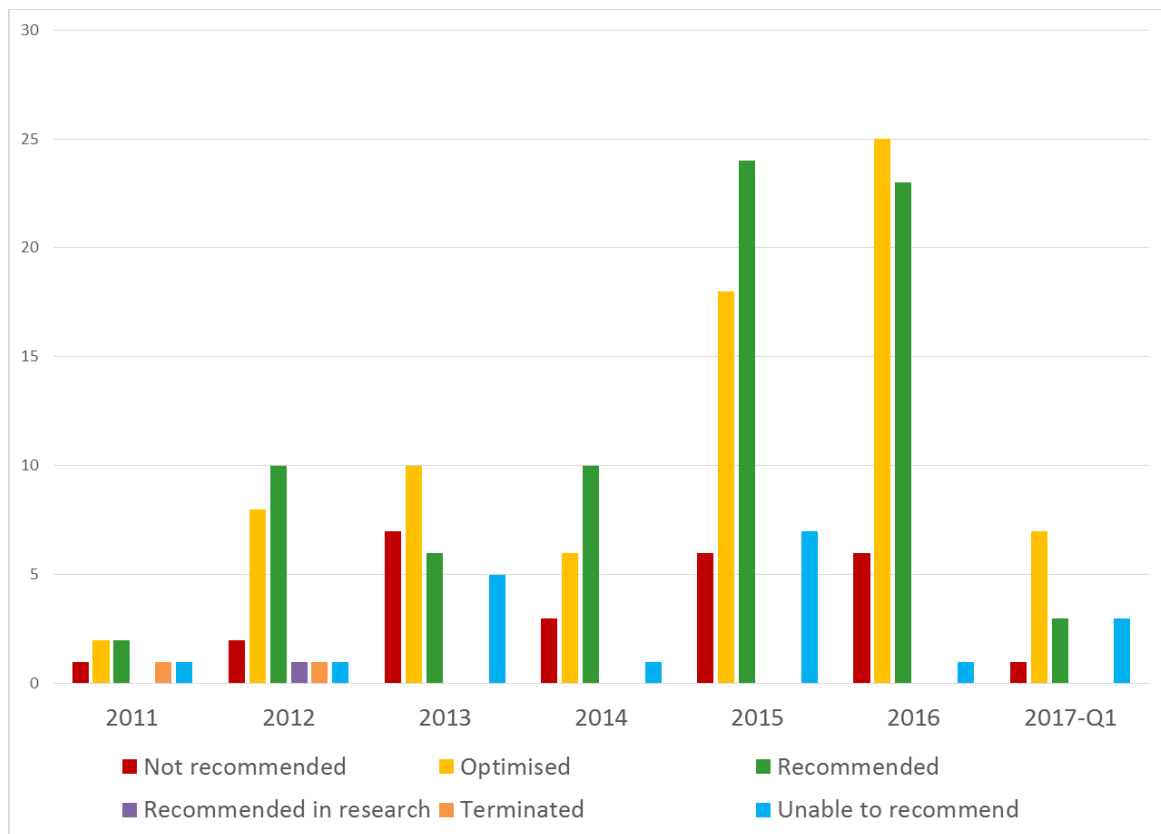
We analysed the outcomes of the NICE decisions published for oncology products (some of these products have a special funding status in the NHS via the Cancer Drugs Fund). As shown in Figure 8, NICE conducted 102 appraisals on anticancer products; of these 24 are ongoing. Figure 11 shows the distribution of recommendations for the 78 completed TAs. The proportion of positive decisions for anticancer products is 64%, increasing up to 74% when considering the appraisals for which the companies submitted evidence for the appraisals. The rate of positive recommendations for oncology products is lower than for the products used in other, non-oncology indications.

Figure 11. Outcomes of NICE technology appraisals conducted on anticancer medicines (n = 78), 2011-2016
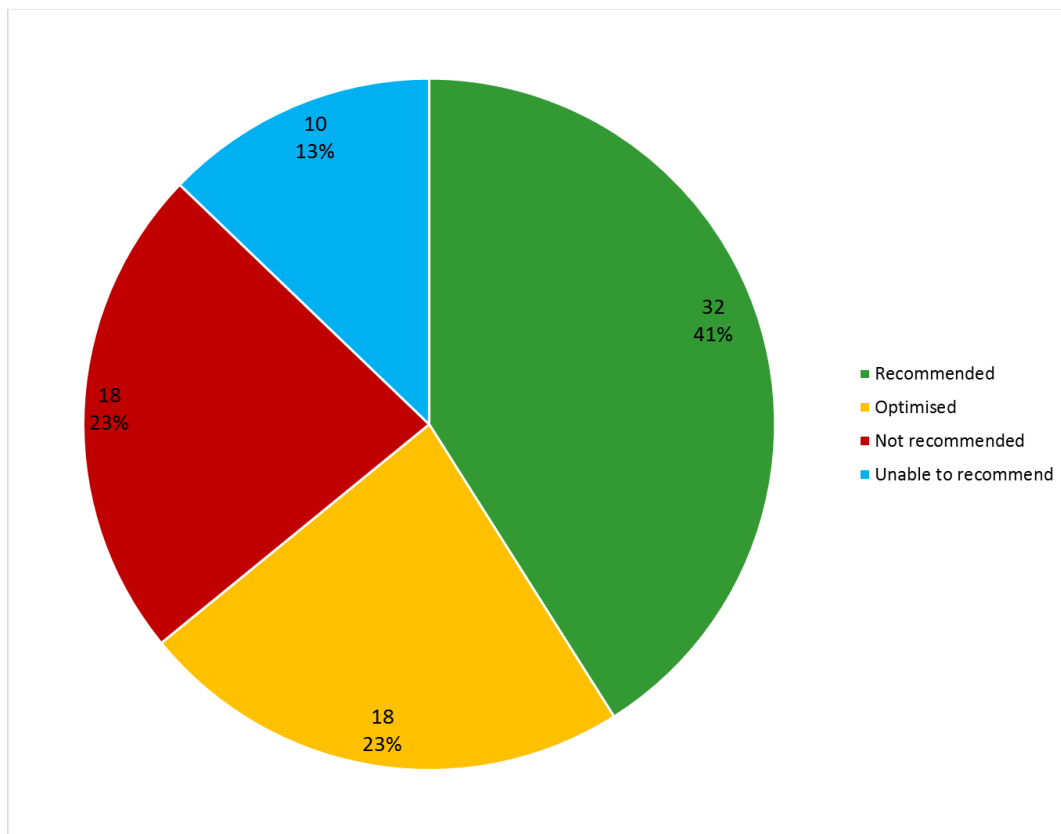

Figure 12 presents the distribution of recommendations for 31 completed TAs involving an OMP (note HST appraisals are not included in this analysis). The proportion of guidance containing a positive recommendation is lower for OMPs compared to the entire set of products (52% vs 76% Figure 9); positive recommendations were granted to approximately half of OMPs. This proportion increases to 64% if we exclude 6 TAs for which no evidence was submitted by the marketing authorisation holder (for which NICE was "unable to recommend" the technology). The number of appraisals involving OMPs conducted every year by NICE is generally low (Figure 13). No TAs for OMPs were published in 2011. Only 1 TA for OMPs was conducted in 2012 while NICE conducted 10 TAs for OMPs in 2016. 6 of the 10 OMPs appraised in 2016 received a positive recommendation ("recommended" or "optimised"). 19 TAs involving OMPs are currently ongoing.

Figure 12. Outcomes of NICE technology appraisals conducted on orphan medicines (n = 31), 2011-2016
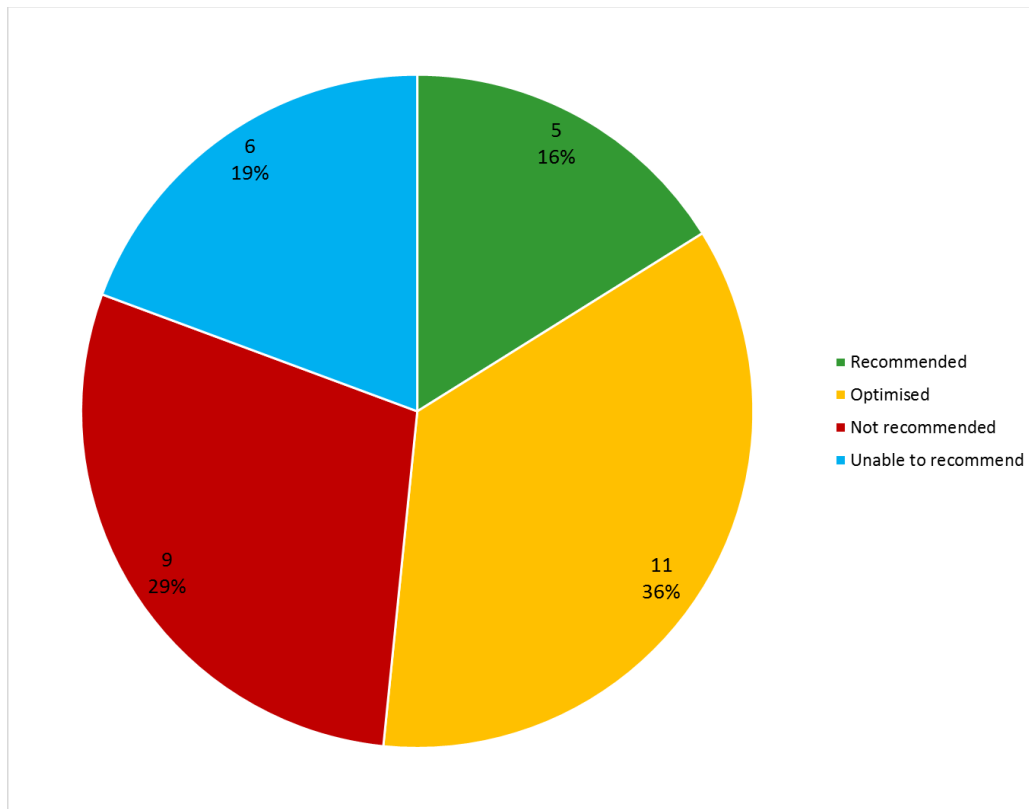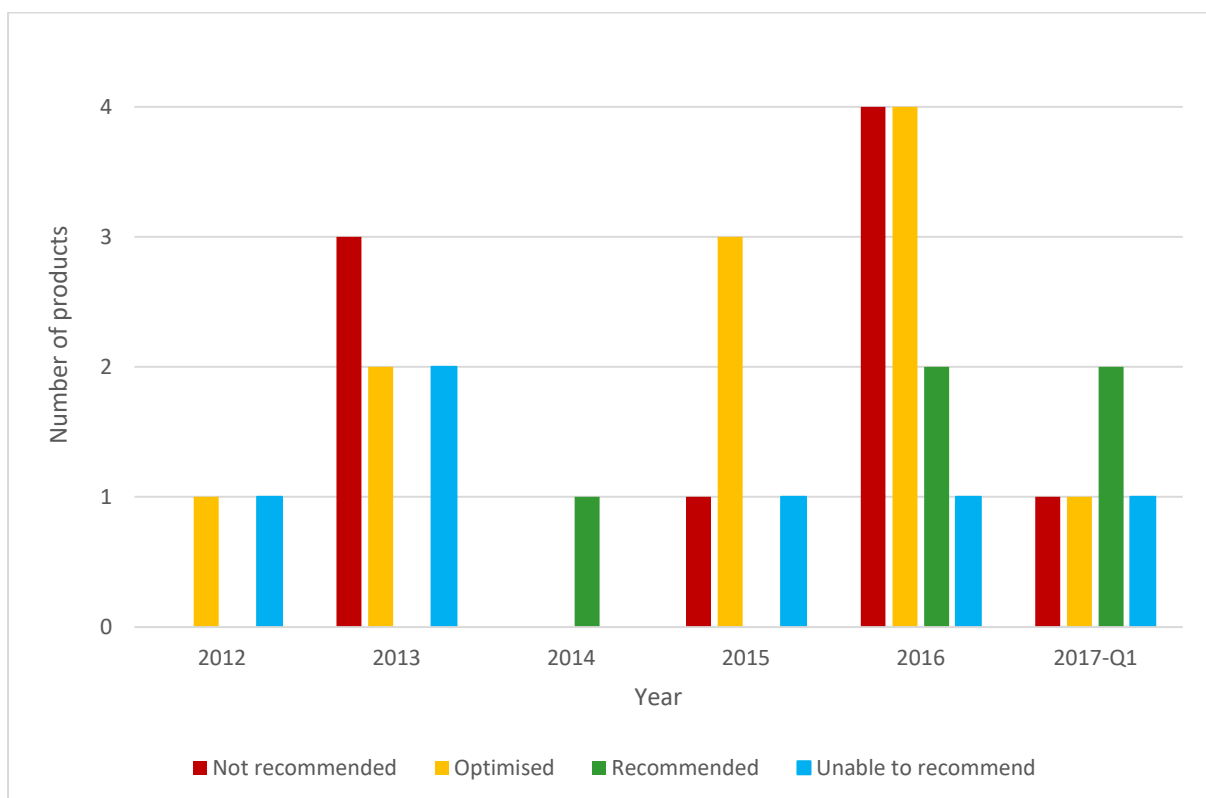

