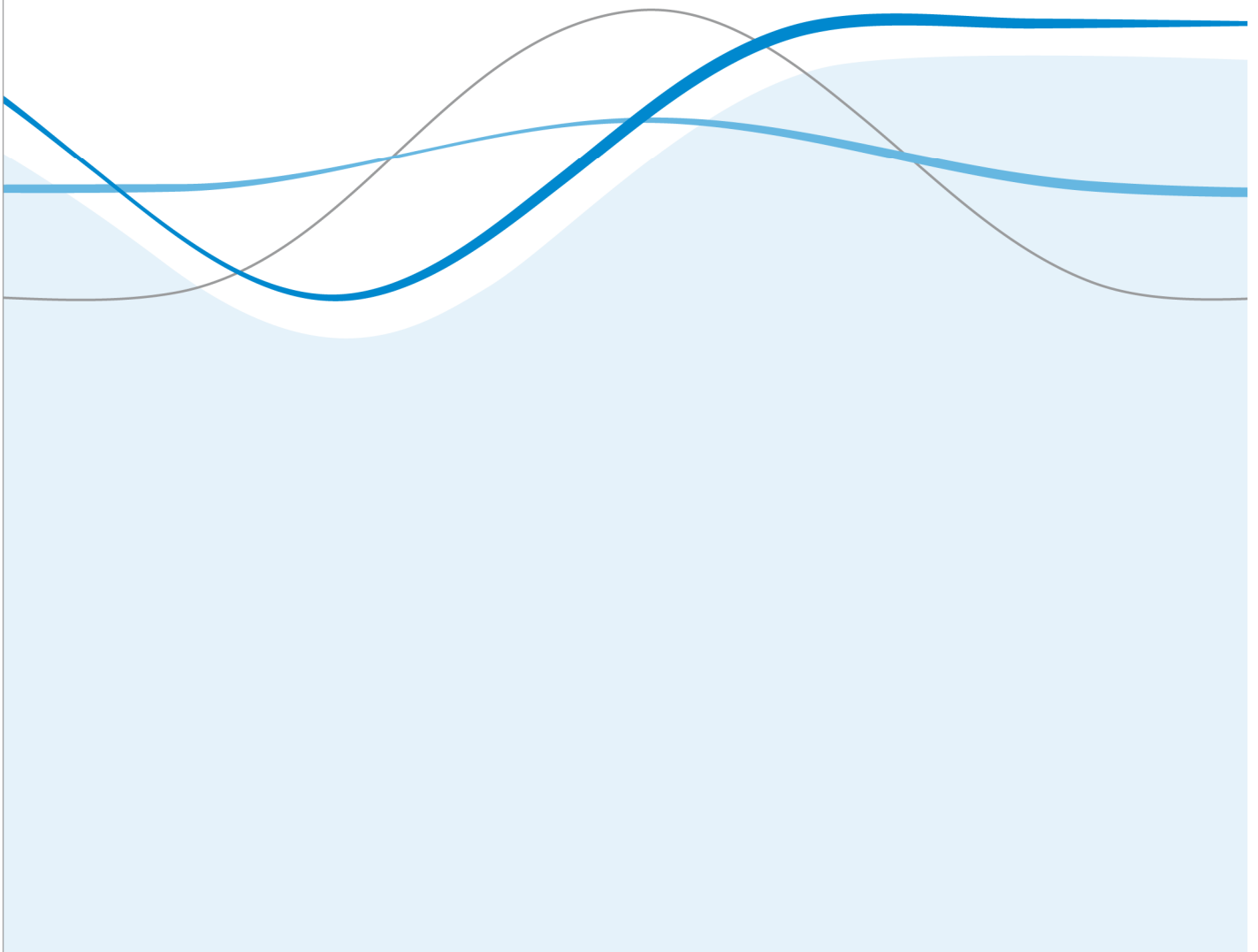# The Expanding Value Footprint of Oncology Treatments

May 2014

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Consulting Report

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The Expanding Value Footprint of Oncology Treatments

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EXECUTIVE SUMMARY

Introduction

- Cost containment has long been a preoccupation of payers in health care systems, and allocating resources to where they are most cost-effective is becoming an ever more pressing imperative. Many payers have established health technology assessment (HTA) activities to inform decisions about whether or not to reimburse new technologies and how much to pay.
- Drugs used in the treatment of cancer patients tend to be more expensive than those in most other therapeutic areas.
- Furthermore, at the time of initial regulatory approval, the health outcome gains from the use of new cancer drugs are often seen as being quite modest, particularly when reported in terms of additional months of survival. The high costs of cancer drugs, combined with the limited evidence about their impact on key health outcome measures in real-world settings, makes for a challenging HTA environment.
- Many new cancer drugs have a therapeutic potential well beyond their initial indication. For example, many oncology drugs can be used to treat a variety of tumours, not just the tumour type that they were originally approved for.

Objectives

- This analysis seeks to provide a better understanding of how changes in the use of an oncology medicine can affect its aggregate value. Specific objectives are to:
  - describe, in both qualitative and quantitative terms, the expansion of value (from the initial clinical value demonstrated at the time of regulatory approval) associated with a cohort of oncology drugs;
  - develop a series of matrices that capture the various sources of value expansion for each of the drugs, and that summarise how these value expansions were assessed and perceived by HTA processes for product valuation in three different health systems;
  - discuss how a range of issues have been addressed within the selection of drugs and HTA systems.

Methodology

- We build on a previous analysis that examined value expansions for a limited selection of oncology treatments. We adopt a more robust methodology, examining all oncology medicines approved by the EMA between 2003 and 2005 – giving a cohort sample of 10 medicines. This choice of time period was guided primarily by our understanding that many oncology medicines that have been on the market for eight years or longer are likely to have been approved for additional indications during this time. The 10 medicines are (in alphabetical order): Alimta, Avastin, Busilvex, Erbitux, Faslodex, Litak, Lysodren, Tarceva, Velcade and Zevalin.
- Our framework sets out seven possible value expansions beyond a given product's initial approved indication: use in different cancer type; use in different disease stage; use in different treatment line/stage; use in different treatment

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regimen; orphan designation; patient sub-population; and use in new route of administration.

- We then assessed how three payers/HTA bodies have recognised, or not, these value expansions: HAS in France, NICE in England and Wales, and Aetna in the US. We chose three very different HTA bodies/payers to highlight how differences in the approach to the assessment of value can impact how value is recognised. Due to the differences between the different bodies (and the data they make publicly available), it is difficult to make "like-for-like" comparisons.
- Finally, we analysed IMS data (between Q1 2004 and Q3 2013) on prices, volumes and sales for the five medicines associated with the largest number of value expansions.

Key results

- Our analysis support previous analyses; seven of the 10 medicines in the cohort sample have additional value expansions following initial indication. Only one of the seven non-orphan drugs has yet to experience a value expansion. Many are now used for indications that are very different from the indication for which they were first approved.
- We have identified a far greater number of decisions made by Aetna (131) than by either HAS (30) or NICE (24) on these value expansions. Aetna has issued guidance on indications that have not been approved by the EMA (and subsequently have not been assessed by HAS or NICE). However, there are some important limitations associated with the data available on the Aetna website.
- Over half of all Aetna judgements extracted (53%) refer to the product being deemed "experimental and investigational" rather than "medically necessary". All of the products in our cohort that have Aetna judgements listed on its website are assigned to copay tier 5 by Aetna (the tier associated with the highest level of copayment).
- The majority of HAS assessments (80%) resulted in positive recommendations. However, none of the drugs/indications in our study achieved the highest possible ASMR rating of level I, and only 37% per cent of the assessments resulted in ASMR rating levels that recognise medicines as "innovative": thus, the remainder were deemed as providing little or no additional value.
- The majority of NICE appraisals (63%) resulted in the drug/indication not being recommended for use in the NHS. For NICE, we identified only one full recommendation without any restriction.
- NICE's recently introduced supplementary end-of-life policy played an important role: Alimta was recommended for use in one of its indications despite its estimated cost-effectiveness being beyond the range normally considered acceptable by NICE. It should also be noted that patients in England and Wales have access to some of the non-recommended medicines via the Cancer Drugs Fund (CDF).
- We have identified examples of "value expansions" which refer to the revisiting of earlier decisions and restrictions of use to smaller patient groups for whom the drug works better. Although the outcomes for those patient groups will be improved as a result, manufacturers may not receive the full rewards from this expansion in value.

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- Our analysis of the IMS data focused on the five drugs with most value expansions: Avastin, Velcade, Erbitux, Tarceva and Alimta. Sales for these five medicines represent around 95% of total sales for the 10 medicines in each country in the last year of available data.

- Prices for individual medicines were imputed by dividing sales (in local currency) by volume (expressed in milligrams) and then converted into USD to enable comparisons across the three countries. Prices from IMS are at list prices and do not capture any discounts to third party payers.

- Overall, the UK had lower prices, volumes and sales than France and the US, but with three provisos: volume for Erbitux is highest in the UK in the latter years; UK price is higher than US price in the earlier years for Velcade; by the end of the time period UK prices relative to France are above 90% for Velcade and Tarceva, and higher for Avastin.

- The comparisons between France and the US were a little more equivocal. For two medicines – Avastin and Erbitux – prices in France were lower than in the US during the whole period. Launch prices for Alimta and Tarceva were similar in the US and France, but after one or two years the French price is lower. Prices for Velcade in France were always higher than in the US. Volumes (per 100,000 people) in France were for four medicines – Avastin, Ertibux, Tarceva and Alimta – higher than the US by 2013; and in one case — Erbitux — significantly so by the end of the period of analysis.

- There is a mixed picture in terms of the correlation between NICE/HAS recommendations and sales in the UK/France. In France, there are cases where uptake has taken off in advance of HAS decisions. Usually the drug in question was made available via the Temporary Authorisations for Use system, which allows medicines to be made available prior to marketing authorisation.

- For the UK, two points are worth raising. First, there are instances where sales have increased after the introduction of the CDF – Avastin, Velcade and Erbitux. Second, for Velcade, Erbitux, Tarceva and Alimta, there is an upward inflexion in sales at the time of a positive (albeit restricted) NICE recommendation.

- Unsurprisingly there is a *prima facie* link between expansions in licensed indications and changes in sales. In a number of cases, we observe strong growth in use as the first post-launch label expansions occur, followed by a flattening or reduction in usage. This could be due to increased competition or changes in treatment patterns for the first approvals, which might then offset the increased opportunity of further expansions of value.

Discussion

- In general, the higher the estimated gains in overall survival, the more likely HAS is to award a higher ASMR level; likewise with NICE, higher overall survival leads to a greater chance of positive recommendations. This relationship is less clear-cut for NICE than for HAS. But both agencies take into account factors other than survival gains when making decisions, such as unmet need and equity.

- In England and Wales, NICE's supplementary policy for appraising life-extending end-of-life treatments appears to be leading to more positive decisions for cancer products, and the CDF (established in 2010) provides access for medicines not recommended by NICE. We could thus infer that the UK government believes that the current HTA system for England and Wales is not appropriate for assessing

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the value of oncology treatments and has set up an alternative route to ensure access to these medicines. Post-CDF, the proportion of oncology drugs being rejected by NICE has increased relative to pre-CDF.

- A key issue going forward for the UK is what will happen to the CDF when the new value-based assessment process is implemented in 2014. The UK Government announced in 2013 an extension to the CDF until 2016 (originally it was supposed to run until the end of March 2014) so the two systems will run in parallel for some time. It is unclear what will happen after 2016. If the CDF is abolished, will that imply the end of reimbursement for medicines currently included under it? Will NICE be more likely to recommend new cancer medicines in the absence of the CDF? Will NICE change its processes for oncology treatments? The relevance and impact of changes in the UK are important given the global attention on NICE, particularly from emerging markets.

- In order to understand the monetary value conferred by the value expansions identified in this study, it is possible to develop dynamic multi-indication, life-cycle drug assessments using an annual cohort-based approach. This requires data on patients initiating treatment with the medicine (by indication) and estimates of the mean incremental cost-effectiveness ratio for each indication or line of treatment.

- A number of researchers have called for flexible, indication-specific pricing for medicines in order to better reflect their expanding value over time. However, few HTA systems allow for flexible pricing schemes in principle, and almost none do in practice.

- Evaluating drugs only on the basis of their value at launch may fail to capture their importance for future developments. It has been argued that when a drug has not only a current value but also an option for additional value, and this option value is not rewarded adequately by payers, this may result in suboptimal R&D spending from a societal welfare economic perspective. Going forward, earlier engagement to discuss the potential future value expansions of drugs under assessment could lead to more positive HTA decisions.

Conclusions and policy recommendations

- This report demonstrates the need for health systems and policy makers to recognise how product life-cycle considerations affect the value of medicines, and in particular, oncology medicines.

- Furthermore, since HTA processes for branded, innovative medicines generally aim give to greater rewards to more significant innovations, it is important to understand that the innovativeness of a given product can be demonstrated in terms of the ways in which its value expands across over time

- We identify five research questions that should be developed further:
  - First, the question of whether HTA systems based on both clinical *and* cost-effectiveness should treat oncology treatments differently from non-oncology treatments (as has been observed for orphan drugs in some jurisdictions).
  - Second, the question of whether – and if so, how – HTA processes should take into account explicitly the issue of path dependency (i.e. temporal interdependencies among indications) when assessing new medicines at launch. One option would be for early dialogue between the HTA agency

and the manufacturer to discuss any future value expansions that depend on the success of the indication being assessed. There are pros and cons associated with this early dialogue, but the issue merits further research.

o Third, the question of whether and how pricing and reimbursement systems should move away from "one price across all indications" to more "flexible pricing" approaches, where flexible pricing can entail differential pricing by indication and/or by patient subgroup (and ultimately, across markets and – depending on the nature of the health insurance coverage – across income groups within the same market).

o Fourth, the question of what factors drive uptake of medicines in practice.

o Fifth, the question of the extent to which the issues identified for oncology treatments – value expansions, path dependency, and multiple indications – are also applicable to non-oncology treatments.

- There are a number of reforms (either being proposed or underway) to the HTA / product valuation systems in France and the UK. It is too early to know what the effects will be of the new value-based assessment system in the UK and the move towards the "*Index Thérapeutique Relatif*" and possibly the use of cost-effectiveness in France. The issues raised in this report should be considered when designing the new systems.

1. INTRODUCTION AND CONTEXT

Cost containment has long been a preoccupation of payers in health care systems, and allocating resources to where they are most cost-effective is becoming an ever more pressing imperative. Many payers have established health technology assessment (HTA) activities to inform decisions about whether or not to reimburse new technologies. In England and Wales, for example, cost-effectiveness is assessed according to a prescribed set of methods (NICE, 2013) that links the prices of technologies to the health benefits that they confer, and the resulting incremental cost-effectiveness ratio (ICER) estimates are compared to a threshold that represent what is considered acceptable and affordable for the National Health Service (NHS).

Drugs used in the treatment of cancer patients tend to be more expensive than those in most other therapeutic areas, due in part to relatively high (and increasing) research and development (R&D) costs and an apparent greater willingness to pay for health gains in this disease area (Seabury et al., 2012). Underpinning these higher R&D costs for cancer treatments is the complexity of the science in this therapeutic area which ultimately leads to longer clinical development stages (Mestre-Ferrandiz, Sussex and Towse, 2012) and lower success rates, especially in the expensive Phase III trials (DiMasi and Grabowski, 2007). The high and rising cost of cancer drugs presents a growing concern for payers, given the increasing incidence of cancer in countries with ageing populations (Yancik, 2005).

Furthermore, the health outcome gains from the use of new cancer drugs are often quite modest, particularly when reported in terms of overall survival at the time of initial regulatory approval. It can be very difficult to demonstrate in a clinical trial that a medicine improves overall survival because of the lengthy period of time and increased numbers of patients that are required to demonstrate a benefit (Shah et al., 2013). Although regulatory agencies often grant marketing authorisation to medicines based on alternative endpoints such as progression-free survival, the use of such "surrogates" for overall survival is not always deemed acceptable by HTA agencies. The acceptability of surrogate endpoints is one of several differences that can often arise between the requirements of regulators, whose approvals are based on benefit-risk assessments, and those of payers, whose reimbursement decisions tend to be based on relative-effectiveness or cost-effectiveness assessments (EMA, 2011a). In addition, there are differences in evidentiary needs across different HTA bodies. For instance, the comparator in a multi-national trial may represent standard therapy in some European countries but not in others. Such differences might make it more challenging to ensure a wider recognition of value from different HTA bodies at launch.