Figure 13. Outcomes of the NICE technology appraisals conducted on orphan medicines per year, 2011-2016

As mentioned earlier, NICE also evaluates orphan medicines which fulfil a certain set of criteria via its HST programme (NICE, 2017). Since 2011, NICE completed 4 HST evaluations. These evaluations were:

- Eculizumab for treating atypical haemolytic uraemic syndrome (HST1). Eculizumab, has been recommended for use in the NHS within its marketing authorisation on 28 January 2015. The funding in the NHS requires a national protocol for starting and stopping treatment, and implementation arrangements for monitoring and research (the routine funding of this product has therefore been "optimised" by NICE).
- Elosulfase alfa for treating mucopolysaccharidosis type IVa (HST2). Elosulfase alfa has been recommended for use in the NHS by NICE on 16 December 2015.
- Ataluren for Duchenne muscular dystrophy (nonsense mutation) (HST3). Ataluren has been recommended for use in the NHS within its marketing authorisation on 20 July 2016.
- Migalastat for Fabry disease (HST4). Migalastat has been recommended for use within its marketing authorisation on 22 February 2017.

In addition, there are 5 ongoing HST evaluations:

- Eliglustat for the long-term treatment of adult patients with Gaucher disease type 1.
- Afamelanotide for the prevention of phototoxicity in adult patients with erythropoietic protoporphyria.
- Sebelipase alfa for long-term enzyme replacement therapy in patients of all ages with lysosomal acid lipase deficiency.
- Asfotase alfa for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia.
- Alipogene tiparvovec for adult patients diagnosed with familial lipoprotein lipase deficiency. Note that on 20 April 2017 UniQure announced that it will not pursue the European marketing renewal for Glybera which is due to expire in October 2017, therefore the HST evaluation is likely to be terminated.

3.2.2. Statistical analysis of type and duration of NICE appraisals

We have computed the unadjusted odds ratio (OR) of a NICE positive recommendation for oncology and orphan products compared to the other products. For the purpose of this analysis, we have grouped "recommended" and "optimised" recommendations under the positive recommendations in the contingency tables used to compute the crude ORs. Table 2 presents the contingency tables built to compute the OR of a NICE positive recommendation (completed TAs and HST) for oncology and orphan compared to non-oncology and non-orphan respectively. The computation of the OR and the estimation of the 95% confidence interval (CI) can be found in Agresti (2013).

Table 3. Contingency tables used to estimate the OR of a positive NICE recommendation

	orphans vs non-orphans				oncology vs non-oncology		
	Positive	Negative	Total		Positive	Negative	Total
Orphans	20*	9	29	Oncology	50	18	68
Non-orphan	138	17	155	Non-oncology	108	8	112
Total	158	26	184[14]	Total	158	26	184

* This total includes the 16 appraisals for which NICE gave a positive recommendation and the 4 HST evaluations.

The crude ORs of receiving a NICE positive recommendation for oncology and for orphan products are significantly lower than one. This means that both products used in oncology and orphan medicines are associated with lower odds of a positive outcome compared with the other products. In particular, the crude OR of a positive recommendation for oncology medicines is significantly lower than one: 0.20 (95% CI: 0.08, 0.50). Similarly, the crude OR of a positive outcome for OMPs is 0.27 (95% CI: 0.11, 0.70).

The median time which elapsed between the publication of the EU marketing authorisation and the publication of the NICE guidance was 325 days. This median time is 404 days if we include right-censored observations corresponding to ongoing appraisals (which we have censored our observations using the 23rd May 2017 as the end-of-study date). The median time from authorisation to NICE appraisal was slightly longer for positive decisions: 306 days for "not recommended", 310 days for "recommended", and 405 days for "optimised". When comparing orphan and non-orphan products, the median time for OMPs was 551 days, this time was longer than for non-orphans (369 days). This longer time for orphan appraisals is due to 19 ongoing (censored) appraisals for OMPs; if we exclude ongoing appraisals the respective median times between the authorisation and the publication of the NICE guidance for orphan and non-orphans are 314 and 330 days, respectively. The median appraisal time of oncology products was very similar to the appraisal time for the other products, regardless of the ongoing appraisals: 404 days (337 days excluding ongoing appraisals) for oncology and 392 days (314 days excluding ongoing appraisals) for non-oncology.

Figures 14 and 15 compare the Kaplan-Meier curves for the duration from EC authorisation to the publication of the final NICE guidance for oncology vs non-oncology products and for orphan vs non-orphan medicines. When considering the ongoing appraisals, the time to publication of the final recommendations is significantly longer for orphan medicines than for non-orphan ones. This is probably due to the length of appraisal procedures of some orphan products which can take a substantial amount of time to be completed. We did not observe any difference for oncology and non-oncology medicines since the Kaplan-Meier curves overlap.

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[14] This total includes the 180 appraisals finalised by NICE (i.e. excluding the terminated appraisals for which no submission was received by the manufacturer) and 4 HST evaluations.

Figure 14. Kaplan-Meier curves NICE TAs: oncology vs non-oncology including ongoing appraisals (the curves are presented with the 95% confidence interval bands)[15]
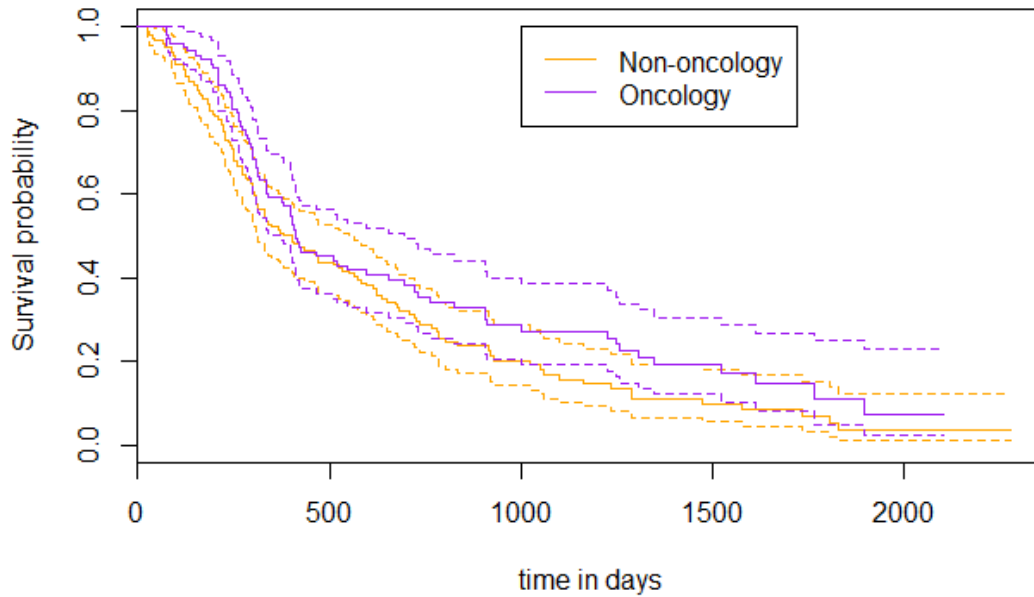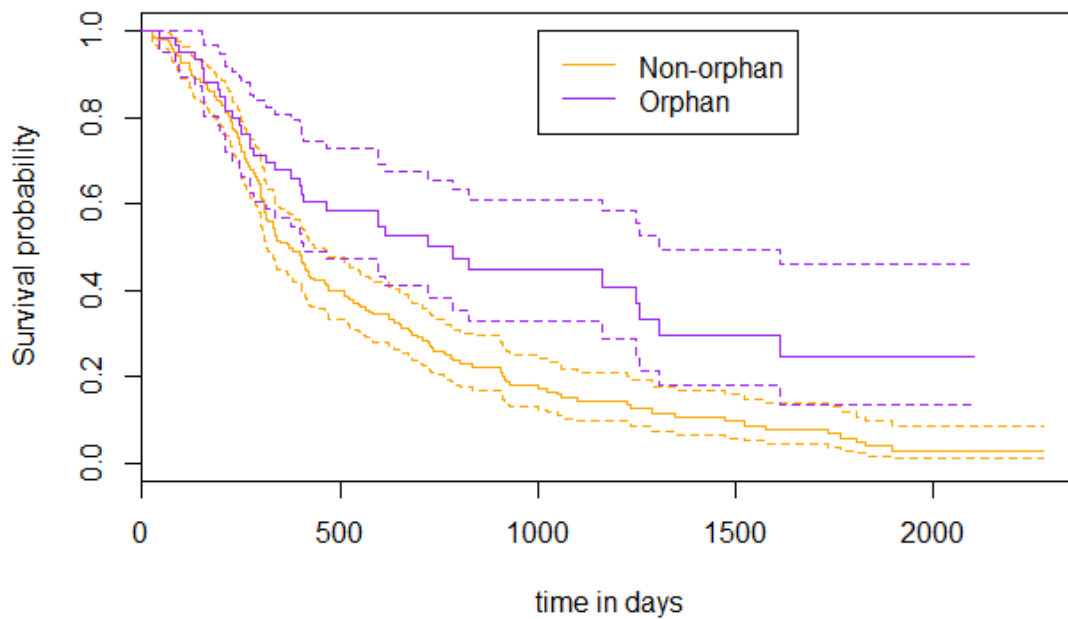

Figure 15. Kaplan-Meier curves for NICE TAs: orphan vs non-orphan including ongoing appraisals (the Kaplan-Meier curves are presented with the 95% confidence interval bands)

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[15] The survival probability denotes the evolution of the percentage of products for which the appraisal was not completed over the period following the marketing authorisation (which defines the starting point of the analysis).
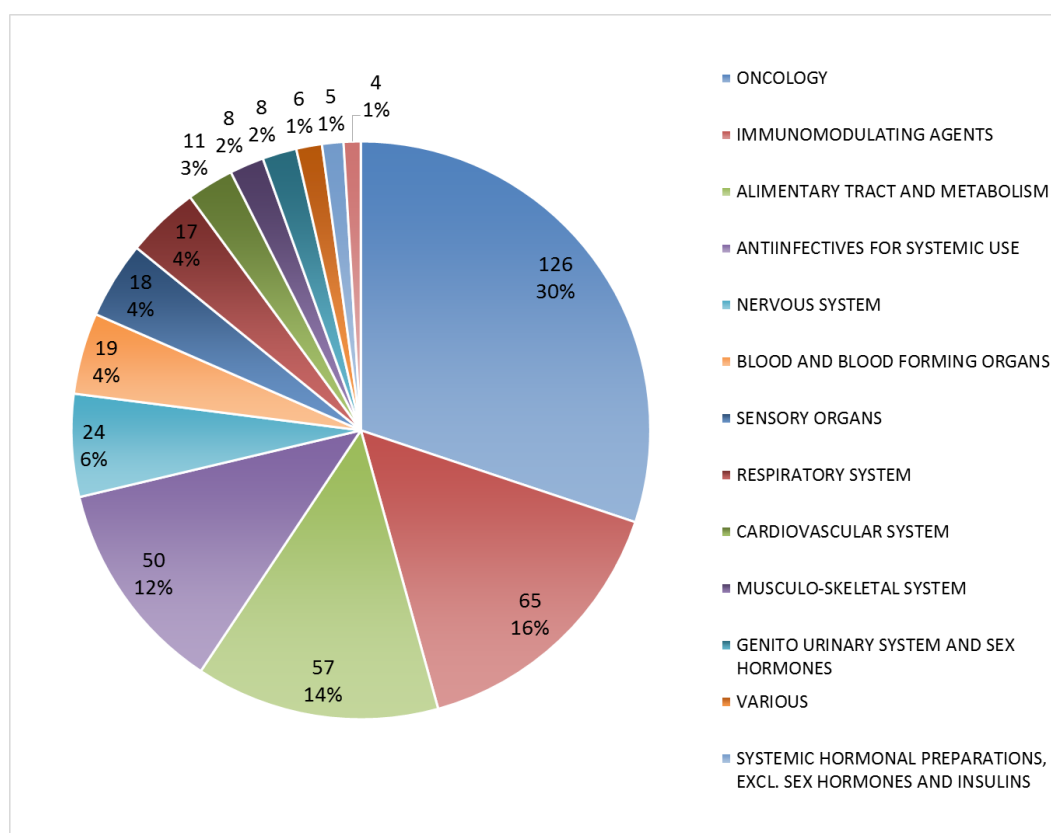
3.3. SMC evaluations

3.3.1. Descriptive analysis

A total number of 418 evaluations were undertaken by the SMC, of which 402 were completed. These 418 evaluations involve 378 of the 512 authorisations granted during the period of the study. Therefore, 74% of the products which received an authorisation via the centralised procedure over the period of our study were evaluated by the SMC. Of these, 38 evaluations correspond to resubmission of additional evidence by the manufacturers following an initial appraisal which implies that 38 products were appraised more than once by the SMC. The analysis shows again that oncology medicines are more often appraised by the SMC than the other products. Of the 378 appraised indications, 106 oncology indications out of 126 (84%) and 78 of the 114 indications granted to OMPs (68%) were evaluated by the SMC.

Figure 16 shows the distributions of the 418 evaluations by ATC class (products of the ATC L class are presented separately as oncology and immunomodulating agents). Anticancer products were involved in 30% of the evaluations conducted by the SMC. During the period of our study, the SMC conducted 126 evaluations involving 112 different anticancer products (14 evaluations correspond to resubmissions). The next most frequently appraised products are immunomodulating agents, followed by products in alimentary tract and metabolism and anti-infectives for systemic use products (see Figure 16).

Figure 16. ATC class of the centrally authorised products which underwent a SMC evaluation (n = 418), 2011-2016

The distribution of the outcomes of the completed evaluations is shown in Figure 17. The distributions of the outcomes of the evaluations conducted on anticancer products and OMPs are shown in Figures 18 and 19. A majority of the medicines were "Recommended" by the SMC which allow the use of the product in accordance with its marketing authorisation (in particular the population defined in the therapeutic indication). For OMPs, the SMC recommended 14 products in an "optimised" way compared to 29 fully "recommended" medicines. The SMC did not recommend approximately a third of the medicines that it appraised. Half of OMPs were also not recommended by the SMC. Any comparison with NICE must be performed cautiously since negative SMC decisions also include products for which the manufacturer did not submit evidence, while NICE decision outcome is classified as "unable to recommend".

Figure 17. Outcome of SMC evaluations conducted on centrally authorised medicines (n = 402), 2011-2016
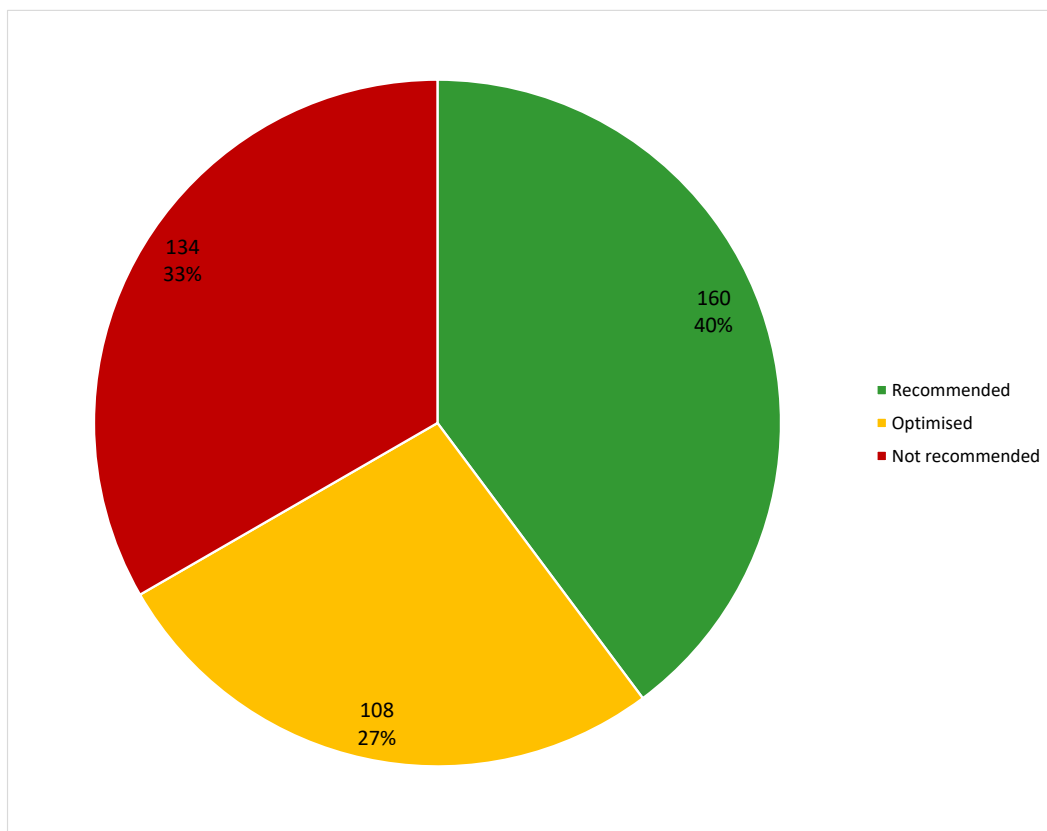
Figure 18. Outcomes of the SMC evaluations conducted on anticancer medicines (n = 126), 2011-2016
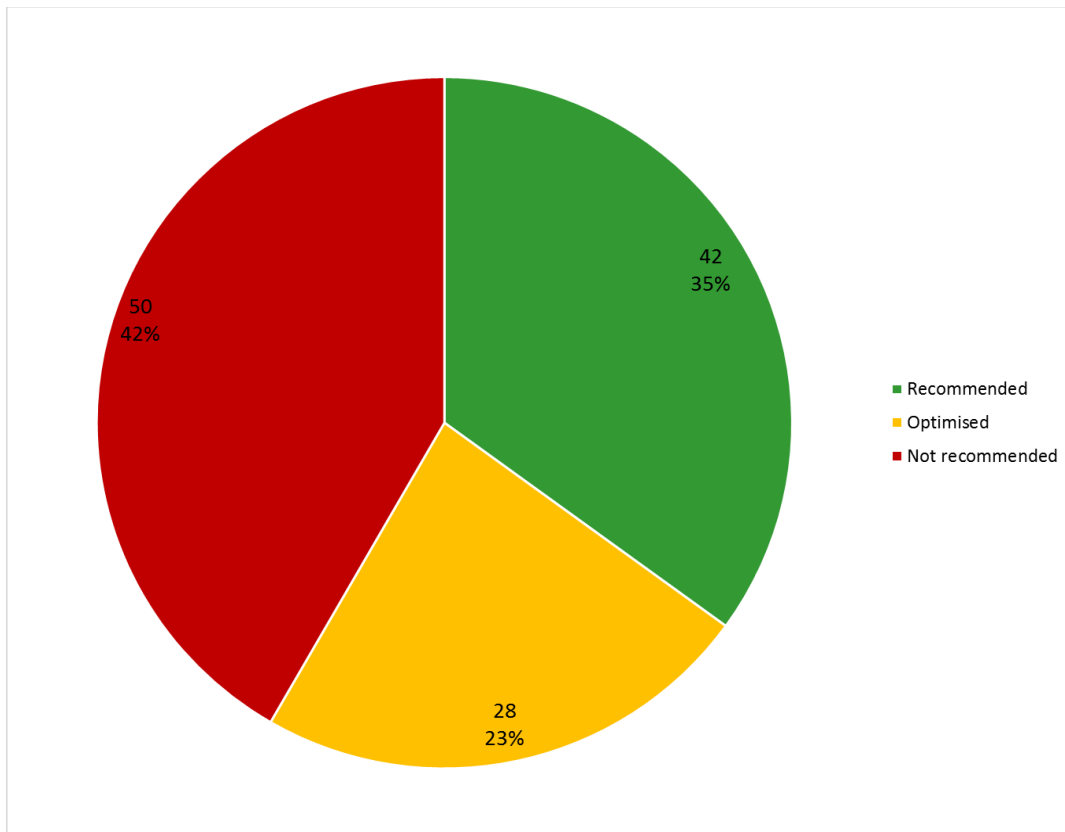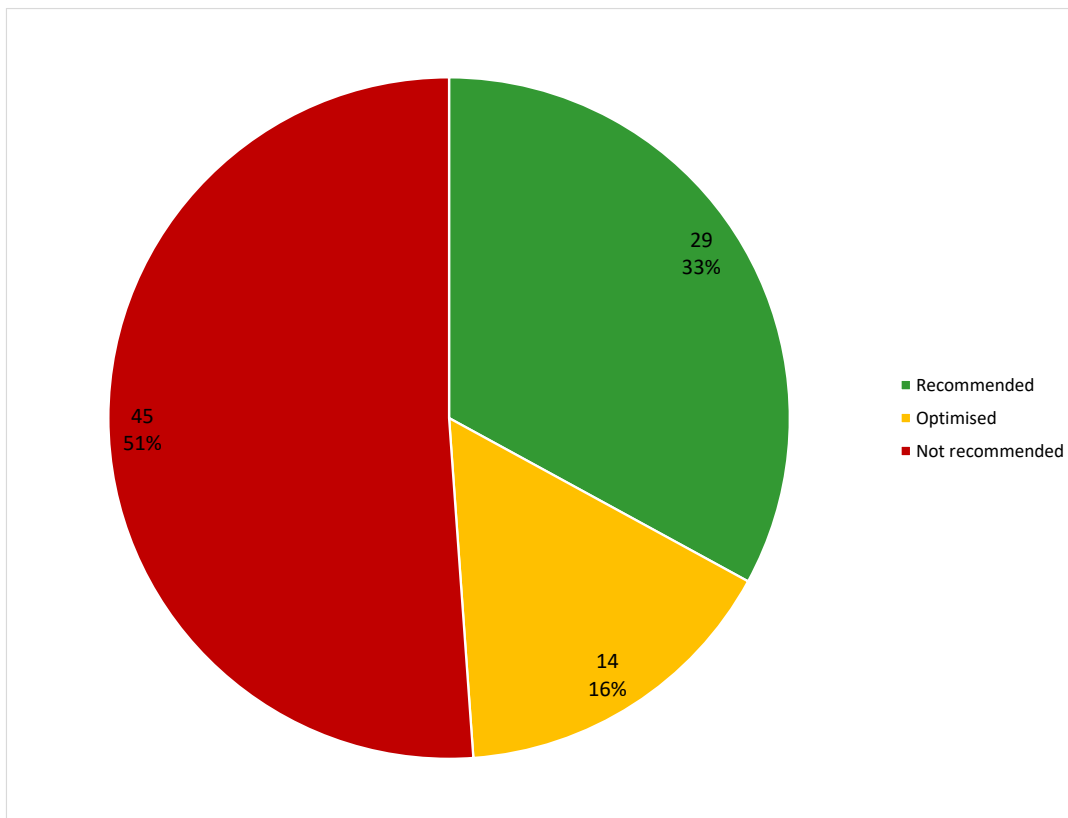