The high costs of cancer drugs, combined with the limited evidence of their impact on key health outcome measures, makes for a challenging HTA environment. For example, three biological treatments for colorectal cancer – cetuximab, bevacizumab and panitumumab – have mostly failed to receive positive recommendations from HTA

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agencies that consider cost-effectiveness (in those cases where positive recommendations were achieved, these tended to be with restrictions on patient eligibility). Shah et al. (2013) report that although agencies considered these medicines to be effective in generating health improvements, they were typically deemed too expensive for the benefit they deliver.

1.1 Incremental innovation in oncology

Assessments of drugs by payers and HTA agencies are typically conducted at the time of (or soon after) drug launch for the initial indication. Yet many new cancer drugs have a therapeutic potential well beyond their initial indication. Ethical and safety considerations dictate that the drugs are first tested for second- or third-line therapy for patients with advanced disease (Garrison and Veenstra, 2009). If efficacy is demonstrated amongst the most severely ill patients who have limited proven treatment options, the drug can be tested at earlier stages of disease progression (for example, moving from use in metastatic disease to adjuvant use) and for earlier lines of therapy. It is in these subsequent indications that patients tend to be healthier and more robust, thereby increasing the likelihood of clinical response. The approval of subsequent indications is often contingent upon success in those developed first (Garrison and Veenstra, 2009; Lu et al., 2012). Furthermore, Garrison (2010) has argued: "It is clear that within the current (global) system, we would want to give greater life cycle rewards to products that create greater aggregate value, other things equal." This analysis aims to provide a better understanding of how changes in the use of a medicine can affect its aggregate value.

As well as being used for different treatment lines and at different stages of disease, a number of oncology drugs can be used to treat a variety of tumour types, not just the one that they were approved for use in. In a study of additional indications approved post-launch in the US, the Boston Consulting Group (2007) highlighted the example of Avastin (bevacizumab), approved by the US Food and Drug Administration (FDA) for the treatment of metastatic carcinoma of the colon and rectum in 2004, but now also approved for advanced nonsquamous non-small cell lung cancer (NSCLC), metastatic kidney cancer and glioblastoma; as well as being explored for its potential for use in several other cancer types and indications. The Boston Consulting Group study also reported that one third of the new indications for biological drugs were approved within three years of, and another third were approved more than seven years after, the initial indication.

In a study sponsored by PhRMA, Boston Healthcare Associates described the expansion of value associated with a small number of high profile oncology treatments (Goss, Picard and Tarab, 2012). They identified the following pathways by which additional clinical value is often recognised:

- Use in the initial approved indication

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- Use earlier in treatment line and easier disease stage
- Use in different disease indications
- Use in combination with other agents
- Use in combination with specific biomarkers

Figure 1 illustrates one example included in Goss, Picard and Tarab (2012).

For the four case studies of Gleevec (imatinib), Taxotere (docetaxel), Herceptin (trastuzumab) and Erbitux (cetiximab), the authors produced simple diagrams that demonstrated how the clinical value of these products expanded over time via the aforementioned pathways. However, a limitation of the Boston Healthcare Associates study is that the sample appears to be biased in favour of products that experienced considerable value expansion. We would expect that a less purposively selected sample would include at least a few products that experienced few or no expansions of value following initial approval. Another limitation is that the expansions of value are described in qualitative terms for a very small number of case studies, so it is difficult to detect any meaningful trends or draw strong conclusions from the analysis. In this study we seek to build on the framework developed by Boston Healthcare Associations whilst seeking to apply a rigorous and unbiased methodology.

Figure 1. Expansion in clinical value of Taxotere (docetaxel) over time
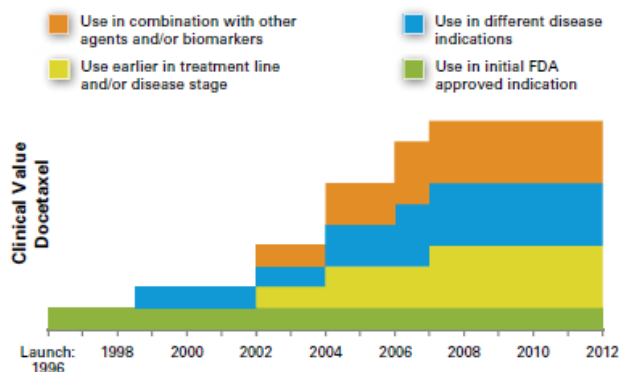
Source: Goss, Picard and Tarab (2012).

A number of other researchers have highlighted the importance of taking into account the long-term benefits of innovative health technologies. According to Refoios Camejo et al. (2013), resources may be misdirected and affordable future health benefits foregone if the dynamics of the factors driving cost-effectiveness potential are not considered. They call for decision-making frameworks to consider explicitly the innovation path (and the potential contribution of each use of each intervention) to better outcomes.

Garrison and Veenstra (2009) note that "the aggregate economic value delivered by a new medicine will ultimately be determined by the different types and number of patients using it over its life cycle, and this may include totally new indications." They

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argue that a short-term perspective focusing on efficacy or cost-effectiveness on an indication-by-indication basis (as taken by payers in Europe and the US) will offer a different view from a long-term perspective that takes into account the interdependence of drug development decisions and expanded indications over time. Building on the work of Garrison and Veenstra, Lu et al. (2012) developed a set of models that measured the long-term cost-effectiveness of two cancer drugs, paclitaxel and docetaxel, through their life cycles. They report that the subsequent uses of the drugs in less severely ill patients tended to be associated with improved clinical benefit and cost-effectiveness estimates, and conclude that the standard methods of cost-effectiveness analysis might not capture accurately the true, long-term value of the drugs.

On the other hand, Fojo and Grady (2009), amongst others, have questioned the assumption that approval of "expensive drugs with marginal overall benefit" will act as a stepping stone to further discoveries that will generate greater benefits and hence give payers a greater return on their investment than was initially apparent. Such scepticism highlights the importance of assessing the available evidence and improving people's understanding of how the value footprint of oncology treatments develops over time.

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2. TERMS OF REFERENCE

OHE Consulting was commissioned by Lilly Global Public Policy to:

- Describe, in both qualitative and quantitative terms, the expansion of value (from the initial clinical value demonstrated at the time of regulatory approval) associated with a cohort of oncology drugs.
- Develop a series of matrices that capture the various sources of value expansion for each of the drugs, and that summarise how these value expansions were assessed and perceived by three HTA/product valuation systems.
- Analyse data on prices, volumes and usage for our cohort of oncology drugs in the countries of interest, covering the time span of our analysis.
- Discuss how a range of issues have been addressed within the selection of drugs and HTA systems. These include: payers' consideration of situations where it is evident that the initial assessment was associated with high and uncertain cost-effectiveness or low added clinical benefit; whether additional evidence of health outcome (in an already reimbursed indication or tumour type) changed the perception of value and if so, how that was reflected in pricing; the role played by biomarkers and companion diagnostics; and whether recent reforms to the selected HTA/product valuation systems have affected the likelihood of oncology products realising their value.

3. OUR APPROACH

We undertook a staged approach, summarised in Figure 2.

Figure 2. Our staged approach
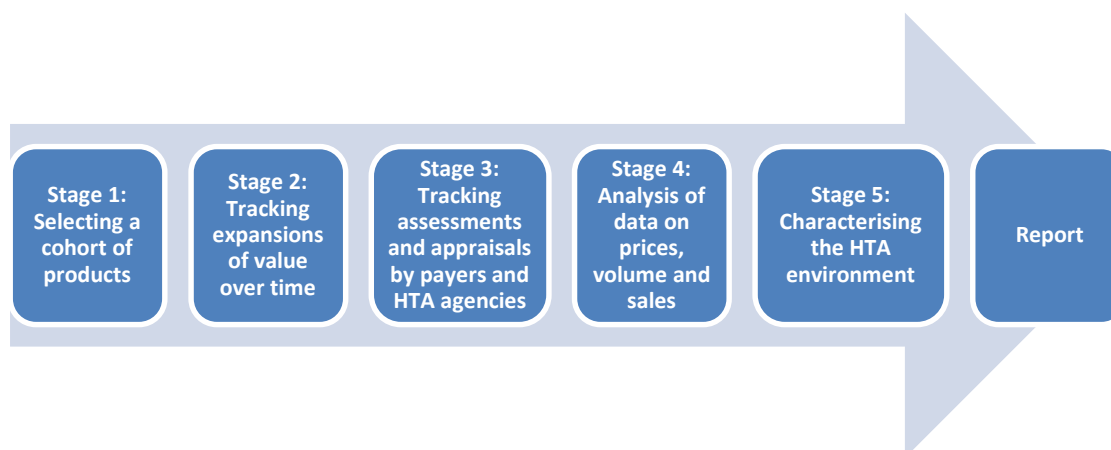
The main sources of data for the study were as follows:

- reviews of regulatory approvals described in the European Public Assessment Reports (EPARs) available for download from the website of the European Medicines Agency (EMA);
- reviews of the websites of the manufacturers of the selected products;
- reviews of the technology assessment and/or appraisal reports available for download from the websites of three payers/HTA agencies:
  - National Institute for Health and Care Excellence (NICE; England and Wales; non-departmental public body of the Department of Health)
  - *Haute Autorité de Santé* (HAS; France; independent public body set up by the French government)
  - Aetna (US; private payer with headquarters in Connecticut)
- IMS for the data on prices, volumes and sales.

Our choice of payers/HTA agencies was guided by the Request for Proposals. This stated that it would be useful to include three archetypes of HTA/product valuation in the analysis, including: a) a cost per QALY-based system such as England/Wales; b) an "added clinical benefit"-based system such as France; and c) a value-based benefits-based system such as the US. In addition, we had to consider agencies that publish their decisions, as well as the criteria used to reach those decisions. Both NICE and HAS publish their decisions on their respective websites.

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For the US, we considered three payers that publish product assessment information on their websites: UnitedHealthcare, BlueCross BlueShield Association (via their Technology Evaluation Center) and Aetna. Once we had agreed our cohort of products, we checked the three payers' websites to identify which one contained the greatest level of information about those products; this was Aetna.

It was agreed that scope of the study would be restricted to EMA-approved drugs/indications, acknowledging the limitation that this could exclude indications approved by the FDA (but not the EMA) that may be of relevance to Aetna.

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4. STAGE 1: SELECTING A COHORT OF PRODUCTS

We began by identifying all of the new drug and biologic assessments listed on the EMA website over the period 2003 to 2005. This choice of time period was guided primarily by our understanding that many medicines that have been on the market for eight years or longer are likely to have been approved for additional indications during this time (Boston Consulting Group, 2007). If we had instead looked at medicines that were first approved more recently – say, since 2008 – then many of the potential additional therapeutic indications would likely still be in development at the time of writing. In order to avoid bias, we wished to select a series of products that had been approved chronologically rather than "cherry-picking" those products that we expected to be of particular interest.

The data were extracted from the EMA website on 22 July 2013. We identified 80 products with assessment dates between 1 January 2003 and 31 December 2005. The status of 65 of these products was "Authorised"; the remaining 15 products were described as being "Withdrawn", "Refused" or "Suspended".

Eleven of the 80 products were identified as being oncology drugs. These are set out in Table 1. One of the drugs, Yondelis, had not been authorised by the EMA and was therefore excluded from the cohort sample. Excluding Yondelis left a cohort of 10 drugs, which was considered by the Steering Group to be within the scope of and agreed budget for the study. One of the drugs was given authorisation in 2003; two were given authorisation in 2005; and the remaining seven were given authorisation in 2004. Three of the 10 drugs – Busilvex, Litak and Lysodren – had been given orphan designation by the EMA.

Table 1. Oncology drugs assessed by the EMA between 2003 and 2005

Medicine	Generic name	Authorisation Holder	Status	Authorisation date	Orphan?
Busilvex	busulfan	Pierre Fabre Médicament	Authorised	09/07/2003	Yes
Zevalin	ibritumomab tiuxetan	Spectrum Pharmaceuticals B.V.	Authorised	16/01/2004	No
Faslodex	fulvestrant	AstraZeneca UK Ltd.	Authorised	10/03/2004	No
Litak	cladribine	Lipomed GmbH	Authorised	14/04/2004	Yes
Velcade	bortezomib	Janssen-Cilag International NV	Authorised	26/04/2004	No
Lysodren	mitotane	Laboratoire HRA Pharma	Authorised	28/04/2004	Yes
Erbitux	cetuximab	Merck KGaA	Authorised	29/06/2004	No
Alimta	pemetrexed	Eli Lilly Nederland B.V.	Authorised	20/09/2004	No
Avastin	bevacizumab	Roche Registration Ltd.	Authorised	12/01/2005	No
Tarceva	erlotinib	Roche Registration Ltd.	Authorised	19/09/2005	No
Yondelis	trabectedin	Pharma Mar S.A.	Refused	-	No

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5. STAGE 2: TRACKING EXPANSIONS OF VALUE OVER TIME

In this section, we propose a new framework to capture and describe different types of value expansions that are relevant to oncology treatments. We then apply this framework to our cohort of medicines in order to examine how the value of that cohort has expanded over time.

5.1 Developing a framework for value expansions

We used Boston Healthcare Associates' report (Goss, Picard and Tarab, 2012) as the point of departure for our model for categorising dimensions of value. We have added three others we deemed appropriate: orphan designation, patient sub-population and use in new route of administration. We used the section of the EMA website where all European Public Assessment Reports (EPARs) are published as our source of data (EMA, 2013). We first extracted the decisions from initial marketing authorisation documents, and then the decisions from the changes since initial authorisation of the medicine (revisions, variations and extensions of indication) agreed by the Committee of Human Medicinal Products (CHMP). We extracted the data available online on 22nd July 2013.[1] This information was extracted for the 10 oncology drugs and biologics that received initial EMA approval between 2003 and 2005. As noted in the previous section, the choice of time period was driven by our understanding that medicines that have been on the market for eight or more years are likely to have been approved for additional indications during that time (Boston Consulting Group, 2007).

The Boston Healthcare paper proposed five pathways by which additional clinical value is usually identified: use in the initial approved indication; use earlier in treatment line and earlier disease stage; use in different disease indications; use in combinations with other agents; use in combination with specific biomarkers. As well as proposing three supplementary sources of value as mentioned above, we propose a conceptual model to represent how these sources may be interpreted. Figure 3 presents all seven sources of value in hierarchical order. This order can be understood as a necessary order of appearance and of relative relevance; i.e. the treatment regimen is specified within a given treatment line/stage, which in turn is specified within a given disease stage of a given cancer type. This categorisation helps identify the type of value expansion that reflects best what each of the EPARs studied represents. For instance, if a drug that was previously approved for use as first-line treatment of metastatic disease is then approved as second-line treatment of locally advanced disease, then this value expansion would be categorised as "Use in different disease stage".

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[1] Please note that summaries of positive opinion are published without prejudice to the Commission decision, which is normally issued within 44 days (Type II variations) and 67 days (Annex II applications) from adoption of the opinion. This may mean that decisions made less than 44 or 67 days prior to our cut-off date have not been included in our database.

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Most of the sources proposed are self-explanatory and are described using commonly used terms. Below we provide brief explanations and examples for those that we have added to or modified from the Boston Healthcare paper.

We broadened Boston Healthcare's "Use earlier in treatment line" category to cover changes in the stage of treatment as well as changes in the treatment line that the drug under study is authorised for. For instance, "Use in different treatment line/stage" refers to the use of a drug in a treatment line other than the one indicated at initial approval. But it also includes changes in treatment *stage* within a given disease stage (e.g. an extension of indication to cover maintenance treatment in addition to first-line and second-line treatment). This should not be confused with "Use in different treatment regimen", which refers solely to changes to the treatment combinations the drug under study may be used for within a given treatment line (e.g. a drug that was previously used as first-line in combination with two other given chemotherapy agents receives an extension of indication to be used as monotherapy or in combination with different agents).