Figure 19. Outcomes of the SMC evaluations conducted on orphan medicines (n = 88), 2011-2016

3.3.2. Statistical analysis of outcomes and duration of SMC appraisals

Oncology and Orphan products were associated with lower odds of receiving a positive decision by SMC compared with the other products. The OR of positive decisions are: OR=0.59 (95% CI: 0.38, 0.92) for oncology and OR=0.38 (95% CI: 0.23, 0.61) for orphan products (compared respectively with the non-oncology and non-orphan medicines).

The median time between authorisations and SMC decisions was 259 days which slightly decreases to 257 days if we exclude 16 ongoing evaluations. The median time was shorter for the medicines which were "not recommended" (249 days) than for positive decisions (320 days for "recommended" and 377 days for "optimised" medicines). The median time from authorisation to the publication of the SMC guidance was longer for oncology products (311 days) than for the others (235 days). Also, the median time was longer for orphan products, 324 days, than for non-orphan products, 235 days. These results can be observed on Figures 20 and 21 showing the Kaplan-Meier curves for oncology and orphan medicines respectively. The Kaplan-Meier curves presented in Figures 20 and 21 include ongoing appraisals (censored observations). Similar Kaplan-Meier curves, which are not presented, were obtained when excluding ongoing appraisals.

Figure 20. Kaplan-Meier curves for SMC decisions: oncology vs non-oncology, including ongoing appraisals (with 95% confidence interval bands)
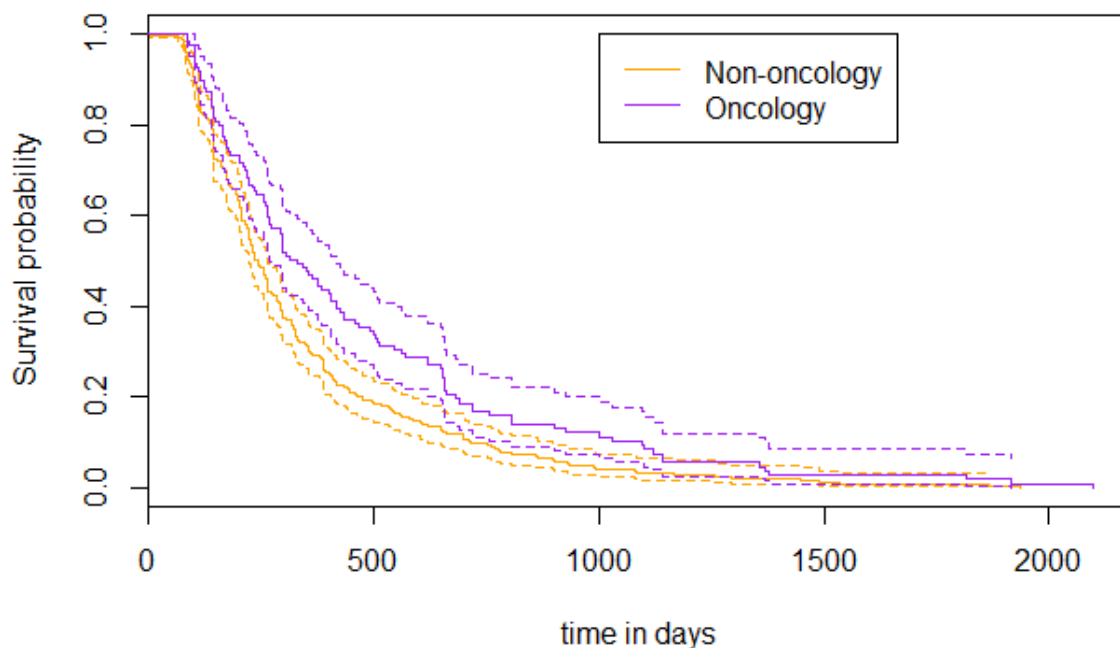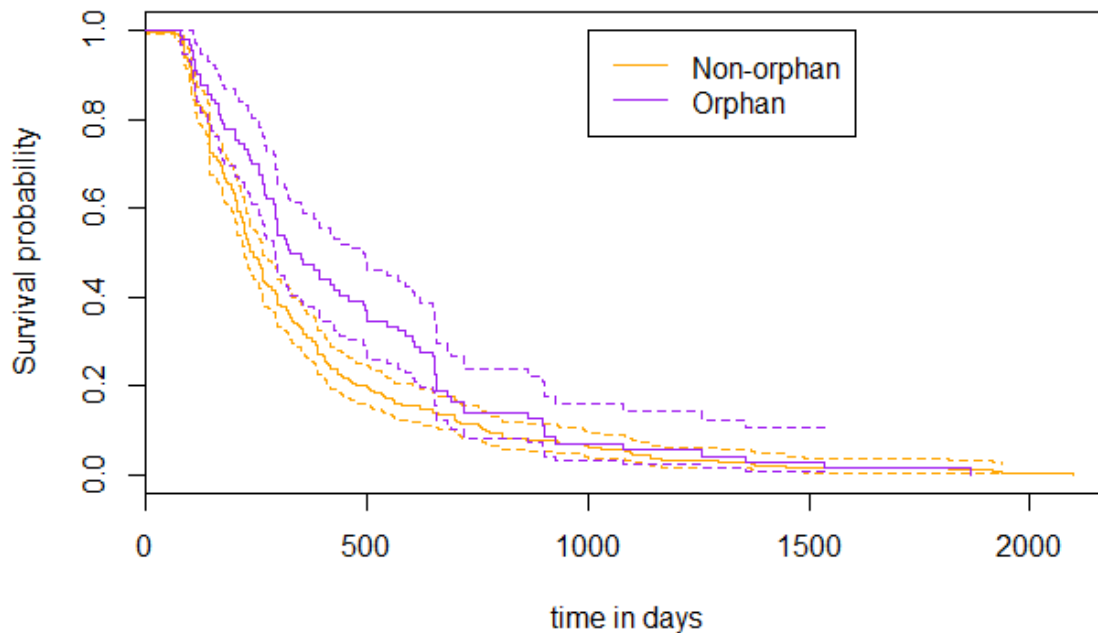
Figure 21. Kaplan-Meier curves for SMC decisions: orphan vs non-orphan, including ongoing appraisals (with 95% confidence interval bands)

3.4. AWMSG evaluations

3.4.1. Descriptive analysis

The AWMSG issues a limited number of independent evaluations with most of the decisions made subsidiary to NICE advice either *ex-ante* (excluding evaluations for products already in NICE scheduled evaluation pipeline) or *ex-post* (superseding a prior decision made by AWMSG with NICE new advice). Since there is a register and reference number for all AWMSG decisions, including for the exclusions due to NICE advice, we can consider the full coverage of EC authorised products in Wales. During the period of the study, 411 of the 512 products which received an authorisation (80%) were evaluated by the AWMSG. The AWMSG conducted 426 evaluations, of which 5 are ongoing. Of these, 158 were superseded by NICE evaluations. 158 AWMSG evaluations replaced by NICE advice and 5 ongoing appraisals were not included in our analysis. Therefore, approximately 83% of authorisations via the central procedure were evaluated by AWMSG (even if the final applicable guidance was not produced by the AWMSG). 118 products of the 126 products used in oncology (94%) and 93 of the 114 OMPs (82%) were evaluated by the AWMSG.

The distribution of evaluation by ATC class is shown in Figure 22 (oncology and immunomodulating agents are presented separately), with the largest proportion of evaluations, 29%, involving oncology products, followed by immunomodulating agents, alimentary track and metabolism, and anti-infectives for systemic use.

The distribution of the outcomes (Figure 23) involves 263 different evaluations conducted by the AWMSG. It is important to highlight that AWMSG were unable to recommend 129 products (i.e. nearly 50% of these procedures) in the absence of submission by the manufacturer (Figure 23). For the remaining 134 finalised appraisals, 123 products (92%) were recommended and consequently 11 (8%) products were not recommended by the AWMSG (Figure 23).

Figure 22. ATC class of the centrally authorised products which underwent an AWMSG evaluation (n = 426), 2011-2016
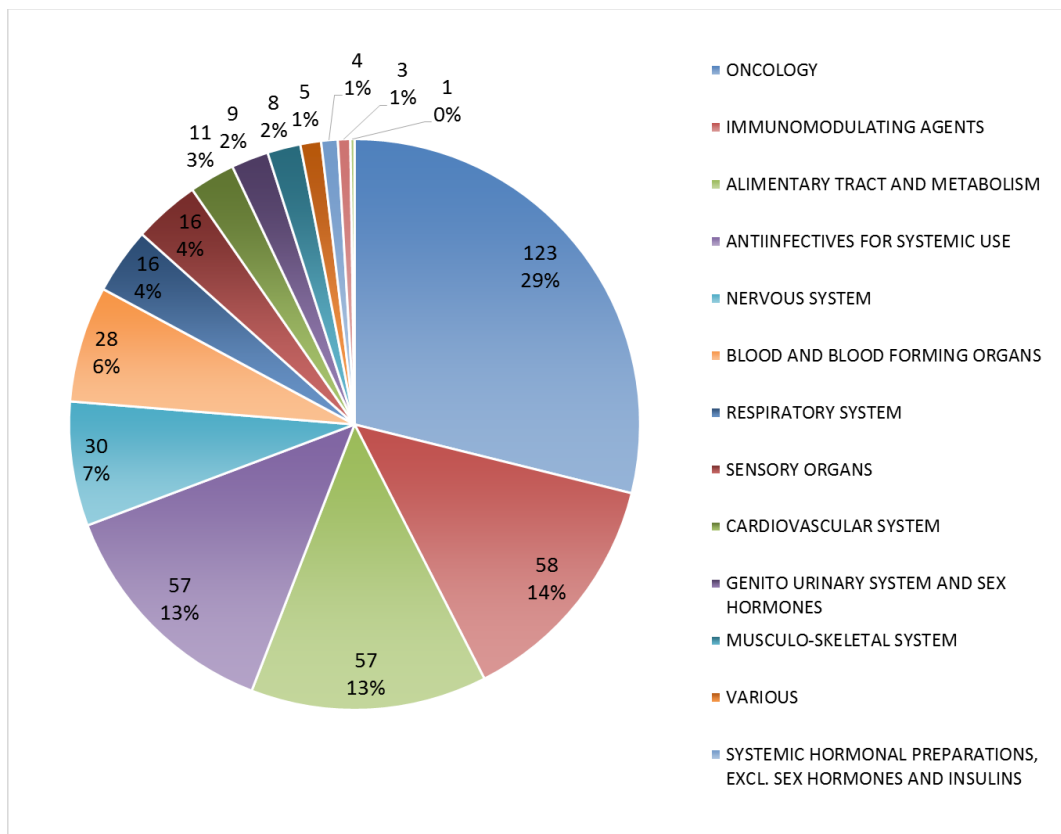

Legend:
- ONCOLOGY
- IMMUNOMODULATING AGENTS
- ALIMENTARY TRACT AND METABOLISM
- ANTIINFECTIVES FOR SYSTEMIC USE
- NERVOUS SYSTEM
- BLOOD AND BLOOD FORMING ORGANS
- RESPIRATORY SYSTEM
- SENSORY ORGANS
- CARDIOVASCULAR SYSTEM
- GENITO URINARY SYSTEM AND SEX HORMONES
- MUSCULO-SKELETAL SYSTEM
- VARIOUS
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS

Values: 123 (29%), 58 (14%), 57 (13%), 57 (13%), 30 (7%), 28 (6%), 16 (4%), 16 (4%), 11 (3%), 9 (2%), 8 (2%), 5 (1%), 4 (1%), 3 (1%), 1 (0%)

Figure 23. Outcome of AWMSG evaluations conducted on centrally authorised medicines, 2011-2016 (n = 263)

Legend:
- Unable to recommend — 129 (49%)
- Recommended — 92 (35%)
- Optimised — 31 (12%)
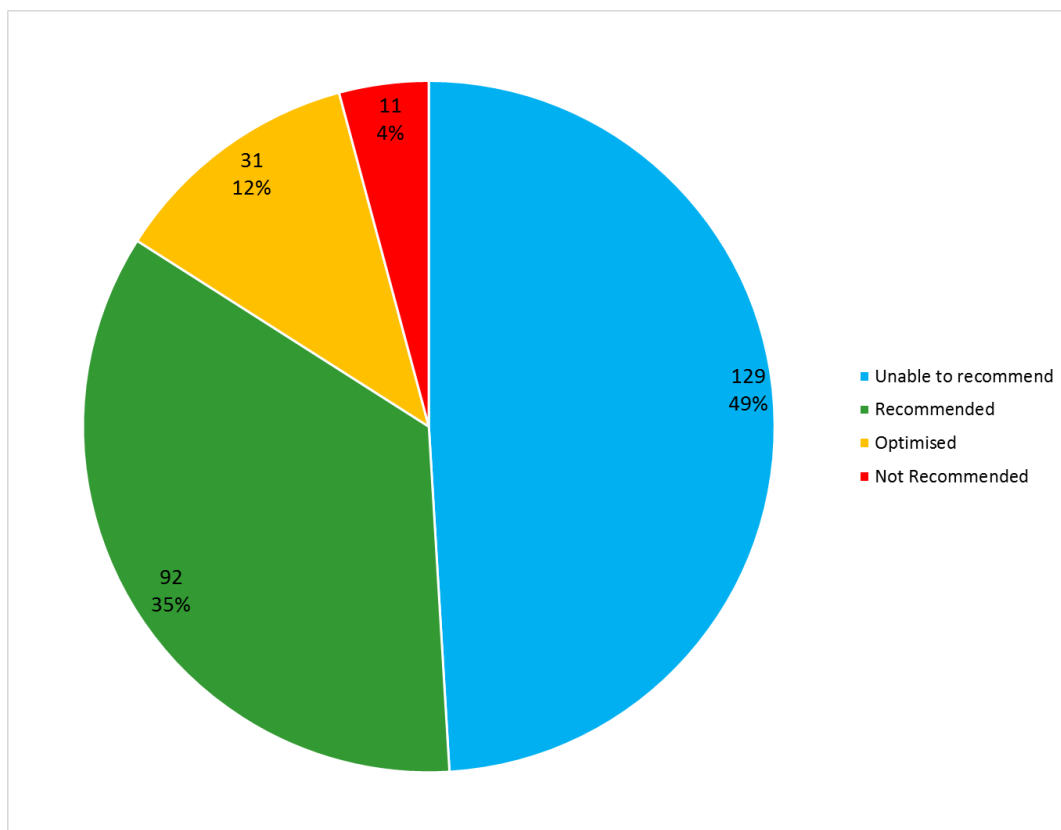- Not Recommended — 11 (4%)

Figure 24 represents the distribution of decision outcomes for 54 evaluations of oncology products. No evidence was submitted in 34 cases (63%). Of the 20 remaining appraisals, positive recommendations were issued in 17 cases (85%) and negative ones in 3 cases (15%).

96 evaluations involved 93 different OMPs, but 26 of them were subsequently replaced by NICE guidance. Figure 25 represents the distribution of decision outcomes for the remaining 70 evaluations of OMPs initiated by the AWMSG; the AWMSG was "unable to recommend" in 63% of the cases in the absence of submission by the manufacturers. All the 26 OMPs for which evidence was submitted by the companies received a positive recommendation from the AWMSG.