The two additional categories of value that we have included in our model do not necessarily fit within a specific position of the linear order we propose in our model of value expansions and appear to be largely independent of the other categories.

An extension of indication to include a new patient sub-population would constitute an expansion of value within a given cancer type, but can appear at any point during the lifetime of the drug regardless of disease stage, treatment line or treatment regimen. Later we discuss in greater detail how we model "patient sub-population" as a value expansion within our cohort of drugs.

We also included a category to represent the approval of a new route of administration. The key benefit of this type of innovation is often to improve patients' experience of care. In our cohort, a subcutaneous form of Velcade was approved as an alternative to intravenous administration for patients with difficult vein access. The literature shows that patients' preferences for one administration over another can be expressed in terms of positive impact on quality of life (Matza et al., 2013). Additionally, the treatment efficacy is the same for the indications for which Velcade was approved at the time, but it is more appropriate for patients with difficult vein access improving some aspects of their safety profile (EMA, 2012). Our understanding is that this type of value expansion is not directly related to the other categories of value and may appear at any point during the lifetime of a product for the indications for which the medicine was previously already authorised. Therefore, we find it most appropriate to represent our model as shown below, leaving the entry points of the categories "Patient sub-population" and "New route of administration" open (Figures 3, 4 and 5).

Furthermore, we observed that the EMA gave orphan designation to three of the 10 drugs in our cohort. Orphan designation has the particularity that it is obtained prior to initial approval. We included "orphan designation" in our diagrammatically representation of value expansions when relevant but not in our model to interpret value expansions over time beyond initial approval.

Figure 4 represents hypothetically the sequence of value expansions that a treatment could follow. Figure 5 builds on Figure 4 and is a representation of the range of possible value expansions that a treatment could experience over its life cycle within the model we propose. For simplicity we have shown two possible expansions for each source of value, but in reality there could be more (e.g. Figure 5 could be expanded to show early stage disease as well as the metastatic and locally advanced stages).

The approach we use is intended to provide a comprehensive set of pathways of value expansions and a common understanding of how to interpret EPARs as types of value expansion. These additions to the existing literature will help to facilitate discussions amongst payers and manufacturers about the true value footprint of oncology drugs and biologics over their life cycles.

Figure 3. Hierarchical framework

Initial approval (e.g. metastatic colorectal cancer)

    ↳ **Cancer type** (e.g. breast cancer)

        ↳ **Disease stage** (e.g. locally advanced)

            ↳ **Treatment line/stage** (e.g. first-line)

                ↳ **Treatment regimen** (e.g. as monotherapy, initial approval being in combination with chemotherapy)

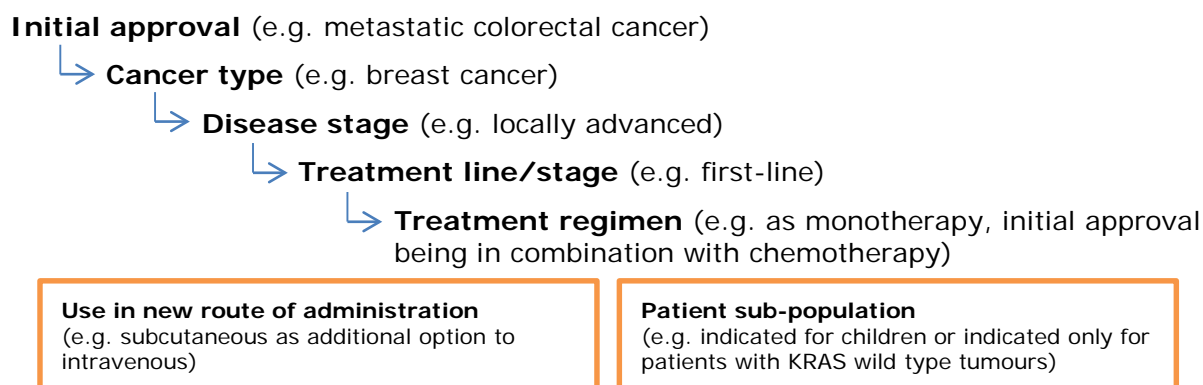|	
Use in new route of administration (e.g. subcutaneous as additional option to intravenous)	**Patient sub-population** (e.g. indicated for children or indicated only for patients with KRAS wild type tumours)

Figure 4. Example of two types of value expansion from initial approval
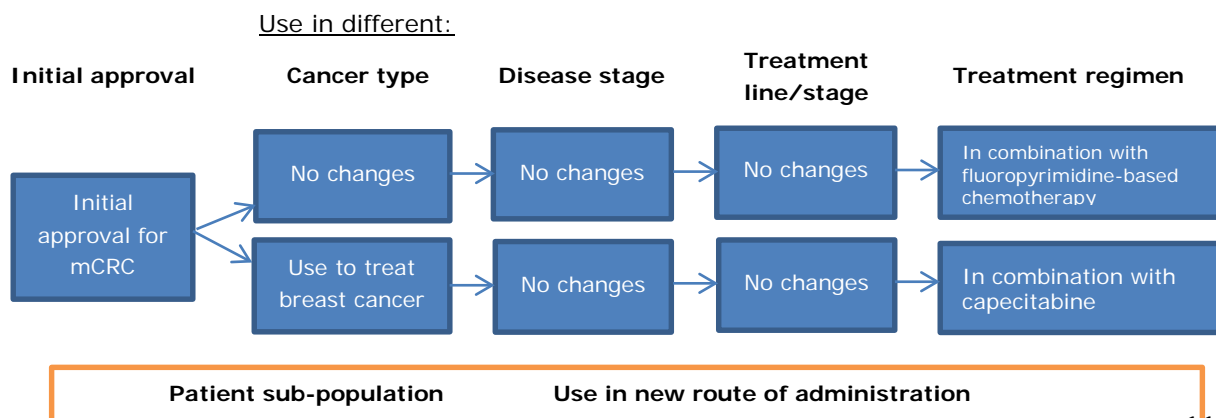
Figure 5. Range of possible value expansions over the life cycle of a product
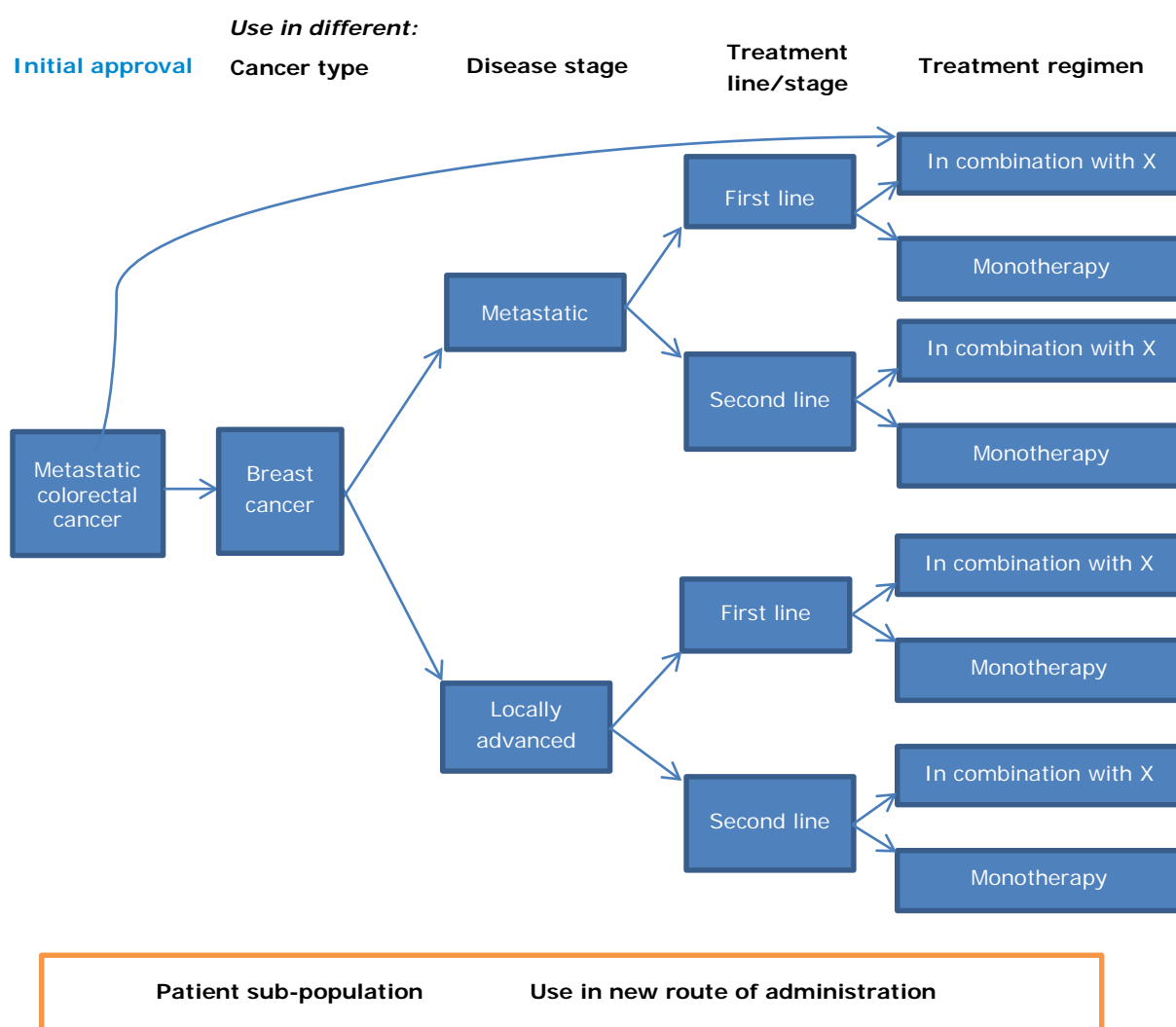
5.2 Applying the framework to our cohort of medicines

Figure 6 shows the expansions of value since initial approval for our cohort of 10 oncology drugs that received EMA initial approval between 2003 and 2005. Three of the 10 oncology drugs did not receive further approvals in the time period observed (January 2000 to July 2013) beyond their initial indication (Faslodex, Litak, Lysodren). Two of these three received orphan designation prior to their initial approval (Litak and Lysondren). We can see in this figure that nine of the 10 drugs were indicated for one type of cancer at launch. Only Alimta was indicated for more than one cancer type at initial approval. There are six expansions related to new cancer types in our cohort of drugs within the time period observed. Two drugs were each approved for one new cancer type over the time period observed (Erbitux and Tarceva), while Avastin was approved for four new cancer types.

One drug experienced a value expansion related to the disease stage that it can be used for (Erbitux: approved for use in locally advanced squamous cell cancer of the head and neck in 2008; then approved for recurrent and/or metastatic disease in 2008).

"Use in different treatment line/stage" was the most frequent value expansion, with 10 such value expansions for six drugs in our cohort (three for Alimta, one for Avastin, one for Erbitux, two for Tarceva, two for Velcade and one for Zevalin). Six value expansions fell under the category "Use in different treatment regimen" (four for Avastin and two for Erbitux). It is worthwhile highlighting that for Erbitux, the change in treatment regimen in 2008 came together with the precondition that patients suffer from KRAS wild type metastatic colorectal cancer. According to the findings presented in the relevant EPAR update, the activity of Erbitux treating metastatic colorectal cancer appears largely to be confined to patients with tumours expressing wild type KRAS (EMA, 2008a). Similarly, in 2008 the approval of Alimta for use in an earlier treatment line in the treatment of NSCLC came with the precondition that the type of cancer is "other than predominantly squamous cell histology". This precondition applied both for the newly approved first-line indication and for the previously approved second-line indication (EMA, 2008b). This precondition persists in subsequent authorisations for NSCLC.

A total of three drugs in our cohort obtained orphan designation prior to initial approval (Busilvex, Litak, Lysodren).

The dimension "Patient sub-population" requires some discussion. Three value expansions were categorised as "Patient sub-population". They correspond to: Busilvex, which was approved for paediatric use in 2005 after initial approval in 2003 for adult patients; Alimta, which was approved for use to other than predominantly squamous cell histology NSCLC in 2008; and Erbitux, which was approved for KRAS wild type metastatic colorectal cancer in 2008.

Broadly speaking, this category can comprise value expansions derived from an extension of indication to include a broader patient population (i.e. extension of indication for use in paediatric population after an initial indication for adult patients) or from a different indication to target the treatment to a smaller patient sub-population more likely to benefit from the treatment (i.e. as a consequence of the use of a biomarker for patient stratification purposes). Busilvex represents a value expansion for the first possibility - a treatment indication for adults was later expanded to include children. When an oncology drug is to be approved for use in paediatric patients for the same indication as it was previously approved in adults, extrapolation of efficacy data is acceptable and safety and pharmacokinetic data for paediatric patients would constitute the main body of the submission (EMA, 2005).

Examples of the second value expansion include Alimta in its use to treat NSCLC, for which a precondition that the cancer treated was other than predominantly squamous

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cell histology was approved in 2008; and Erbitux, for which the precondition that patients suffer from KRAS wild type metastatic colorectal cancer was approved also in 2008.

It is important to note that when a medicine receives the authorisation to treat a specific patient sub-population within any one indication it can apply to all approvals in that cancer type (e.g. the cases of Erbitux and Alimta), but it can also affect exclusively the extension of indication being approved. The last example is not regarded in our model as a "patient sub-population" value expansion. For example, Tarceva was approved in 2011 for use in first-line for patients with NSCLC with EGFR activating mutations; we have considered this as a value expansion "new treatment line/stage for that indication". The rationale behind is that the targeting of a patient sub-population for Tarceva only applies to its use in the newly approved treatment line for a cancer type whereas for Alimta and Erbitux the targeting of patient sub-population applies to all uses of those drugs to treat NSCLC and metastatic colorectal cancer respectively. However, we treat the indications of use in a new treatment line/stage and new treatment regimen of Alimta and Erbitux respectively, also as value expansions of their own due to the use of a biomarker to define a new patient sub-population. The same rationale used for Tarceva also applies to Avastin, which was first approved for the treatment of NSCLC other than predominantly squamous cell histology in 2007. In this case we assigned the value expansion of this extension of indication to its use in a new cancer type.

In 2012 Velcade obtained approval for use in a new route of administration, as subcutaneous use as an alternative to IV injections that are inconvenient for patients with poor vein access.

Altogether, seven of the 10 oncology products under study experienced expansions of value beyond their initial indications (Figure 6). These findings are in line with those of Boston Healthcare paper (Goss, Picard and Tarab, 2012). Since our cohort of products, however, considers all drugs approved within a specified period rather than a convenience sample or "hand-picked" set of examples, this adds robustness and generalisability to our findings. The EMA approvals described above reflect how the EMA recognised expansions in the clinical value of the products in our cohort over time. In different countries, the overall value of therapies is recognised differently by payers. In the next section we will analyse how three different payers appraised the 10 products in our cohort.