Figure 24. Outcome of AWMSG evaluations conducted on anticancer medicines (n = 54), 2011-2016
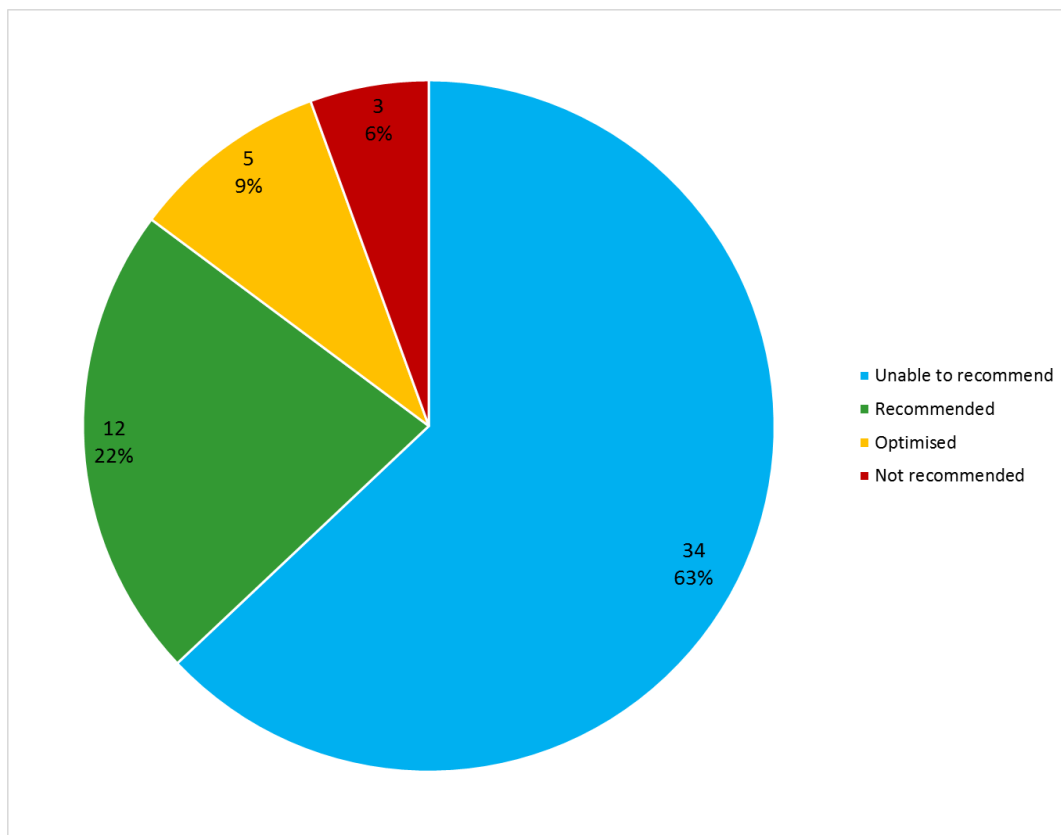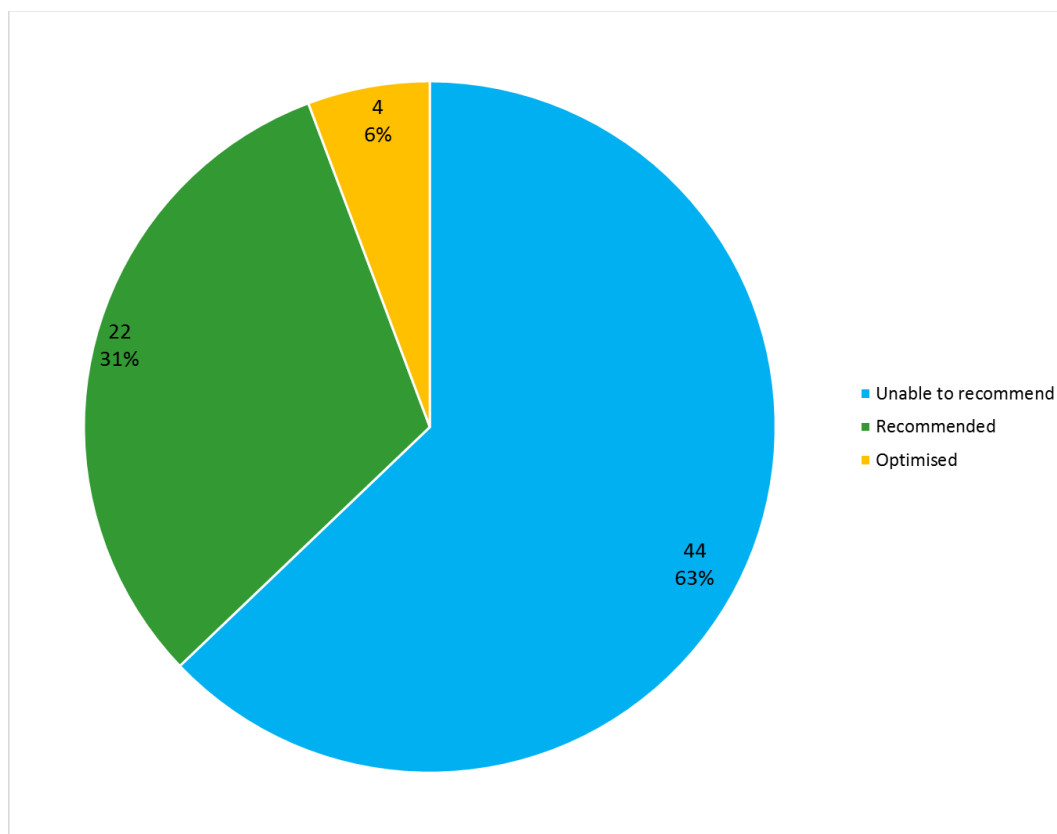
Figure 25. Outcome of AWMSG evaluations conducted on orphan medicines (n = 70), 2011-2016

3.4.2. Statistical analysis

In the absence of negative recommendation, the ORs of receiving a positive decision for orphan medicines could not be computed. The number of evaluations conducted by the AWMSG involving orphan products was low compared with NICE (158) and SMC (88).

For the AWMSG, the odds of receiving a positive decision was not significantly lower for oncology products than for the other products (the confidence interval of the crude odds ratio includes 1). The OR of a positive decision for oncology products is OR=0.43 (95% CI: 0.10, 1.77). The OR is estimated on a low number of evaluations conducted on these products (see Figure 24) which explains the wide confidence interval.

The estimation of time between EC authorisation and AWMSG has included all evaluations, including the 158 AWMSG evaluations subsequently superseded by a NICE advice. In addition, 70 of the 129 evaluations for which the manufacturer did not submit any evidence to the AWMSG were not included in the time-to-event analysis since the date of termination of the appraisal was prior to the EC authorisation date. The date range covered by AWMSG evaluations is 1st January 2011 to 3rd April 2017, during this period only 5 procedures were still ongoing (these observations were censored). Therefore, the results analysis on time elapsed between EC authorisation and AWMSG evaluation are almost identical whether we include or exclude ongoing appraisals.

The median delay in AWMSG evaluations is 173 days, with 690 days for the products not recommended, 406 days for optimised, 321 for recommended, 175 days for "superseded" (i.e. by a NICE decision), and 134 days for "unable to recommend". The

appraisals terminated in the absence of evidence submission have a very short duration (median of 49 days). Therefore, their occurrence shorten the overall median delay of the AWMSG appraisals compared to NICE and SMC for which the proportion of terminated appraisals in the absence of evidence submission was much lower.

Figures 26 and 27 present the Kaplan-Meier curves for the timeframes of AWMSG evaluations by comparing oncology with non-oncology and orphan with non-orphan evaluations. We did not observe any difference for the median evaluation time between the orphan and non-orphan medicines (it is likely that these evaluation times might be biased by the absence of evidence submission by companies). Our analysis shows that AWMSG prioritised the evaluations of oncology products and appraised these products with shorter evaluation times compared to the products of other therapeutic classes.

Figure 26. Kaplan-Meier curves for AWMSG decisions: oncology vs non-oncology including ongoing appraisals (with 95% confidence interval bands)
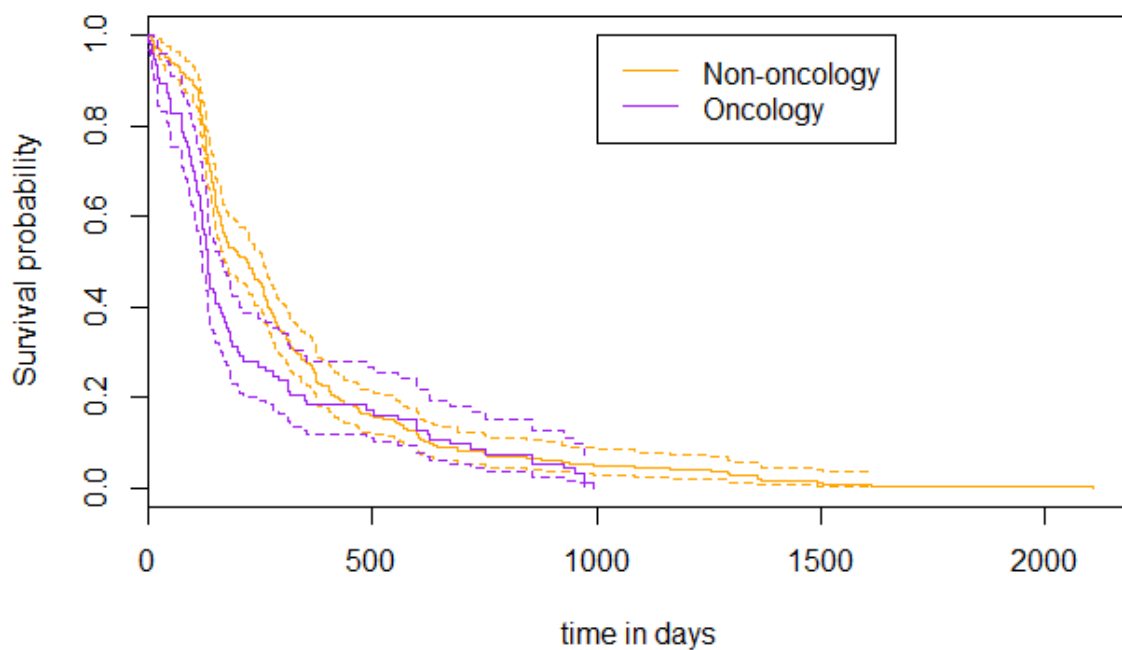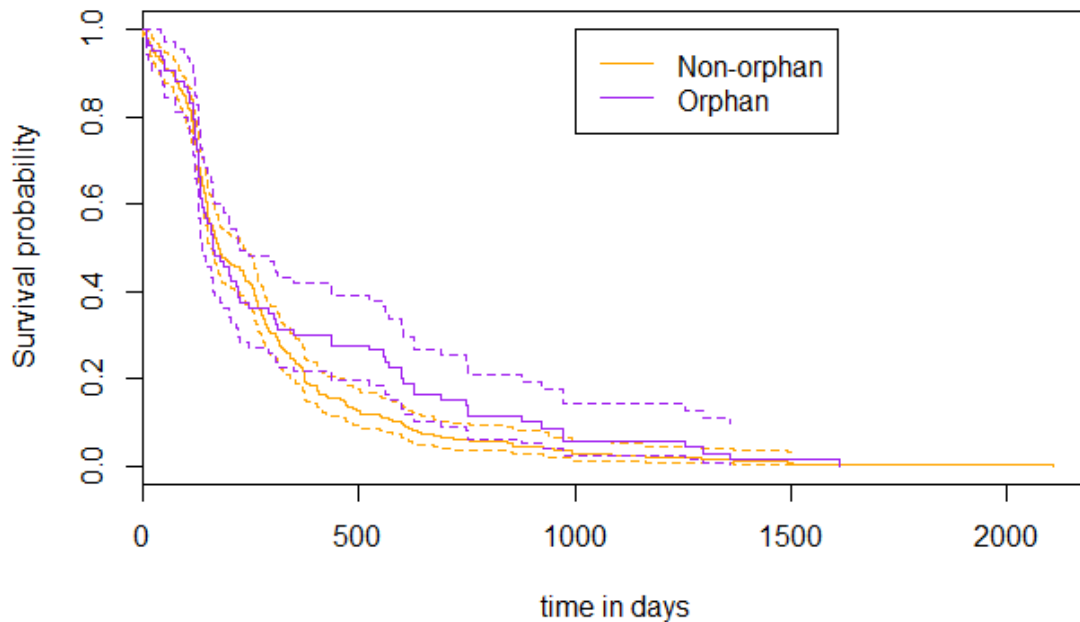
Figure 27. Kaplan-Meier curves for AWMSG decisions: orphan vs non-orphan including ongoing appraisals (with 95% confidence interval bands)

4. COMPARATIVE ANALYSES

We have analysed the consistency of the recommendations between NICE, SMC, and AWMSG by computing the kappa coefficient of interrater agreement. We estimated the Fleiss kappa of interrater agreement (Fleiss, 1971) for evaluations with three categories of appraisal outcomes (recommended, optimised, and not recommended). Secondly, we fitted a logistic regression model to estimate the odds associated with the outcomes of the appraisals of the three HTA bodies and the odds of receiving positive recommendations for certain classes of products of interest (orphan and oncology products). Considering that an important proportion of orphan designations are granted to anticancer medicines, we have added an interaction factor to account for this overlap. We fitted a saturated model from which we have taken out the parameters which were not associated with a statistically significant effect to fit a new, unsaturated model that we present in our final analysis. The odds ratios were derived from the parameters of the unsaturated model.

4.1. Consistency of recommendations across the three HTA bodies

The Fleiss kappa of interrater agreement estimates the proportion of non-chance agreement among different raters assigning categorical outcomes to every observation. A significantly positive kappa informs on some level of agreement which is not the result of pure chance. However, there is not an established threshold above which the interrater agreement level can be qualified as high or acceptable.

We computed the Fleiss kappa to assess agreement among NICE, SMC, and AWMSG regarding 20 evaluations completed by the three HTA agencies for the same CAPs. This includes 3 CAPs with duplicated evaluations: pomalidomide with two different TAs by NICE, fingolimod and evolocumab with two evaluations by SMC. The resulting Fleiss kappa is 0.19 with significance p-value=0.050. Therefore, the agreement among the three HTA agencies is very low.

We also computed the Fleiss kappa to assess agreement among NICE and SMC regarding 169 evaluations completed by the two HTA agencies for the same CAPs. The resulting Fleiss kappa is 0.29 with significance p-value<0.001. Therefore, our analysis the agreement between NICE and the SMC on the medicines appraised by the two HTA bodies is very low.

4.2. Logistic regression analysis

The results of the logistic regressions presented in Table 4 show the final selected model after removing insignificant explanatory variables, such as the interaction between orphan designation and oncology.

Table 4 presents results from a logistic regression performed in two different datasets. Analysis 1 presents results from the first dataset which includes 720 completed evaluations with positive recommendations (recommended or optimised) or negative (not recommended): 184 from NICE, 402 from SMC, and 134 from AWMSG. Analysis 2 is performed in a dataset where NICE evaluations substitute AWMSG evaluations when there is no independent decision by AWMSG (this increases the number of evaluations for AWMSG to 311). The mean of the dependent variable presented at the bottom of Table 4 gives the percentage of positive decisions in the overall sample. The small increase from 75% in sample 2 to 76% in sample 1 indicates more favourable outcomes from AWMSG independent decisions than from NICE decisions.

The comparison of the odds of issuing a positive recommendations between the three agencies is captured by the coefficient estimate of the parameter corresponding to the HTA body. The AWMSG was used as a reference for the fitting of the model. Therefore, the sign of the parameters estimates in the rows indicate whether the OR of a positive decision is larger than one (positive coefficient) or smaller than one (negative coefficient) as compared to AWMSG. The results of the logistic regression confirm that the products appraised by the SMC have the highest odds of receiving a negative decision. The parameters of the model indicate lower odds (OR=0.25, 95% CI: 0.11, 0.51) of positive decision for SMC than for AWMSG (analysis 1). This result confirms the findings in Figure 9 for NICE, Figure 17 for SMC, and Figure 23 for AWMSG.

The remaining coefficients inform of the odds of a positive decision associated with oncology and orphan drugs within each HTA agency. All significant coefficients for NICE and SMC are negative indicating that the odds of a positive decision for these products is lower compared with the other products appraised by these HTAs. In particular, for NICE the odds ratio of a positive recommendation for products used in oncology is OR=0.25 (95% CI: 0.09, 0.61), and the odds ratio for the orphan medicines is OR=0.40 (95% CI: 0.15, 1.12) compared to the other products (non-oncology, non-orphan) also appraised by NICE. For SMC the OR associated with oncology products is higher than the OR obtained from NICE, and not significantly lower than one: OR=0.74 (95% CI: 0.47, 1.2). However, the OR of a positive decision by SMC associated with orphan designation compared to non-orphan is significantly lower than one: OR=0.41 (95% CI: 0.25, 0.68) for orphan designation.

For AWMSG independent decisions (analysis 1), there is no significant difference between the odds of positive decisions for oncology as compared with non-oncology products. Due to the absence of negative recommendations for OMPs issued by the AWMSG, the OR could not be computed. However, when we consider all implemented decisions, including headline NICE decisions for AWMSG excluded and superseded evaluations, we found lower odds of a positive decision associated to orphan designation

in Scotland than in Wales (OR=0.95, 95% CI: 0.47, 1.99). For oncology, the lower odds of a positive decision (OR=0.27, 95% CI: 0.15, 0.50) are similar to those obtained from NICE.

**Table 4. Logistic regression: positive decision outcomes**

	Analysis 1 (AWMSG independent decision outcomes)		Analysis 2 (AWMSG all evaluation outcomes)	
	Estimate	Std. error	Estimate	Std. error
(Intercept)	2.398***	0.369	1.931***	0.210
NICE	0.315	0.528	0.7836	0.431
SMC	-1.399***	0.395	-0.932***	0.252
AWMSG: Oncology	-1.299	0.762	-1.309***	0.306
NICE: Oncology	-1.403**	0.472	-1.403**	0.472
SMC: Oncology	-0.296	0.240	-0.296	0.240
AWMSG: Orphan	N/A	N/A	-0.055	0.367
NICE: Orphan	-0.904	0.504	-0.904	0.504
SMC: Orphan	-0.8829***	0.258	-0.883***	0.258
	Number of evaluations: 720 Mean dependent variable: 0.7625		Number of evaluations: 897 Mean dependent variable : 0.7525	
p-values: <0.001 *** ; <0.01 ** ; <0.05 *				

5. MEDICINES DIRECTLY COMMISSIONED BY THE NHS OR INCLUDED IN THE CANCER DRUGS FUND

A number of CAPs are funded in England and Wales via alternative public funding mechanisms.

In England, NHS commissioning policies provide routine funding for 61 of the CAPs included in our study. Figure 28 presents the ATC class distribution of the 61 CAPs funded through NHS England commissioning. The most important class is the anti-infectives for systemic use, with 27 (44%) products, mainly due to the commissioning policy for antiretrovirals (in accordance with the British HIV Association (BHIVA) Guidelines), followed by immunommodulating agents which account for 15%, and blood and blood forming organs (10%). Anticancer products represent 5% of the products directly commissioned by NHS England (excluding the products made available via the Cancer Drugs Fund). NHS England commissioning policies did not include any products in the ATC classes of sensory organs, dermatologicals, musculo-skeletal system, or antiparasitic products.

Figure 28. ATC class of the products subject of a commissioning by NHS England, 2011-2016
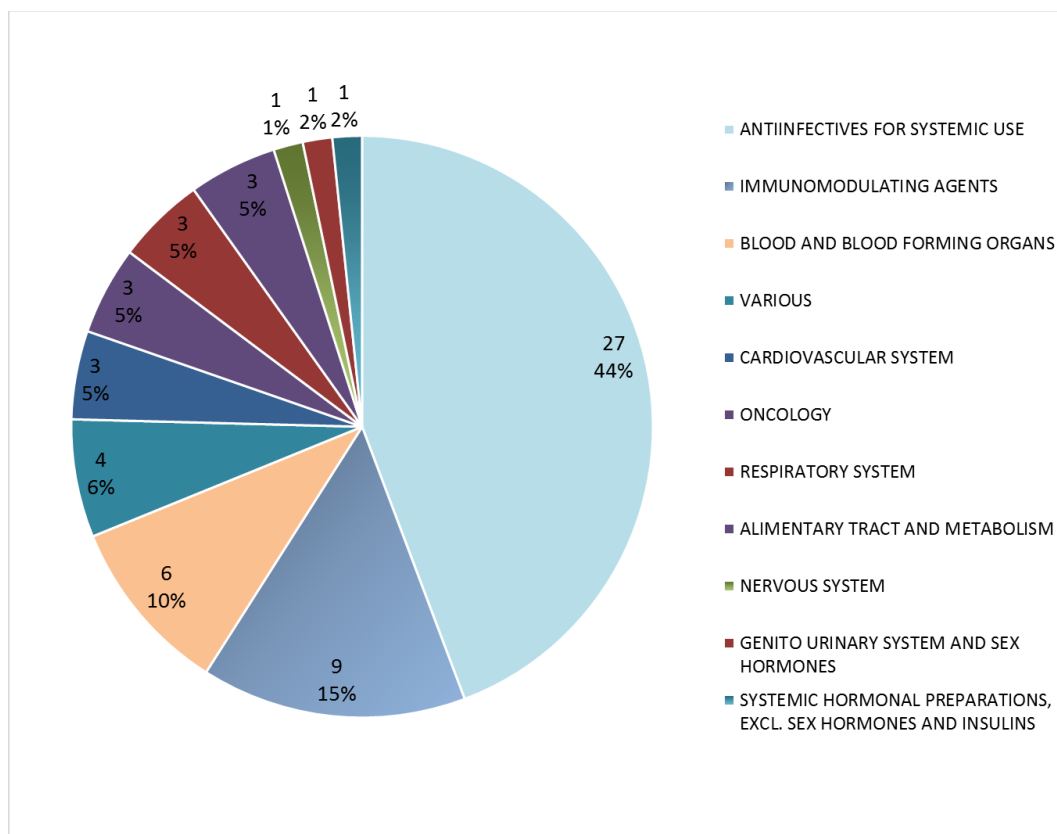
In particular, 25 OMPs are among the 61 CAPs directly commissioned by NHS England. These include 3 anticancer products (everolimus for 3 different indications), and 4 blood or blood forming organ products. The remaining 18 OMPs belong to other different ATC classes.

At the time when our study was conducted, the Cancer Drugs Fund provided routine funding for 17 CAPs (most of the products currently included in the Cancer Drugs Fund i.e. 11 out of 15 were authorised more than 3 years ago i.e. before July 2014). Of these, 11 products are undergoing a NICE evaluation, 4 products received a negative recommendation and 1 product was directly included in the Cancer Drugs Fund by NICE. The manufacturer did not submit evidence dossier for 1 product. 8 of these products are OMPs: ponatinib and brentuximab vedotin in 2 indications each, everolimus, pomalidomide, sorafenib and ibrutinib.