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Figure 6. Expansions of value since initial approval for the study cohort
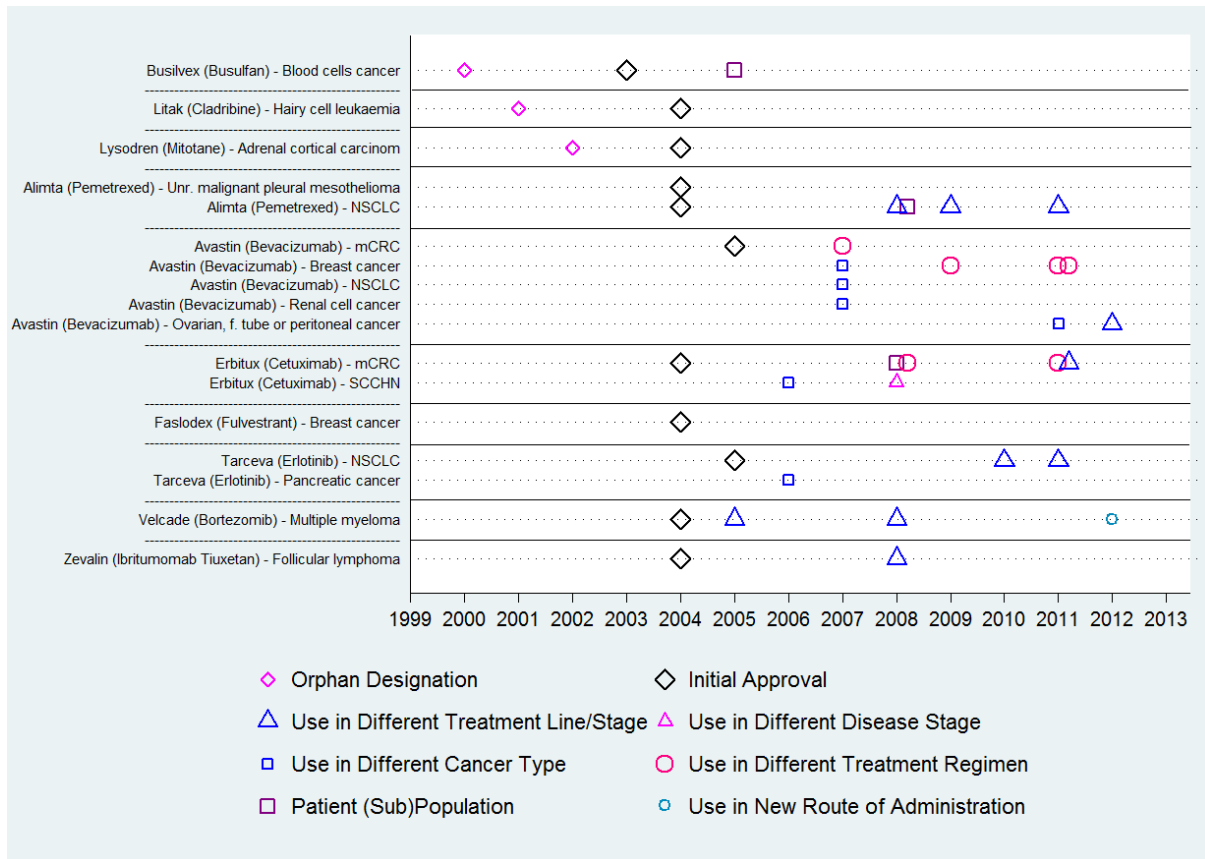
The full list of EMA authorisations included in our analysis is shown in Table 2.

Table 2. List of 39 EMA authorised indications included in the analysis

No.	Product name	Complete approved indication (taken directly from the EPAR)
1	Alimta (pemetrexed)	Alimta in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.
2	Alimta (pemetrexed)	The benefit/risk ratio of Alimta as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy was favourable, and therefore recommended the granting of the marketing authorisation.
3	Alimta (pemetrexed)	Alimta in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.
4	Alimta (pemetrexed)	Alimta is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.
5	Alimta (pemetrexed)	Alimta is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.
6	Avastin (bevacizumab)	Avastin (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
7	Avastin (bevacizumab)	In combination with paclitaxel is indicated for first-line treatment of patients with locally recurrent or metastatic breast cancer.
8	Avastin (bevacizumab)	Extension of the indication for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology, in addition to platinum-based chemotherapy.
9	Avastin (bevacizumab)	In combination with interferon alfa-2a for first-line treatment of patients with advanced and/or metastatic renal cell cancer.
10	Avastin (bevacizumab)	In combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.
11	Avastin (bevacizumab)	Avastin in combination with paclitaxel or docetaxel is indicated for first-line treatment of patients with metastatic breast cancer.
12	Avastin (bevacizumab)	Bevacizumab in combination with paclitaxel for the treatment of first-line metastatic breast cancer.
13	Avastin (bevacizumab)	Avastin in combination with capecitabine is indicated for first-line treatment of metastatic breast cancer in whom treatment with other chemotherapy options anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.
14	Avastin (bevacizumab)	In combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
15	Avastin (bevacizumab)	In combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelian ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
16	Busilvex (busulfan)	Busulfan (intravenous use) for the conditioning treatment prior to haematopoietic-progenitor-cell transplantation.

No.	Product name	Complete approved indication (taken directly from the EPAR)
17	Busilvex (busulfan)	Busilvex is indicated as conditioning treatment prior to haematopoietic progenitor cell transplantation in adult patients when the combination of busulfan and cyclophosphamide (Bu/Cy2) is considered the best available option.
18	Busilvex (busulfan)	Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.
19	Erbitux (cetuximab)	The benefit/risk ratio of Erbitux in combination with irinotecan in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy was favourable and therefore recommended the granting of the marketing authorisation.
20	Erbitux (cetuximab)	Erbitux in combination with radiation therapy is indicated for the treatment of patients with locally advanced squamous cell cancer of the head and neck.
21	Erbitux (cetuximab)	Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)- expressing, KRAS wild-type metastatic colorectal cancer: in combination with chemotherapy; as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.
22	Erbitux (cetuximab)	Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.
23	Erbitux (cetuximab)	Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy or FOLFOX4.
24	Erbitux (cetuximab)	Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)- expressing, KRAS wild-type metastatic colorectal cancer in first-line in combination with FOLFOX.
25	Faslodex (fulvestrant)	The therapeutic indication for Faslodex is for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant antioestrogen therapy or disease progression on therapy with an antioestrogen.
26	Litak (cladribine)	Treatment of indolent non-Hodgkin's lymphoma.
27	Litak (cladribine)	Litak administered subcutaneously has a positive benefit/risk ratio in the first-line treatment of patients with hairy cell leukaemia
28	Lysodren (mitotane)	Treatment of adrenal carcinoma
29	Lysodren (mitotane)	The CPMP considered by majority decision that the benefit/risk profile of Lysodren was favourable in the treatment of adrenal cortical carcinoma. The CPMP considered that the indication should be restricted to unresectable adrenal carcinoma (i.e. no possible surgical removal of tumour or metastases, or incomplete removal of tumour and/or metastases). Mitotane is clinically beneficial for the symptomatic treatment of patients with advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma.
30	Tarceva (erlotinib)	The CHMP considered that the benefit-risk ratio of Tarceva indicated for: "the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR negative tumours (see section 5.1)" was favourable and therefore recommended the granting of the marketing authorisation.

No.	Product name	Complete approved indication (taken directly from the EPAR)
31	Tarceva (erlotinib)	Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival advantage could be shown for patients with locally advanced disease.
32	Tarceva (erlotinib)	Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.
33	Tarceva (erlotinib)	Tarceva is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations.
34	Velcade (bortezomib)	The CPMP considered that the benefit/risk ratio of bortezomib in the treatment of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy, was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.
35	Velcade (bortezomib)	Velcade is indicated as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.
36	Velcade (bortezomib)	Velcade in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.
37	Velcade (bortezomib)	The CHMP considers by consensus that the risk-benefit balance of Velcade 3.5mg powder for solution for injection for subcutaneous use, as monotherapy for the treatment of patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation and in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant, is favourable and therefore recommends the granting of the extension of the marketing authorisation.
38	Zevalin (ibritumomab tiuxetan)	Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Zevalin in the treatment of patients with rituximab-relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL) was favorable and therefore recommended the granting of the marketing authorization under exceptional circumstances.
39	Zevalin (ibritumomab tiuxetan)	The [90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established.

Source: Stage 3 database.

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6. STAGE 3: TRACKING ASSESSMENTS AND APPRAISALS BY PAYERS AND HTA AGENCIES

In this section, we identify and review the assessments undertaken by our three payers/HTA agencies of interest (NICE, HAS and Aetna) for each of the EMA-approved indications set out in Stage 2. We present the "value footprint" of each product graphically using novel diagrams (see Figures 7 to 16).

Appendix II describes in detail the process used by HAS, NICE and Aetna to assess medicines.

6.1 Methodology and data sources

Our search for assessments and appraisals of the 10 products in our cohort was undertaken in November 2013. Below we describe the strategy used to identify and extract the relevant information made publicly available by the three agencies.

For NICE: we conducted searches of the HTAinSite database (www.htainsite.com) using the "recommendation by product" feature to identify all appraisals that NICE had made publicly available for our cohort of drugs by the cut-off date. HTAinSite's contents at the time of data extraction include all appraisals up to and including TA 295 (published in August 2013). In cases when information was required beyond HTAinSite's summary tables, we downloaded the original appraisal documentation (guidance document, assessment report, manufacturer submission), accessed via HTAinSite's "View appraisal guidance documents" section.

For HAS: we included appraisals identified both in French and in English. To identify the relevant appraisals we used the search engine available on the HAS website (www.has-sante.fr) under the heading "Rechercher un medicament". Searches were conducted using both the brand names and the international non-proprietary names of the products. We then scanned the search results to identify the records that were relevant to the drug that we were searching for.

For Aetna: we used the information contained in the Clinical Policy Bulletins (CPBs) available on Aetna's website for those drugs in our cohort for which there was a CPB available (http://www.aetna.com/healthcare-professionals/policies-guidelines/cpb_alpha.html). Information on the copayment tier of each product was taken from the 2013 Aetna Comprehensive Formulary Drug List (Premier) (Aetna, 2013a).

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Once all of the relevant information had been extracted, we matched the EMA authorised indications (Table 2) with the assessments that NICE and HAS had undertaken of those indications. If the HTA agency recommended the value expansion in full (i.e. the entire indication, as approved by the EMA), we classified the decision as "recommended". If the HTA agency rejected the value expansion by not recommending any part of the EMA-approved indication for public reimbursement, we classified the decision as "not recommended". If the HTA agency recommended the value expansion only for a subgroup of the patient population covered by the EMA authorisation but not for the entire EMA-authorised population, then we classified the decision as "recommended with restrictions". For HAS, some of decisions were classified as "recommended with further guidance". This typically refers to assessments in which the HAS Transparency Committee called for a follow-up monitoring study, with the guidance that the product should be review again when the data from the follow-up study become available. As mentioned below, it is difficult to make "like-for-like" comparisons across the three bodies.

Extraction and interpretation of NICE ICERs

When extracting NICE appraisal data we originally sought to summarise cost-effectiveness estimates by organising the reported ICERs into one of two categories: (1) lower than £30,000 per quality-adjusted life year (QALY) gained, the upper limit of the range normally considered acceptable (NICE, 2013b); and (2) higher than £30,000 per QALY gained. However, we observed that multiple ICERs are often reported for a given indication, either because of uncertainty or because different ICERs were estimated for different patient sub-populations. It was not always the case that all ICERs (or the entire ICER range) could be assigned to the same category. We therefore included a third category: (3) multiple ICERs estimated, of which some were lower than and some were higher than £30,000 per QALY gained. Because of the difficulties in interpreting situations where multiple ICERs were reported, we considered it to be more meaningful to use our graphs (Figures 7 to 16) to present whether each indication as a whole was recommended/not recommended/recommended with restrictions, rather than to attempt to summarise whether or not the entire indication was considered to be cost-effective.

Limitations of the available Aetna data

The information in the CPBs that Aetna makes publicly available on its website comes with an important caveat that limits the scope of our analysis for this payer. The dates when decisions were made by Aetna are available in the "policy history" box of the CPBs. These are often linked to the changes that were made to the original CPB on each individual date. However, not all dates have a link available that allow us to access information about the changes that were made to the CPB on those dates. Furthermore, the CPBs present lists of indications that are "medically necessary" or "experimental and investigational" as an introduction to a number of paragraphs that describe the evidence base available for the drug. However, the description of the evidence refers to the drug as a whole rather than focusing on specific indications. This, combined to the unlinked policy history dates, means that each CPB effectiveness comprises two independent parts without a clear link between them: the evidence base and the dates when that

evidence base was used to make judgements about the uses of the drug – that is, whether they were considered medically necessary or experimental and investigational for the indications under review.

6.2 Database of payer decisions and judgements

The Excel database of payer and HTA agency decisions and judgements includes the following fields:

General

- **EMA Authorisation** – which EMA authorisation/value expansion (as identified in Stage 2) does this assessment refer to?
- **Agency** – NICE/HAS/Aetna
- **Name of product** – brand name and generic name

Approved indication

- **Complete Approved Indication** – full description of indication under assessment, taken directly from the relevant report
    - o **Cancer Type** – as defined in Stage 2
    - o **Disease Stage** – as defined in Stage 2
    - o **Treatment Line** – as defined in Stage 2
    - o **Treatment Regimen** – as defined in Stage 2
    - o **Patient Subgroup** – as defined in Stage 2

Assessment/appraisal information

- **Appraisal number** – relevant for NICE and Aetna, who allocate numbers to their appraisals/judgements
- **Issue date** – when was the guidance first issued?
- **Review date** – when was the guidance reviewed, or when is it due to be reviewed?
- **Link** – URL for the relevant assessment report or clinical policy bulletin

Decision

- **Summary** – e.g. recommended/recommended with restriction/not recommended/medically necessary
- **Full decision** – taken directly from the relevant report

Headline impact on health outcomes

- Overall survival (product under assessment) – in months
- Overall survival (comparator) – in months
- Gain in overall survival vs. comparator – in months
- **Significance** – was the gain in overall survival considered to be statistically significant?
- Median progression-free survival – in weeks or months
- Gain in progression-free survival vs. comparator – in weeks or months

- **Significance** – was the gain in progression-free survival considered to be statistically significant?
- **From the Document** – detailed description of the impact on health outcomes, taken directly from the relevant report

Rationale

- Aetna
    - **Tier** – copayment tier, where tier 1 (lowest copay amount) covers preferred generic prescription drugs; tier 2 covers non-preferred generic prescription drugs; tier 3 covers preferred brand name prescription drugs; tier 4 covers non-preferred brand name prescription drugs; and tier 5 covers specialty drugs – as noted in Aetna (2013a)
    - **Requirements/limitations** – any requirements or limitations specified – e.g. prior authorisation (does Aetna require the patient or their provider to get prior authorisation for this drug?); step therapy (does Aetna require the patient to try other drugs first in order for the drug under review to be covered?)
- NICE
    - **ICER** – best estimate of incremental cost-effectiveness ratio (or range), where reported
    - **Comparison of ICER to threshold** – was the reported ICER (or range) smaller or greater than £30,000/QALY gained?
    - Manufacturer model base case ICER
    - Assessment group (ERG) base case ICER
    - **End of life criteria applied?** – was the drug considered under NICE's supplementary criteria for assessing life-extending, end of life medicines?
- HAS
    - **ASMR** – improvement in medical service (*amelioration du service medical rendu*) rating
    - **SMR** – medical value (*service medical rendu*) rating
    - **Efficacy/adverse effects ratio** – high / important / significant / low
    - **Alternative Medicines?** – did the report state that there are alternative treatments available?
    - **Public Health Benefit** – expected public health impact, as stated in the report
- **From the document** – full description of the rationale behind the decision, taken directly from the report

Other

- Dosage
- **Target population** – target population covered by the drug/indication under assessment, taken directly from the relevant report
- Other potentially relevant information

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6.3 Overall summary tables

Table 3 summarises the total number of decisions/judgements extracted, for each product and agency (listed in alphabetical order). Unsurprisingly, the products with greater numbers of EMA authorised indications (e.g. Avastin) are associated with greater numbers of decisions and judgements by payers and HTA agencies. Indeed, three products – Alimta, Avastin and Erbitux – account for approximately three-quarters of all decisions/judgements extracted.

Table 3. Number of decisions/judgements extracted, by product/agency

Product	EMA	Aetna	HAS	NICE	Total
Alimta (Pemetrexed)	5	25	5	4	39
Avastin (Bevacizumab)	10	60	7	8	85
Busilvex (Busulfan)	3	0	2	0	5
Erbitux (Cetuximab)	6	28	4	5	43
Faslodex (Fulvestrant)	1	0	1	1	3
Litak (Cladribine)	2	0	1	0	3
Lysodren (Mitotane)	2	0	1	0	3
Tarceva (Erlotinib)	4	0	5	3	12
Velcade (Bortezomib)	4	16	3	3	26
Zevalin (Ibritumomab Tiuxetan)	2	2	1	0	5
Total	39	131	30	24	224

Source: Stage 3 database.

We identified a far greater number of decisions made by Aetna (131) than by either HAS (30) or NICE (24). Our understanding is that this is because Aetna has issued guidance on indications that have not been approved by the EMA (and subsequently have not been assessed by HAS or NICE). For example, in August 2013 the CPB for Alimta has revised to state that it is considered medically necessary for the treatment of urothelial carcinoma of the prostate. This does not match any of the EMA-approved indications for Alimta that we identified in Stage 2. Indeed, Aetna has issued guidance on the use of Alimta for more than 10 different types of cancer; by comparison, the EMA has approved its use for only two (NSCLC and malignant pleural mesothelioma).

A detailed examination of FDA-approved indications was outside the scope of this project, as we decided at project initiation to focus only on EMA-approved indications. Nevertheless, information on the FDA website (FDA, n.d.) shows that the FDA-approved indications are the same as those approved by the EMA, which indicates that some of Aetna's guidance relates to off-label use of the drugs for indications that are yet to receive regulatory approval.

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Three products – Busilvex, Litak and Lysodren – were assessed by HAS but our search strategy did not identify any instances of them being considered by either Aetna or NICE. This is likely to be linked to the fact that these three products are designated as orphan drugs (see Table 1). NICE does not usually assess orphan medicines.

Table 4 summarises the decisions and judgements made by Aetna, HAS and NICE. Over half of all Aetna judgements extracted (52.7%) refer to the product being deemed "experimental and investigational" rather than "medically necessary". The majority of HAS assessments (80.0%) resulted in positive recommendations, whereas the majority of NICE appraisals (62.5%) resulted in the drug/indication not being recommended for use in the NHS. Most of NICE's positive recommendations involved some form of restriction being imposed (for example, restrictions to the patient populations). This is examined in greater detail throughout the remainder of this report.

Table 4. Summary of decisions and judgements, by agency

Decision/judgement	Aetna	HAS	NICE	Total
Experimental and investigational	69 (52.7%)	N/A	N/A	69
Medically necessary	62 (47.3%)	N/A	N/A	62
Not recommended	N/A	2 (6.7%)	15 (62.5%)	17
Recommended	N/A	24 (80.0%)	1 (4.2%)	25
Recommended with further guidance	N/A	3 (10.0%)	0 (0.0%)	3
Recommended with restrictions	N/A	1 (3.3%)	8 (33.3%)	9
Total	131	30	24	185

Source: Stage 3 database.

Tables 5 and 6 summarise the HAS decisions following assessment of the 10 products together with the SMR (Table 5) and ASMR (Table 6) ratings given to those products. See Appendix II for the definitions of SMR and ASMR, and for the criteria used for HAS to determine SMR and ASMR ratings.

Table 5. HAS – summary of decisions, by SMR

Decision	Level I High	Level II Important	Level III Moderate	Level IV Low	Level V Insufficient	Total
Not recommended	0	0	0	0	2	2
Recommended	1	23	0	0	0	24
Recommended with further guidance	0	3	0	0	0	3
Recommended with restrictions	0	0	0	1	0	1
Total	1	26	0	1	2	30

Source: Stage 3 database.

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Table 6. HAS – summary of decisions, by ASMR

Decision	Level I	Level II	Level III	Level IV	Level V	N/A	Total
Not recommended	0	0	0	0	0	2	2
Recommended	0	2	7	9	6	0	24
Recommended with further guidance	0	2	0	0	1	0	3
Recommended with restrictions	0	0	0	0	1	0	1
Total	0	4	7	9	8	2	30

Source: Stage 3 database.

Note: N/A refers to observations where the medicine received a Level V (insufficient) SMR rating, thus no ASMR rating was provided.

Of the 30 HAS assessments considered in this study, only two resulted in "not recommended" decisions. In these cases (both of which refer to assessments of Tarceva), the SMR rating given was level V (insufficient) and no ASMR rating was given. The vast majority of assessments (90.0%) were associated with SMR ratings of level I (high) or level II (important) – these assessments all resulted in "recommended" or "recommended with further guidance" decisions. These results are similar to the overall picture in 2008 (which is the latest information we have identified summarising SMR/ASMR for any one year) – see Appendix II.

None of the drugs/indications in our study achieved the highest possible ASMR rating of level I. Thirty-seven per cent of the assessments resulted in ASMR rating levels of II or III. Medicines given ASMR levels I, II or III are recognised as "innovative" (CEPS, 2004), whereas medicines given ASMR levels of IV or V would not normally be considered to be eligible for inclusion on the formulary list covering costly hospital medicines (*Secretariat d'etat a la Sante*, 2010; see Appendix II). There does not appear to be a clear link between the ASMR level and the decision about whether to recommend the use of a drug – most of the drugs/indications with the lowest possible ASMR rating (level V) were nevertheless given "recommended" decisions (though their low ASMR rating will have implications for the pricing of the drug).

Table 7 summarises the NICE decisions extracted together with the ICERs estimated for the relevant product/indication. Three ICER categories are presented: (1) all ICERs for the product/indication under appraisal were *lower* than £30,000 per QALY gained, the upper limit of the range normally considered acceptable (NICE, 2013b); (2) all ICERs for the product/indication under appraisal were *higher* than £30,000 per QALY gained; and (3) multiple ICERs were estimated (for different patient subgroups), of which some were lower than and some were higher than £30,000 per QALY gained.

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Table 7. NICE – summary of decisions, by ICER category

Decision	ICER(s) < £30k/QALY	ICER(s) > £30k/QALY	ICERs both < & > £30k/QALY	No ICER given	Total
Not Recommended	0	11	0	4	15
Recommended	0	1	0	0	1
Recommended with restrictions	3	2	3	0	8
Total	3	14	3	4	24

Source: Stage 3 database.

We identified only one example of a NICE appraisal resulting in a full recommendation without any restrictions being made to the indication – Alimta for the maintenance treatment of NSCLC. The estimated ICER was £47,000 per QALY gained, which is above the range normally considered acceptable. However, the product/indication was deemed by the Appraisal Committee to fulfil the criteria for consideration under NICE's supplementary advice for the appraisal of life-extending end of life treatments (NICE, 2009).

There were three cases of NICE estimating ICERs that were lower than £30,000 per QALY gained but still imposing restrictions on the recommendations. In all three cases, the estimated ICERs were higher than £20,000 per QALY, which is the lower bound of the threshold range.

We identified 15 "not recommended" decisions (62.5% of all NICE decisions extracted). All of these decisions were associated either with estimated ICERs that were higher than £30,000 per QALY or with a failure to report an ICER (e.g. due to uncertainty).

All of the products in our cohort were assigned to copay tier 5 by Aetna (2013a). Patient copayment levels differ according to the tier at which their drug resides, though Aetna states that the actual "copay amounts and coinsurance percentages for each tier vary by Aetna Medicare plan" (Aetna, 2013a; p.7). Tier 5 covers "specialty tier brand and generic prescription drugs" and is associated with the higher copay levels.

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6.4 Drug-by-drug value footprints

6.4.1 Key to markers used in Figures 7 through 16

High Value	Moderate Value	Low or Null Value	Not Value Available
◆ Initial approval-HV	◇ Initial approval-MV	◆ Initial approval-LV	◇ Initial approval-NVA
▲ Dif treatment line/stage-HV	△ Dif treatment line/stage-MV	▲ Dif treatment line/stage-LV	△ Dif treatment line/stage-NVA
▲ Dif disease stage-HV	△ Dif disease stage-MV	▲ Dif disease stage-LV	△ Dif disease stage-NVA
■ Dif cancer type-HV	□ Dif cancer type-MV	■ Dif cancer type-LV	□ Dif cancer type-NVA
● Dif treatment regimen-HV	○ Dif treatment regimen-MV	● Dif treatment regimen-LV	○ Dif treatment regimen-NVA
■ Patient Sub-population-HV	□ Patient Sub-population-MV	■ Patient Sub-population-LV	□ Patient Sub-population-NVA
● New route of administration-HV	○ New route of administration-MV	● New route of administration-LV	○ New route of administration-NVA

For HAS, the classification in based on the ASMR level:

Level I, II or III = high value (green)
Level IV = moderate value (yellow)
Level V = low value (red).

For NICE, the classification is based on the decision:

Recommended = high value (green)
Recommended with restrictions: moderate value (yellow)
• Not Recommended = low or no value (red).

Figures 7 through 16 show how the value footprints of the products in our cohort have developed over time since they were first given marketing authorisation. The figures show how the value expansions recognised in EMA authorisations were later appraised by HAS and NICE leading to one of three outcomes: (1) recommending the use of the drug as it was authorised; (2) recommending the use of the drug but with restrictions to the patient population; or (3) not recommending the use of the drug.

The upper half of the each figure contain the types of value expansions approved in EMA authorisations which were subsequently appraised by NICE and HAS. The shapes of the symbols identify the types of value expansions considered (see key above). Value expansions appear in the same chronological order as approved by the EMA, with the oldest approvals on the left and the most recent approvals on the right of the figure.

The colour coding relates to how the two HTA agencies interpreted the added value of the product: green represents high value; yellow represents moderate value; and red represents low or no added value.

For HAS, we have based this characterisation on the ASMR rating: an ASMR level of I, II and III has been characterised as high value (green), an ASMR level of IV as moderate value (yellow), and a level V as low value (red). As described above and in Appendix II,

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products given ASMR levels of I, II or III are treated differently from those that are given ASMR levels of IV or V.

The colour coding for NICE relates to whether EMA's authorisation was recommended (green), recommended with restrictions (yellow), or not recommended (red). It is important to note that the "recommended with restrictions" category is used when NICE recommended the use of the product for only part of the EMA-authorised indication, rather than when the EMA had itself restricted the population in its marketing authorisation (for example, as it did for Erbitux). In the latter case, the use in a different patient sub-population would be treated as a value expansion in itself. If NICE recommended the drug for the patient sub-population exactly as defined in EMA's corresponding authorisation, then the value expansion would appear as green for NICE. If the patient sub population is not explicitly addressed in the Guidance section of NICE appraisal documents, then the colour of the squared symbol (i.e. value expansion referring to patient sub-population) will be transparent (to denote the fact that no value is available). A "not recommended" decision by NICE has been classified as 'low value' (red).

It is important to clarify that the colour red for NICE is used to denote a lack of access to the therapy, whereas for HAS the colour red is an important predictor for the price that the French health care system will reimburse the drug for (as noted both above and in Appendix II, HAS distinguishes between and differentially rewards drugs based on their level of innovativeness, as summarised by their ASMR level). An alternative approach would have been to apply the NICE colour coding system (green = recommended; yellow = recommended with restrictions; red = not recommended) to HAS. However, the differences between the two HTA systems is such that a "recommended" decision by NICE is very different from a "recommended" decision by HAS. Indeed, most of the HAS assessments resulted in the drug being recommended (see Table 4 – i.e. sufficient SMR level so that the medicine is at least covered partially by public funding): yet, the rewards to the manufacturers were in many cases relatively low because few of the recommended drugs were given ASMR levels I, II or III (Table 6). We believe that our chosen colour coding system better serves our aim of representing graphically the extent to which the value and innovativeness of the products have been recognised and rewarded by the two agencies.

Figures 7 through 16 do not present any information related to Aetna. This is because we were unable to link all Aetna decisions with specific dates (as described above in the "Limitations of the available Aetna data" sub-section) hence any representation of an expanding value footprint over time using Aetna data would be incomplete.

Figure 7 below shows the results for Alimta. The upper part of the figure, as described above, corresponds to the value expansions of this drug since initial approval. Alimta was approved by the EMA in 2004 for two cancer types: NSCLC and malignant pleural mesothelioma. The upper part of the figure is therefore split into two sections – one for

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each cancer type. For the treatment of unresectable malignant pleural mesothelioma, there were no value expansions after 2004. The initially-approved indication has been evaluated by both HAS and NICE. In the case of HAS the green diamond means that HAS awarded Alimta an ASMR level of between I and III ("high value"). The yellow diamond for NICE denotes that the use of Alimta was recommended for this indication but with restrictions to the patient population approved by the EMA.

Regarding the treatment of NSCLC, we can see in Figure 7 that HAS recommended the use of Alimta in all five value expansions approved by the EMA. However, in all cases HAS considered Alimta to provide moderate or low value (shown by the yellow and red shading of the relevant markers, respectively). NICE appraised the use of Alimta for the treatment of NSCLC for four of the five value expansions identified. The Institute recommended Alimta for the first-line treatment of NSCLC (value expansion – Different treatment line/stage: first green triangle), only for patients for whom the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma, which is in line with EMA's approval (value expansion – Patient sub-population: green square). In addition, NICE recommended Alimta as maintenance monotherapy (value expansion – Different treatment line/stage: second green triangle).

The lower half of each graph is a representation of the differences in the number of value expansions that each agency has recommended. When a positive opinion about a value expansion is published by one of the three agencies, the shaded area for that agency increases by one level on the y-axis (an incremental step), which we have labelled as "Number of recognitions of value".

The main idea is to represent the accumulation of value expansions over time: hence, the shaded areas representing the three agencies are superimposed. Each value expansion corresponds to the new use of the drug that the EMA authorises. Recommendations by HAS and NICE are always linked to previous EMA approvals as these HTA agencies only evaluate EMA-approved indications. Thus, a positive recommendation from NICE and/or HAS does not add a *new* value expansion relative to the EMA's approved indication. The superimposition is such that HAS decisions overlap EMA decisions, and NICE decisions overlap both HAS and EMA decisions. This means that if NICE and HAS both approve all EMA-authorised indications without delay, the only colour visible will be the one assigned to NICE. However, if only HAS approved all EMA-authorised indications without delays, the dominant colour will be the one assigned to HAS. There are two reasons why the three agencies overlap in this way: first, EMA is the one that first authorises the use of a drug for a given indication, after which HAS and NICE can either assess or not assess that indication; second, we identified a greater number of assessments by HAS (30) than by NICE (24). This is explained by the fact that NICE does not appraise all indications.

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6.4.2 Alimta

Figure 7. Value footprint of Alimta (pemetrexed)
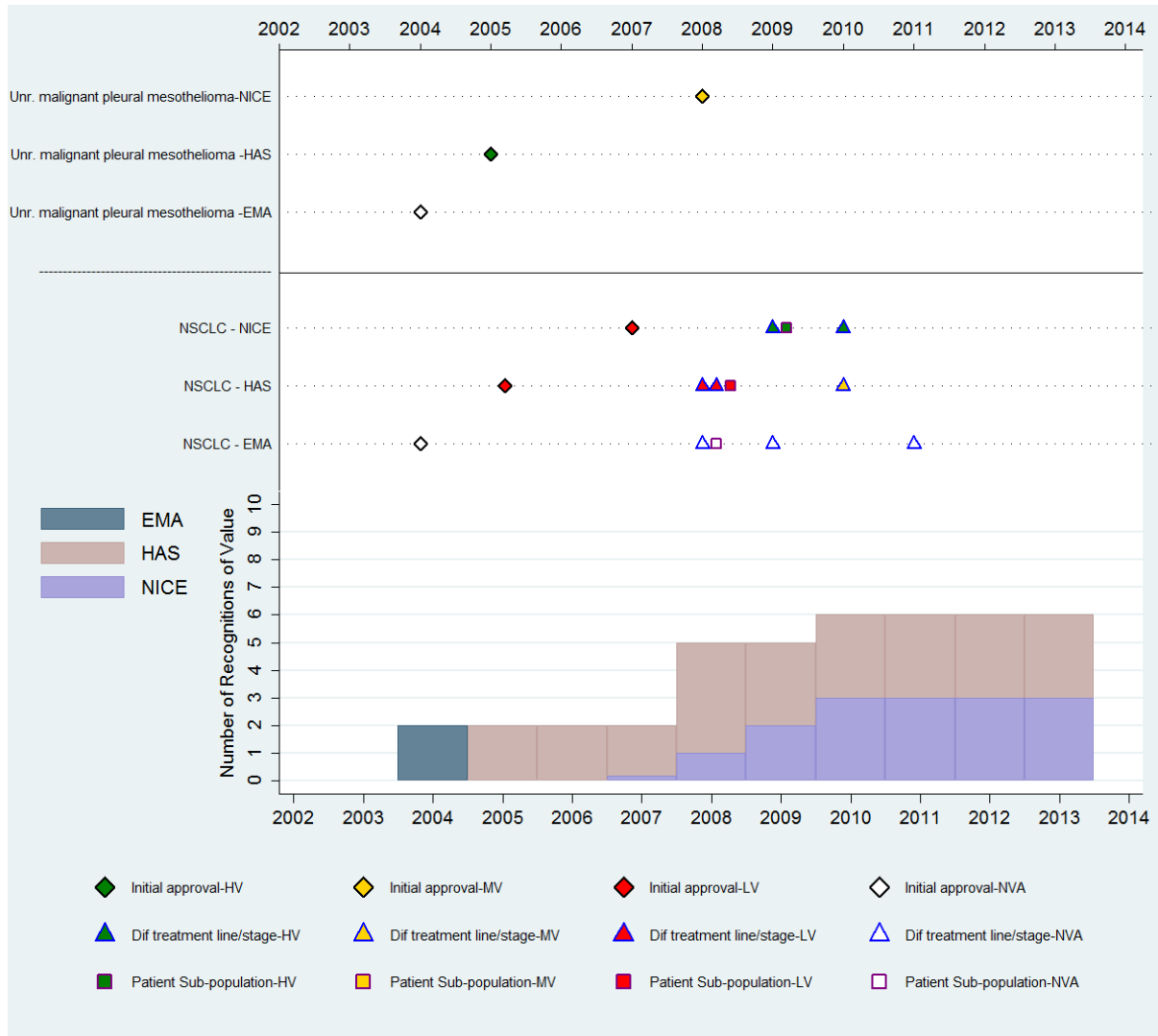
The lower half of Figure 7 shows the two initial EMA-approved indications in 2004 for Alimta. HAS evaluated and recommended the use of Alimta for these two indications in 2005. The colour of the bar in 2005 therefore corresponds to that assigned to HAS. In 2007, NICE evaluated the initial approval related with the treatment of NSCLC, resulting in a negative decision. It is therefore not possible to add a full block (which would be equivalent to a positive decision about a value expansion) for that decision since there was no recognition of the additional value by NICE. Anytime NICE rejects the first indication that it appraises for a given product, this is represented by a thin line with a height of 0.15 on the y-axis (this value is arbitrary and is used here to make interpretation easier for the reader). We do this to distinguish between NICE's first decision being a negative one (thin line) and a delay in NICE conducting its first appraisal (no line). In Figure 7, we see that HAS recommended all six EMA-approved value expansions for Alimta (though the upper part of the figure shows that only in one

of those was it considered to provide a high improvement in actual benefit). NICE, on the other hand, recommended only three.