In November 2015, Wales adopted an interim commissioning policy to promote equity of access to those medicines not routinely available in NHS Wales in circumstances where an unmet clinical need has been identified for a patient cohort (AWTTC, 2015). Since October 2016, 8 CAPs were recommended for interim commissioning in NHS Wales; of these, 2 products were recommended in non-authorised indications.[16]

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[16] The Interim Pathways Commissioning Group (IPCG) recommendations endorsed by health board Chief Executives in Wales can be found at the following URL: https://www.awttc.org/pams/current-one-wales-interim-commissioning-decisions (accessed on 13 November 2017).

6. COMPARISON OF ACCESS IN ENGLAND AND SCOTLAND

The comparison of access in England and Scotland to the 512 products which received a new authorisation during the period of our study shows some substantial heterogeneity between these two countries (Table 5). We found less heterogeneity between England and Wales due to the high number of AWMSG appraisals subsequently replaced by NICE recommendations (data not shown).

Table 5. Comparison of the access to the medicines[17] which received an authorisation between 2011 and 2016 in England and Scotland

Therapeutic class	Funding	England	Scotland (SMC)
Oncology	Positive HTA recommendation	43	63
	Negative recommendation	17	39
	Ongoing evaluation	13	4
	Commissioning by NHS England	3	N/A
	Positive recommendation: Cancer Drugs Fund	15	N/A
	Not evaluated	35	20
Total oncology products		126	126
Anti-infectives	Positive HTA recommendation	11	41
	Negative recommendation	2	7
	Ongoing evaluation	N/A	1
	Commissioning by NHS England	27	N/A
	Not evaluated	27	18
Total anti-infectives		67	67

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[17] This table only considers the outcome of the last evaluation conducted on the products included in our study.

Therapeutic class	Funding	England	Scotland (SMC)
Other	Positive HTA recommendation	85	146
	Negative recommendation	11	68
	Ongoing evaluation	21	9
	Commissioning by NHS England	31	N/A
	Not evaluated	171	96
Total other classes		319	319
Total (all therapeutic classes)		512	512

7. DISCUSSION

We present a comprehensive analysis of the HTA evaluations conducted by NICE, AWMSG and SMC on the CAPs authorised between 1 January 2011 and 31 December 2016 or which received an extension of their therapeutic indication during the same period.

Oncology products were the highest number of products which received marketing authorisations (initial and extension of indications) via the centralised procedure. Anticancer medicines and orphan drugs represent an important proportion of newly authorised products both in the US and in the EU (Mullard 2014, 2015, 2016). There is also a large overlap between anticancer medicines and medicinal products which receive orphan designations in the EU (Morel et al. 2016). Our study shows that anticancer and orphan drugs were disproportionately evaluated by HTA bodies in Great Britain. Whereas anticancer medicines account for a quarter of the products which received authorisations via the centralised procedure (initial or extension of indications), these products account for 40% of the products referred to NICE and approximately 30% of the products evaluated by the AWMSG and SMC. We have also shown that these products receive proportionately more negative recommendations than the products of other classes, particularly from NICE and SMC.

In a study performed on the NICE appraisals conducted before 31 December 2011, Dakin et al. showed that the odds of a positive NICE recommendation were 3.1-fold higher (p=0.029; 95% CI: 1.1, 8.4) for decisions concerning technologies used for the treatment, prevention or diagnosis of cancer appraised before 31 December 2011. The authors did not find any difference in the probability of receiving a negative NICE recommendation for orphan medicines (Dakin et al, 2015). Charopokou et al. found that orphan medicines and anticancer medicines had a lower odd of receiving a positive recommendation from the SMC for the appraisals conducted by the SMC between 2006 and 2013 (Charopokou et al. 2015). Our results demonstrate that anticancer medicines (oncology products classified under the ATC L class) and orphan drugs authorised between 2011 and 2016 tend to proportionately receive negative recommendations from NICE and SMC compared to the other products appraised by these HTA agencies.

We did not study the clinical and cost-effectiveness parameters which influenced the HTA decisions in England, Wales and Scotland, however, the HTA recommendations of new technologies in these 3 countries are not only made on the basis of additional clinical effectiveness but on their cost-effectiveness compared to the standard of care of the health system (AWMSG, 2016; NICE, 2013; SMC, 2017). In addition, HTA bodies often assess the clinical effectiveness of new technologies on the basis of clinical endpoints (in opposition to surrogate endpoints) which are relevant to the patients and their carers, these include quality of life and survival (NICE, 2017). Many anticancer medicines can be authorised on the basis of surrogate endpoints such as progression or disease free-survival (PFS or DFS) (EMA, 2012) without any direct evidence of improved overall survival (Bauer et al, 2017, Rupp et al., 2017).

In a recent study, anticancer medicines were shown to be the products most frequently involved in early engagement activities between HTA bodies and manufacturers (Maignen et al. 2017a). Such early engagement will likely improve the generation of clinical effectiveness evidence to meet HTA expectations in the development of new medicines, including anticancer medicines and hopefully increase the likelihood of recommendation of these products in the future.

All the HTA bodies included in our study have implemented criteria and modifiers which usually increase the threshold of cost-effectiveness if these criteria are met (e.g. orphan and ultra-orphan criteria for the AWMSG and SMC, end-of-life criteria for NICE) (AWMSG, 2015; NICE, 2013; SMC, 2015). In addition, in the specific case of orphan drugs, all the HTA bodies included in the study consider other elements than the cost-effectiveness of the technology when issuing recommendations for orphan drugs (including for example the degree of severity of the disease in terms of survival and quality of life for the patients and their carers, any unmet needs, the added value for the family, etc,). NICE has put in place the highly specialised technology programme for orphan products which fulfil certain criteria (NICE, 2017).

Our analysis also shows that orphan medicines authorised between 2011 and 2016 were more likely to receive negative NICE or SMC recommendations. It is important to note that the granting of an orphan designation does not imply that the technology will be appraised according to different cost-effectiveness criteria or under the highly specialised technologies programme by NICE. Most of the orphan products referred to NICE were routed and appraised under the TA programme (77%). Our study shows that the outcome of the appraisals for orphan medicines depended on the evaluation process undertaken by the products. All the 4 orphan products evaluated under the HST programme by NICE received positive recommendations. On the other hand, this was the case for only 64% (16/25) of the orphan products appraised under the TA programme.

Our study showed that the appraisal of medicines in the UK still involves a substantial amount of time after the granting of the marketing authorisation (the median time is between 4 months in Wales, approx. 9 months in Scotland and approx. 1 year in England). We found that this time was consistently substantially longer for orphan medicines in England and Wales. Differences in the length of appraisals between oncology products and non-oncology products were only observed in Scotland.

We found little agreement in the decisions made by the three HTA bodies and by NICE and the SMC for the products which were appraised by all these bodies. We did not

explore the reasons underlying these disagreements, nor for the 169 products both appraised by NICE and by the SMC.

Finally, it is important to note that a substantial number of CAPs are directly commissioned by NHS England, anti-retrovirals in particular. It is also important to note that 25 OMPs are among the 61 CAPs directly commissioned by NHS England. Therefore, the findings of our study on the appraisal of orphan drugs need to be put in to perspective with the fact that a large number of orphan drugs do not undergo any NICE evaluation. Our study shows despite the fact that the NHS has put several mechanisms to grant access to orphan drugs in England, only approx. 60% of the orphan drugs authorised during the period of our study were accessible to patients in England.

We could not evaluate access to the medicines included in our study via individual funding requests (IFR) in England, Wales and Scotland[18] which is an important limitation of our study. While the All Wales Therapeutic and Toxicology Centre published two annual analyses of the IFR in Wales between 1 April 2015 and 31 March 2017 (AWTCC 2016, 2017) following the IFR review in 2014, we could not find any report covering the entire period of our study for England, Scotland and Wales. For that reason, it was difficult to compare access to the products across the three countries. In addition, we did not study the clinical effectiveness (e.g. type of endpoints used in the clinical studies) and cost-effectiveness mechanisms which can influence the decisions made by these three HTA agencies. It was difficult to compare the recommendations issued by the three HTA bodies considering that the appraisals for which manufacturers do not submit any evidence is reflected differently in the decisions published by the three HTA bodies and to the partial role of AWMSG as HTA advisory agency in Wales, with the largest part of advice implemented in Wales being taken from NICE.

Importantly, our analysis show that only 70% (88) of the indications for products used in oncology and less than 50% of the indications for OMPs (52 or 46%) were referred to NICE by the Department of Health, an additional 3 oncology products and 25 OMPs are directly commissioned by NHS England. In addition, 84% of the indications for oncology products and 68% of the indications for OMPs were evaluated by the SMC and 94% of the indications in oncology and 82% of the indications for OMPs were evaluated by the AWMSG. Therefore, our study shows that an important number of the uses for oncology and OMPs products granted during the period of our study were not evaluated, especially in England. Consequently, an important proportion of these uses are not routinely funded by the NHS in England despite an important recognised unmet medical need, we could not check whether these were accessible to patients in Scotland and Wales (WHO, 2015).

8. CONCLUSIONS

This study describes the central marketing authorisation, HTA evaluation and routine funding in the NHS in the UK of medicines authorised in the six-year period from 2011 to 2016. The descriptive and statistical analyses presented allow us to assess access to medicines in the UK as compared with the total number and types of CAPs. Further comparisons are provided to assess different availability in England, Scotland and Wales.

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[18] The processes are called Individual Funding Request (IFR) in England, Individual Patient Funding Request (IPFR) in Wales and Individual Patient Treatment Request (IPTR) in Scotland. We have used the expression "individual funding requests" through the document to identify these 3 procedures.

Our results show that oncology medicines are more frequently subject to technology appraisal procedures than the products from the other therapeutic classes. However, the odds of receiving a positive recommendation is lower for oncology than for non-oncology products in England and Scotland, but not in Wales. OMPs are also associated with a lower odds of receiving a positive decision than non-orphan products in Scotland. AWMSG issued a positive recommendation for all 26 OMPs for which some evidence was provided by the companies. The routine funding of additional OMPs in the NHS in Wales is dependent on NICE advice.

Our study showed that the appraisal of medicines in Great Britain requires a substantial amount of time after the granting of the marketing authorisation, the median times separating the authorisation and the publication of the HTA recommendation was between 4 months in Wales and approximately 1 year in England. We found that this time was consistently substantially longer for orphan medicines in England and Scotland. A direct commissioning of medicines by NHS England mostly involves antiretrovirals and products used in specialised services provided in relatively few hospitals, accessed by comparatively small numbers of patients.

We show that there is both variation across agencies and variation across therapeutic classes in terms of adoption decisions. A substantial proportion of new medicines and indications granted to products used in oncology and to OMPs were not evaluated and therefore these uses may not be routinely funded by the NHS in these devolved nations. Therefore, our study suggests that one of the primary aims of the European centralised procedure to facilitate timely and consistent access to innovative medicines was partially achieved in the United Kingdom.

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