We note that one of HAS assessments of Alimta was published in November 2008, a few months prior to the EMA authorisation of the indication under assessment (indication 4 in Table 2) being made publicly available. We conjecture that this may be due to the HAS assessment being conducted in anticipation of the then forthcoming EMA approval.

It is worth noting that an orphan designation was granted by the European Commission for Alimta for the treatment of malignant mesothelioma in 2001, but the product was withdrawn from the register of designated orphan drugs in 2004 on request from the sponsor (EMA, 2011b). It therefore does not appear as an orphan-designated drug in our analyses.

We identified 25 Aetna judgements regarding Alimta indications, of which 13 (52.0%) were deemed medically necessary and 12 (48.0%) were deemed experimental and investigational.

6.4.3 Avastin

Figure 8. Value footprint of Avastin (bevacizumab)
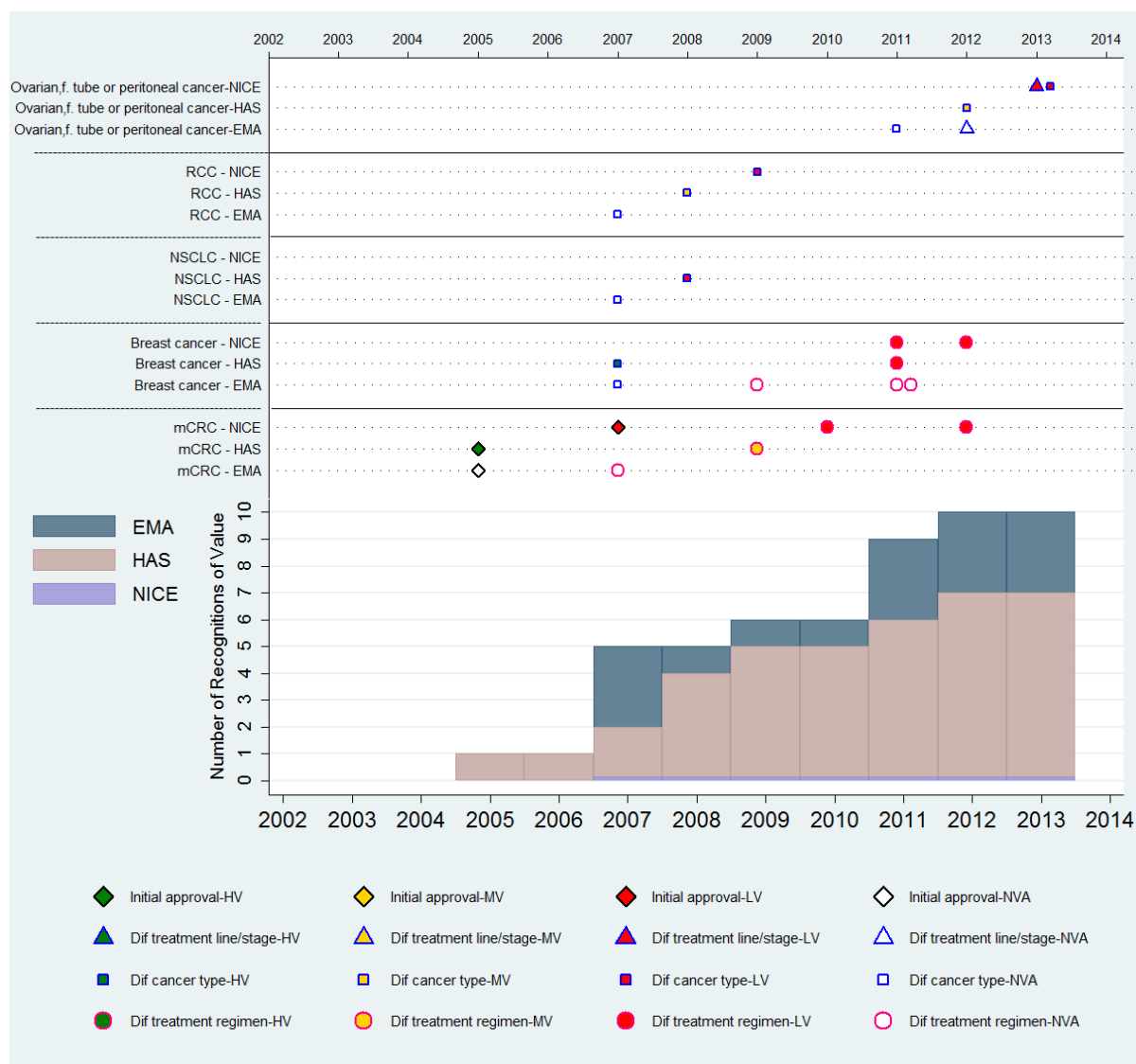
Avastin (Figure 8) was initially authorised for use in metastatic colorectal cancer in 2005 by the EMA. In the same year, HAS recommended it for that indication with a high value tag. Avastin was authorised for use in four other cancer types in subsequent years by the EMA. HAS recommended all value expansions authorised by the EMA except for three indications for which no HAS assessments were identified using our search strategy (which is why at the end of our time period there is an absolute difference of 3 between EMA (10 approved indications) and HAS (seven recommendations/recognitions of value). The value deemed by HAS for each of these value expansions ranges from low value (e.g. treatment of breast cancer in 2011) to high value (e.g. treatment of metastatic colorectal cancer in 2005).

By contrast, NICE published an appraisal in 2007 not recommending the use of Avastin for its initial indication for the treatment of metastatic colorectal cancer (Figure 8). The thin purple line at the bottom of the figure indicates that all NICE appraisals since then resulted in negative opinions (i.e. NICE did not recommend the use of Avastin in any one of the 10 value expansions that the EMA authorised between 2005 and 2013). For some value expansions no NICE appraisal was found using our search strategy (e.g. treatment of NSCLC). The reason why NICE published three technology appraisals for two EMA authorisations is that NICE TA 242 ("Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy", January 2012) was a multiple technology appraisal that updated and replaced NICE TA 118 (Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer, January 2007).

60 Aetna judgements regarding Avastin indications were identified, of which 25 (41.7%) were deemed medically necessary and 35 (58.3%) were deemed experimental and investigational.

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6.4.4 Busilvex

Figure 9. Value footprint of Busilvex (busulfan)

Busilvex (Figure 9) is one of the three drugs in our cohort that received orphan designation prior to its initial EMA approval. The small patient populations that orphan drugs treat and their particularities in terms of market incentives are reasons that may explain why the value of this therapy experienced so few changes over time. However, we also observe that HAS rated both of the uses that the EMA approved this drug for as having a high value.

Busilvex was approved by the EMA as conditioning treatment for hematopoietic progenitor cell transplantation of adult patients in 2003. In 2005 the treatment was also approved for the same indication for paediatric patients, a new patient population. HAS recommended both uses of the drug and regarded them as having a high value. NICE has not published any guidance for this drug in our study period.

We did not identify any Aetna judgements regarding Busilvex.

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6.4.5 Erbitux

**Figure 10. Value expansion of Erbitux (cetuximab)**

Erbitux (Figure 10) has been authorised by the EMA for the treatment of two cancer types: metastatic colorectal cancer and squamous cell cancer of the head and neck (SCCHN). From the EMA, we have identified seven value expansions over the life cycle of Erbitux since 2004, five associated with metastatic colorectal cancer and two for SCCHN. The nature of each value expansion is depicted by the shape, outline colour and size of the symbol. In both indications the shapes of the symbols are the same in some cases. Consequently, to denote that in both indications the nature of the value expansions was different, we used smaller-sized symbols for the value expansions "use in different cancer type", and "use in different disease stage", which can be seen for SCCHN, and larger ones for "use in different treatment line/stage" and "patient sub population", which can be seen for metastatic colorectal cancer (see legend).

Of the EMA-approved value expansions, HAS has recommended four and NICE has recommended two. Both NICE recommendations were recommendations with restrictions to the patient population for which the indication was approved by the EMA: in 2008 the recommended use was restricted to patients whose Karnofsky performance status score is 90% or greater and for whom all forms of platinum based chemoradiotherapy treatment are contraindicated; and in 2009 the recommended use was restricted to surgically fit patients. The value expansion related to the use of Erbitux in a patient sub-population that the EMA captured in 2008 (i.e. patients with epidermal growth factor receptor expressing, KRAS wild-type cancer) was not explicitly addressed in the guidance section of the NICE appraisal documents published in 2009 and 2012. Thus, as explained above, we classified those as having no value available in NICE appraisals.

We identified 28 Aetna judgements regarding Erbitux indications, of which 12 (42.9%) were deemed medically necessary and 16 (57.1%) were deemed experimental and investigational.

6.4.6 Faslodex

**Figure 11. Value footprint of Faslodex (fulvestrant)**
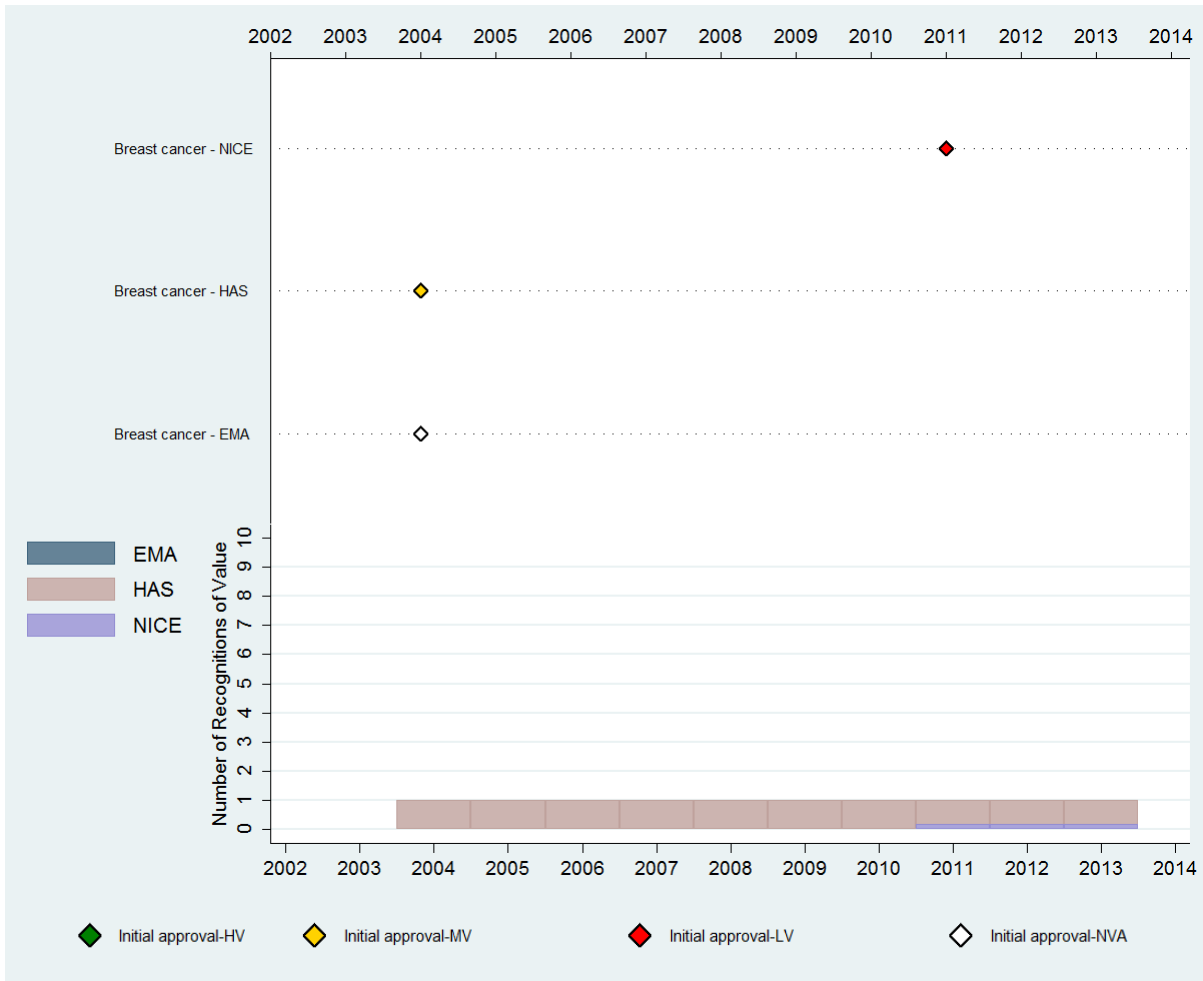
Faslodex (Figure 11) only had one EMA approval, for the treatment of breast cancer, over the period of analysis. HAS recommended Faslodex for this indication with a middle value in the same year that it received EMA approval. However, NICE did not recommend the use of Faslodex when it appraised it some years later.

We did not identify any Aetna judgements regarding Faslodex.

6.4.7 Litak

Figure 12. Value footprint of Litak (cladribine)
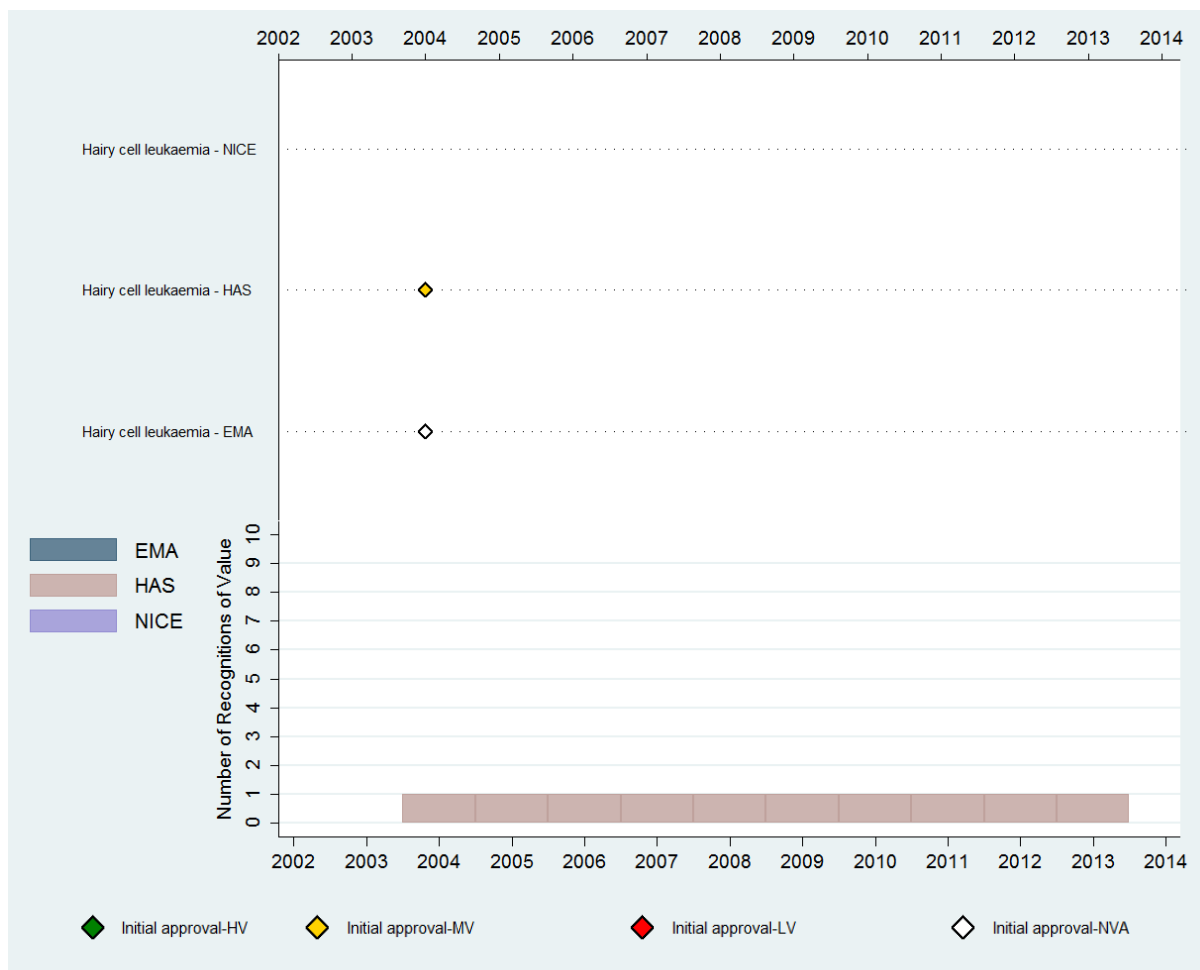
Litak (Figure 12) received orphan designation in 2001. In 2004 the EMA approved Litak for the treatment of hairy cell leukaemia. Later in the same year, HAS recommended the use of Litak for that same indication, tagging it as a treatment of moderate value.

Just as we observed when examining the value footprint of Busilvex (Figure 9), the small patient populations that orphan drugs treat and their particularities in terms of market incentives are reasons that may explain why the value of this therapy experienced no changes over time. However, in this case the value that HAS considered this therapy to confer was not high, as in the case of Busilvex, but moderate.

For NICE, no appraisals were found for Litak.

We did not identify any Aetna judgements regarding Litak.

6.4.8 Lysodren

**Figure 13. Value footprint of Lysodren (Mitotane)**

Lysodren (Figure 13) received orphan designation in 2002. In 2004 it was approved by the EMA for the treatment of adrenal cortical carcinoma. Again, we confirm the pattern that orphan drugs follow in our cohort of drugs of a value footprint, with a very low number of value expansions since initial approval. Just as with Busilvex (Figure 9), the indication approved by the EMA was regarded as having a high value by HAS.

For NICE, no appraisals were found for Lysodren.

We did not identify any Aetna judgements regarding Lysodren.

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6.4.9 Tarceva

**Figure 14. Value footprint of Tarceva**
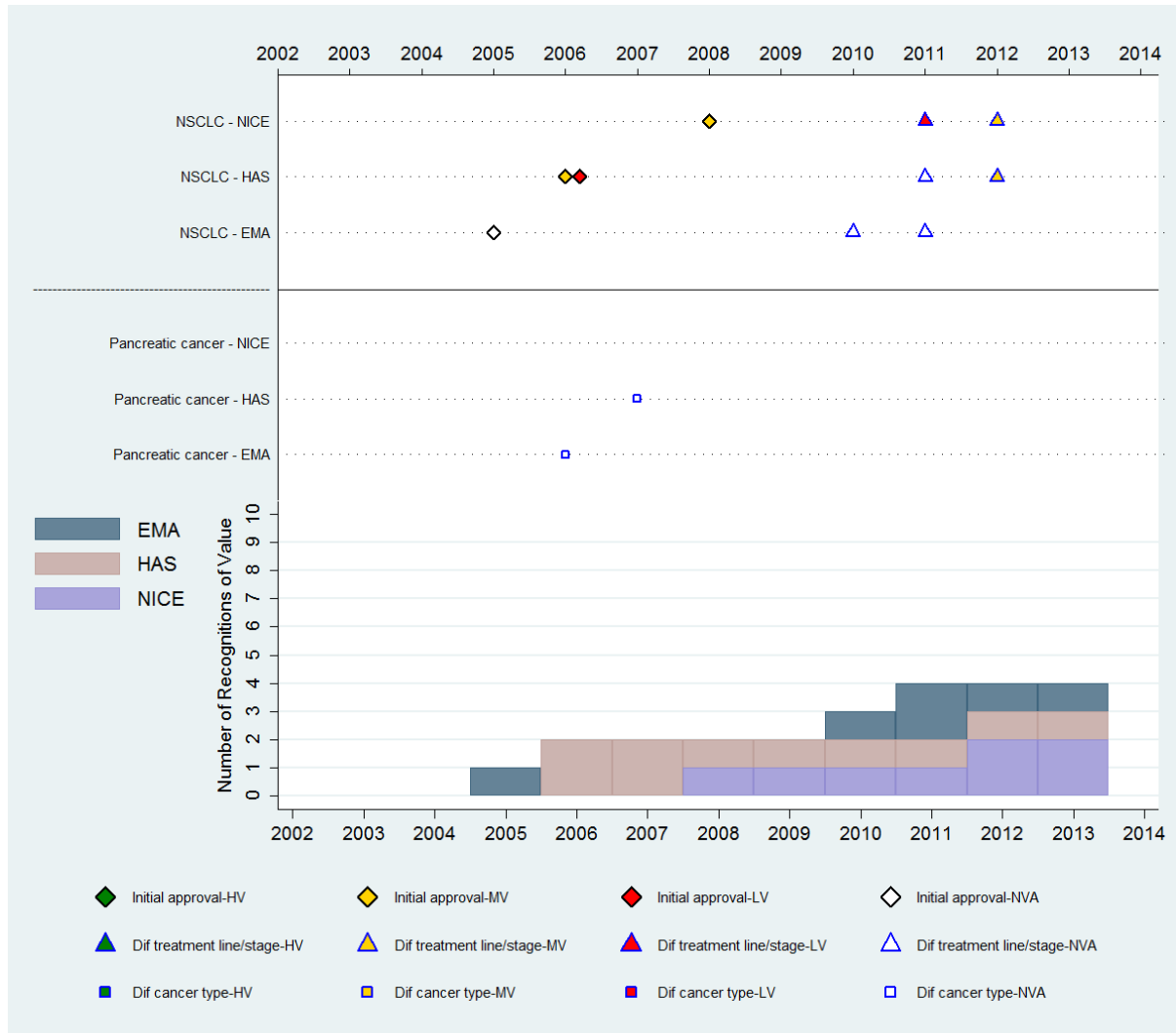
Tarceva (Figure 14) has been approved by the EMA as treatment of NSCLC (after failure of at least one chemotherapy regimen) and pancreatic cancer. Two value expansions for the use of Tarceva to treat NSCLC are uses in a different treatment line/stage. It was approved as maintenance treatment after four cycles of standard platinum-based first-line chemotherapy in 2010 and then as first-line therapy of NSCLC with EGFR activating mutations (2011). HAS assessments in 2007 (for treatment of pancreatic cancer) and 2011 (for maintenance treatment of NSCLC) did not recommend these uses due to insufficient SMR ratings. These are the only two "insufficient" SMRs identified in our study. HAS does not recommend treatments that it regards as having no actual benefit (SMR). In those cases, HAS does not determine the improvement in actual benefit of the therapy (ASMR), so the two symbols related to these assessments in the upper part of Figure 14 are white. HAS did, however, recommend the other three uses of Tarceva for the treatment of NSCLS approved by the EMA.

NICE recommended, with restrictions to the patient sub-population in both cases, two of the authorisations that the EMA granted to Tarceva for the treatment of NSCLC.

We did not identify any Aetna judgements regarding Tarceva.

6.4.10 Velcade

Figure 15. Value footprint of Velcade (bortezomib)
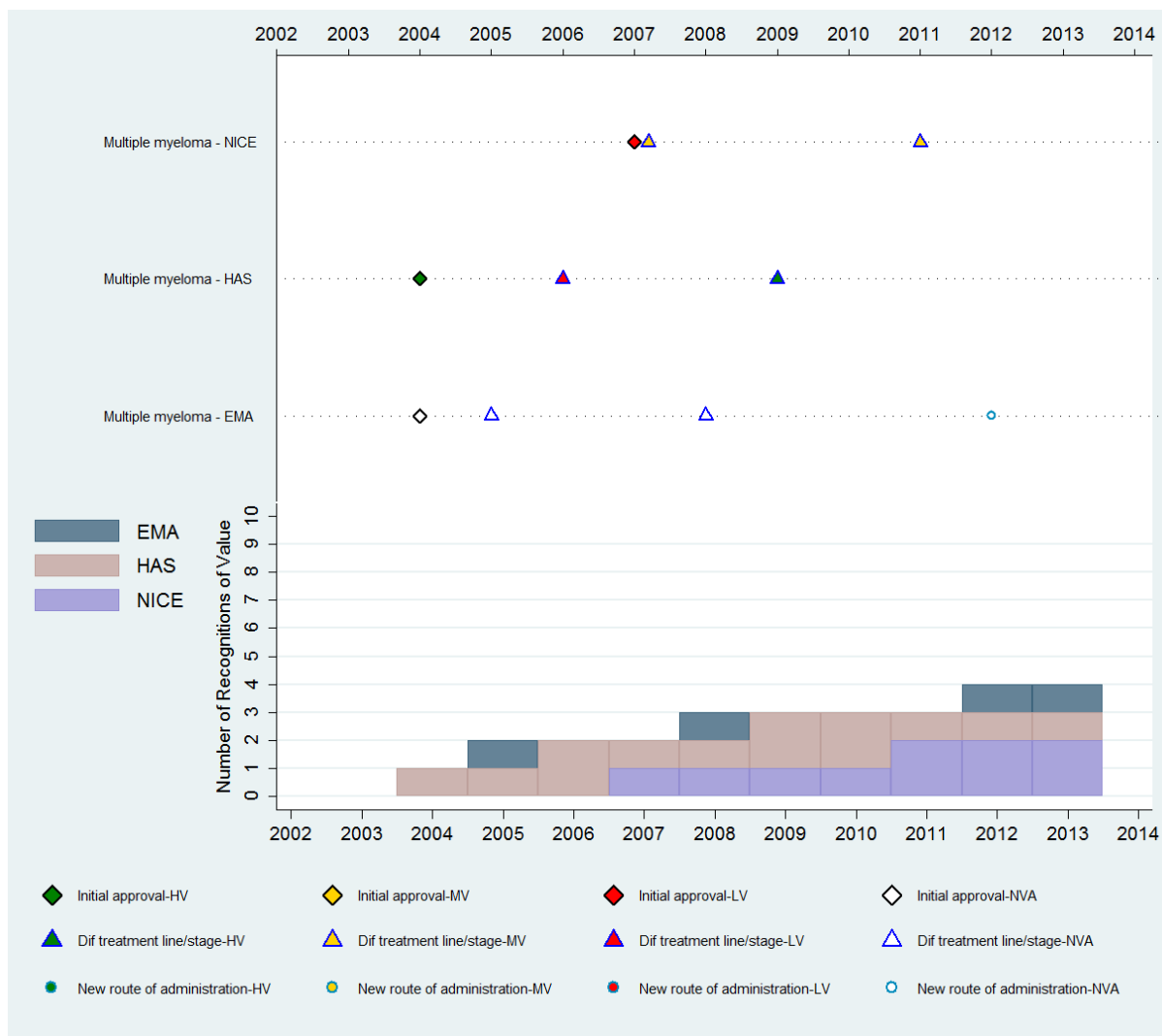
Velcade (Figure 15) was first authorised for use as a treatment for multiple myeloma by the EMA in 2004 in patients who have received at least two prior therapies and have demonstrated disease progression on the last one. Then, in 2005 the EMA authorised its use in a new treatment line/stage, as a monotherapy in patients who have received at least one prior therapy. In 2008 the EMA authorised its use in the first-line of treatment of multiple myeloma in combination with melphalan and prednisone. Additionally, in 2012 the EMA approved the use of Velcade as a subcutaneous form of administration, a new route of administration for Velcade, which had initially been approved as intravenous infusion.

HAS recommended all value expansions authorised by the EMA between 2004 and 2013, except for the subcutaneous use authorisation.

NICE did not recommend the initial approval that the EMA authorised (in 2004, for patients who have received at least two prior therapies), but recommended the two subsequent uses in different treatment line/stage in 2007 and 2011. Our search strategy identified no assessments by either NICE or HAS for the subcutaneous use of Velcade (as approved by the EMA in 2012).

We identified 16 Aetna judgements regarding Velcade indications, of which 11 (68.1%) were deemed medically necessary and 5 (31.3%) were deemed experimental and investigational.

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6.4.11 Zevalin

Figure 16. Value footprint of Zevalin (ibritumomab tiuxetan)
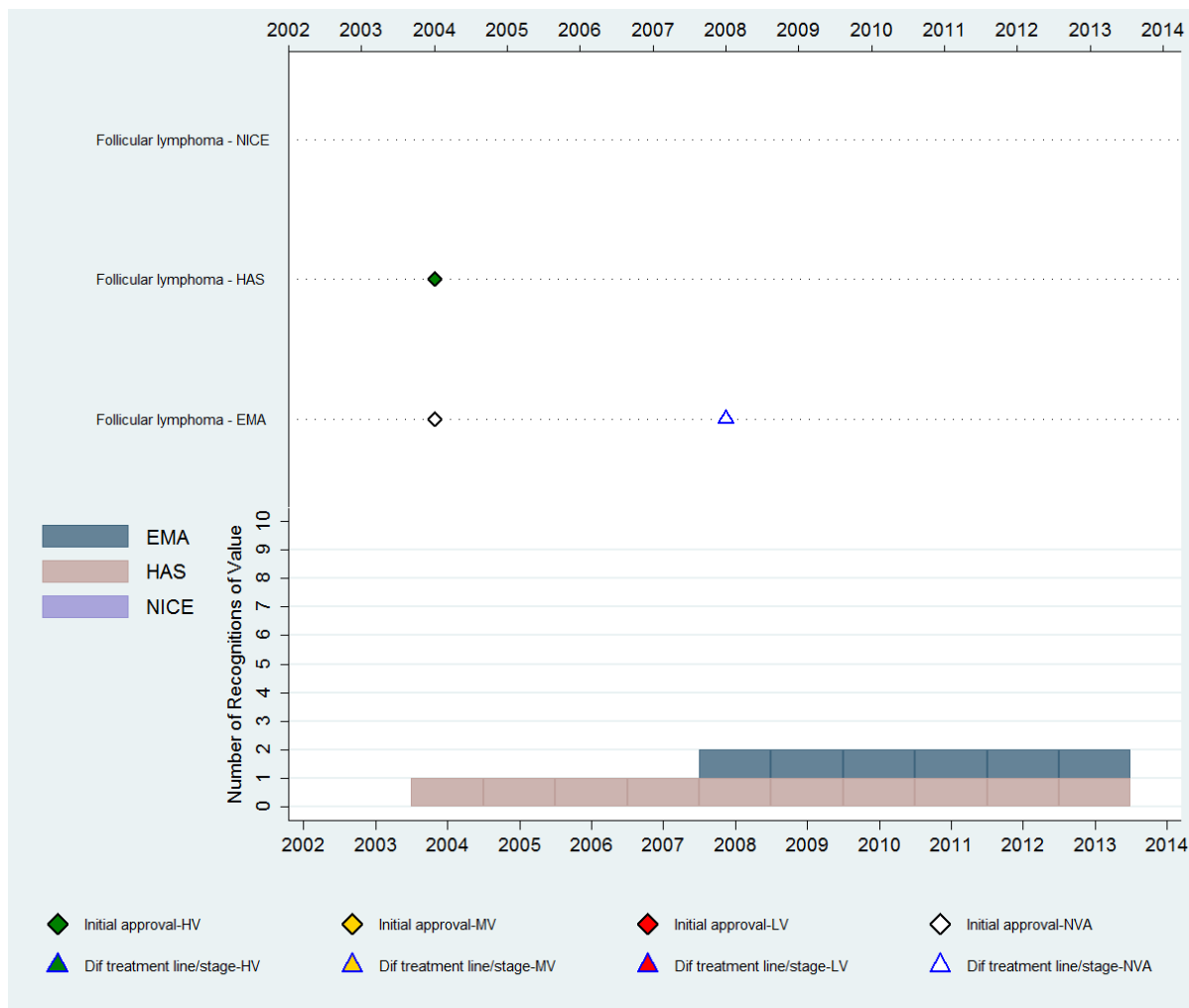
Zevalin (Figure 16) was approved by the EMA in 2004 for the treatment of patients with relapsed or refractory follicular lymphoma. In 2008 the use of Zevalin as consolidation therapy after remission induction was authorised by the EMA.

We identified only one HAS assessment of Zevalin: in mid-2004, HAS recommended the use of Zevalin to treat patients with relapsed or refractory follicular lymphoma.

Using our search strategy, no NICE appraisals of Zevalin were found.

We identified two Aetna judgements regarding Zevalin indications, of which one was deemed medically necessary and the other was deemed experimental and investigational.

7. STAGE 4: ANALYSIS OF DATA ON PRICES, VOLUMES AND SALES

We have analysed IMS data for five of the medicines in our cohort in our three countries of interest: Avastin (bevacizumab), Velcade (bortezomib), Erbitux (cetuximab), Tarceva (erlotinib) and Alimta (pemetrexed). We focused on these five medicines, rather than the full sample of 10 medicines, for two reasons: (1) these medicines have had significant numbers of value expansions and HTA assessments; (2) the total sales of these five medicines represent between 94% and 96% of total sales for the 10 medicines in each country in the last year of available data (Q4 2012 – Q3 2013) at the time of data extraction. It should be noted that:

- Our IMS data covers the UK as a whole, without separating between the four nations (England, Scotland, Wales and Northern Ireland). NICE covers England and Wales, which together represent around 87% of total UK sales.
- Our IMS data covers the US as a whole. Aetna covers approximately 22.1 million members (Aetna, 2013b), which represents around 7% of the US population.

The structure of this section is as follows. We first outline the data and our methods used to analyse the data. Results then follow, first grouping all five medicines and then reporting on individual medicines. Finally, we offer some observations based on the analysis.

7.1 Data and method

IMS primary and secondary care sales data were extracted for the five medicines considered in this report. Specifically, we extracted quarterly MIDAS data from Q1 2004 to Q3 2013 measured in value (local currency), packs and standard units. Data were also extracted for launch date, pack strength and pack size for each pack per country. IMS audits use list prices to estimate the value of sales in each specific market. This may overestimate the relative value of sales as negotiated discounts will not be captured. Generally, the quality of volume data produced by IMS is considered good for the three countries under consideration, and comparison among these markets is reasonable. It is the case that for the UK some usage may not be captured, notably medicines dispensed through the homecare channel, but recent OHE audits of IMS data in cooperation with pharmaceutical companies suggests that this will be marginal (O'Neill et al., 2013).

In common with existing analyses comparing use of cancer medicines internationally (see for instance, Richards (2010)), it was decided to present the results using milligrams as the common denominator for volume. This is because cancer medicines generally have a greater variety of complex formulations than medicines in other classes. Usage was converted to milligrams using pack sales and details of packs. For example, if there were 10 packs sold of a medicine where each pack comprises 20 units

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of 100 milligram tablets, volume for those 10 packs would be converted into 20,000 milligrams (10 * 20 * 100).

As is standard with IMS data, prices were imputed using sales value divided by milligrams. Our original data were requested in local currencies, to avoid the impact of any changes in exchange rates when making comparisons. Receiving the data in a common currency (such as USD) would not enable us to ascertain the effects of changing exchange rates over time. Prices in local currency were then converted to USD, but using two exchange rates. First, prices were converted into dollars using Bank of England average annual exchange rates (Bank of England, 2014; extracted in January 2014). Second, prices were converted using constant exchange rates based on 2004 annual exchange rates, thus isolating the effect of exchange rates changing over time on prices. For instance, prices in local currency could have remained constant over time, but if the exchange rate between the three currencies (USD, GBP and EUR) changed, prices expressed in USD would also have changed.

In order to take into account the size of the market, we converted both total usage per molecule per milligram and sales per molecule per 100,000 population. This conversion makes comparisons across countries useful. Population figures from the three countries come from the United Nations (2012).

7.2 Overall results

7.2.1 Launch dates

Table 8 details the launch dates for the five medicines included in the analysis. Note that for Velcade the US launch date preceded our study's data collection period. In all instances, the US was the country where the medicine was first launched; in two instances, the delay between the US launch and the France or UK launch was longer than 12 months. For France, the launch date may not correspond to the first period in which sales are recorded as launch may precede pricing and reimbursement decisions. The results are presented chronologically, so comparisons will be made only for those periods where data are available in at least two countries.

Table 8. Launch dates for medicines included in the analysis (first reported date)

Medicine	US	UK	France
AVASTIN	Mar 2004	Mar 2005	Apr 2005
VELCADE	May 2003	Jun 2004	Jun 2004
ERBITUX	Feb 2004	Jun 2004	Jul 2004

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Medicine	US	UK	France
TARCEVA	Nov 2004	Sep 2005	Oct 2006
ALIMTA	Feb 2004	Dec 2004	May 2004

Source: authors' analysis from IMS.

7.2.2 Sales per medicine per country

Table 9 shows IMS sales data for the 10 medicines included in our original report for the last year of available data (sum of four quarters, from Q4 2012 to Q3 2013 inclusive). The five medicines we have focused on in this part of the report represent between 94% and 96% of total sales for the 10 medicines in each of the three countries.

Avastin represents around 43% of total sales for our full cohort of medicines in France and the US, followed by Alimta, which accounts for almost 20%. In the UK the picture is different, as Avastin only represents 26% of total sales, which is still the highest share for any one medicine, albeit tied with Velcade. Alimta has similar share of sales in the UK relative to France and the US, but represents a smaller share of sales than Velcade in that country.

Table 9. Sales in local currency (Q4 2012 – Q3 2013)

	UK		France		US	
	Annual sales GBP	Share (%)	Annual sales EUR	Share (%)	Annual sales USD	Share (%)
AVASTIN	39,202,868	26.1	296,381,785	42.6	2,601,404,326	43.2
ALIMTA	28,746,700	19.2	126,571,130	18.2	1,160,280,352	19.3
ERBITUX	20,665,454	13.8	101,475,955	14.6	636,979,606	10.6
VELCADE	38,578,231	25.7	76,902,464	11.1	601,378,829	10.0
TARCEVA	15,989,617	10.7	65,752,286	9.5	630,114,604	10.5
SUBTOTAL	**143,182,870**	**95.5**	**667,083,620**	**96.0**	**5,630,157,717**	**93.5**
FULVESTRANT	4,894,566	3.3	20,316,963	2.9	313,501,824	5.2
BUSULFAN	702,093	0.5	4,010,322	0.6	64,555,003	1.1
CLADRIBINE	440,222	0.3	947,460	0.1	4,854,919	0.1
IBRITUMOMAB TIUXETAN	5,981	0.0	361,547	0.1	1,033,370	0.0
MITOTANE	753,929	0.5	2,263,487	0.3	5,643,486	0.1
TOTAL	**149,979,661**	**100**	**694,983,400**	**100**	**6,019,746,319**	**100**

Source: authors' analysis from IMS.

7.2.3 Bilateral price and volume comparisons by country

This sub-section provides overall summaries of the price and volume data, bilaterally comparing the three countries. Firstly, in order to observe the evolution of the prices

after the initial assessment, an exploratory analysis of the behaviour of prices has been carried out. As mentioned above, prices were imputed by dividing sales (in local currency) by volume (expressed in milligrams) and then converted into USD to enable comparisons across the three countries. As highlighted above, prices from IMS are at list prices and do not capture any discounts to third party payers.

Price results are shown using a *fixed exchange rate* (at the level of 2004). This ameliorates the problem of fluctuating currencies, noticeable since 2008. As shown below, the key results for the price comparisons remain unchanged when using *annual* and 2004 exchange rates.

Regarding volumes, these have been adjusted for population to provide a more meaningful benchmark. Because of the wide range of results from a small sample, averages have not been computed.

Tables 10, 11 and 12 show the details of the bilateral comparisons between France and the US (US is the reference – this means that if the value exceeds 100%, the parameter in question is higher for France relative to the US); UK and US (US is the reference); and UK and France (France is the reference) respectively. Note that a blank cell means that the medicine was not available in one of the two countries (either France or the UK when relevant). Prices and sales are both expressed in USD.

Overall, the UK had lower prices, volumes and sales than either the US or France (with one notable exception for volume in the later years in the period – Erbitux). Two further exceptions are: (1) the UK price for Velcade starts above the US price, but by the end of the period is below; (2) the UK price of Avastin in 2012 and 2013 is higher than the price in France (at constant 2004 exchange rates only). It is worth noting that sales in the UK are significantly lower per 100,000 people relative to both the US and France – not higher than 13% in all cases.

The comparison between France and the US can be found in Table 10. For two medicines (Avastin and Erbitux), prices in France were lower than in the US during the whole period. For Alimta and Tarceva, launch prices (expressed in USD) were very similar in both countries, but after one or two years the price is France was lower. Velcade is the only product for which its price in France is higher than in the US for the whole period – although the differences decrease considerably by 2013.

Volumes (per 100,000 people) in France were in four out of five instances (Alimta, Avastin, Erbitux and Tarceva) higher than the US by 2013, and in one case (Erbitux) significantly so by the end of the period of analysis. With the exception of Erbitux, where relative volume is higher in France throughout the entire period, relative use of the other four medicines starts lower than the in US, but as stated above, ends up above the US.

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Velcade is associated with highest prices and lowest usage in France relative to the US. Erbitux is the opposite; lowest prices but highest volume.

In terms of average annual sales in France, Erbitux sales are higher than those of Velcade in the last six years, but both Erbitux and Velcade have lower sales (per 100,000 population) in France versus the US. The best performance in terms of sales in France relative to the US is observed for Alimta, with the highest relative value across the entire period, reaching the maximum level of 111.6% in 2006.

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Table 10. Bilateral price, sales and volume comparisons between France and US

Average annual price, sales and volume: France compared with US (Values presented in percentages)										
Price (comparison between average annual prices USD per mg at annual exchange rates)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		83.9	85.6	93.3	100.7	95.5	88.6	87.3	67.2	67.8
Velcade	189.8	180.9	171.0	178.9	151.2	134.3	119.9	122.2	109.3	111.4
Erbitux	27.7	28.2	28.5	28.8	38.4	33.7	31.5	33.8	32.1	32.5
Tarceva			100.1	92.8	91.7	79.4	67.7	64.6	51.8	48.2
Alimta	101.5	102.3	99.5	83.8	83.4	78.0	71.6	73.8	61.0	61.0
Price (comparison between average annual prices USD per mg fixed at 2004 exchange rates)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		83.9	84.7	84.7	85.5	85.3	83.1	78.0	65.0	63.5
Velcade	189.8	181.0	169.3	162.4	128.5	120.0	112.5	109.2	105.7	104.3
Erbitux	27.7	28.2	28.2	26.1	32.6	30.1	29.5	30.2	31.1	30.4
Tarceva			99.1	84.2	77.9	70.9	63.5	57.7	50.1	45.1
Alimta	101.5	102.4	98.5	76.0	70.9	69.7	67.2	66.0	59.0	57.1
Volume (comparison between average annual volumes mg per 100k population)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		13.8	32.3	51.4	100.8	100.0	100.4	102.5	111.1	113.5
Velcade	32.0	57.9	68.0	93.3	85.3	76.3	65.5	52.3	57.9	75.4
Erbitux	115.7	289.5	269.4	341.8	351.5	354.8	369.8	335.6	318.4	277.5
Tarceva			64.2	116.0	126.6	134.6	134.5	129.4	130.3	137.7
Alimta	57.0	98.1	112.1	117.1	133.6	120.6	113.9	115.4	128.3	118.1
Sales (comparison between average annual sales USD per mg at annual exchange rates per 100k population)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		5.9	18.6	32.2	68.1	64.0	59.5	59.3	48.5	49.9
Velcade	15.3	53.0	58.8	84.3	65.1	51.6	39.6	32.2	32.5	42.3
Erbitux	21.3	54.4	51.1	70.8	78.2	71.1	72.7	73.5	70.6	70.3
Tarceva			34.2	58.3	63.0	57.2	48.9	44.9	35.3	34.7
Alimta	29.4	101.7	112.8	99.1	111.5	91.6	79.6	83.4	78.4	72.1

Source: authors' analysis from IMS.

Table 11 shows the comparisons between the UK and the US. Similarly to Table 10, we observe a negative relationship between volumes and prices when comparing these two countries. Avastin is associated with the highest relative prices and the lowest relative volumes in the UK versus the US. Erbitux, however, is associated with the lowest relative prices and the highest relative volumes. In contrast with the comparison between France and the US, sales in the UK are far lower relative to the US (per 100,000 population) –

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between 0% and 5%. This can be explained by two characteristics of the UK market relative to the US for our cohort: low relative prices and low relative volumes. The lower values of sales for the UK observed in Table 11 are similar to Table 12, which compares France and the UK.

Table 11. Bilateral price, sales and volume comparisons between UK and US

Average annual price, sales and volume: UK compared with US (Values presented in percentages)									
Price (comparison between average annual prices USD per mg at annual exchange rates)									
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		73.6	75.0	81.5	75.4	64.0	61.7	62.8	61.3	59.0
Velcade	134.3	127.0	120.4	125.5	110.7	89.2	84.9	85.4	83.5	81.4
Erbitux	23.3	23.5	23.9	25.0	21.5	19.4	20.9	21.7	22.3	21.5
Tarceva		93.4	81.2	84.1	72.7	56.4	50.0	47.1	41.3	36.8
Alimta	67.6	67.6	65.9	68.4	59.3	48.3	46.0	46.9	45.1	43.3
Price (comparison between average annual prices USD per mg fixed at 2004 exchange rates)									
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		74.2	74.6	74.6	75.3	75.1	73.2	71.7	70.8	69.2
Velcade	134.3	128.0	119.8	114.9	110.6	104.7	100.6	97.7	96.5	95.3
Erbitux	23.3	23.7	23.7	22.8	21.5	22.8	24.7	24.8	25.7	25.2
Tarceva		94.1	80.8	77.0	72.6	66.2	59.3	53.8	47.8	43.1
Alimta	67.6	68.2	65.6	62.6	59.2	56.6	54.6	53.6	52.1	50.7
Volume (comparison between average annual volumes mg per 100k population)									
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		7.2	7.7	6.3	4.0	3.9	3.8	9.3	13.8	18.6
Velcade	19.6	25.3	27.5	23.8	47.4	52.0	56.8	70.4	82.8	83.6
Erbitux	9.2	6.3	6.5	13.6	28.3	50.6	84.9	182.8	243.6	316.5
Tarceva		7.0	13.0	11.6	16.6	31.7	35.7	36.2	34.4	35.5
Alimta	8.6	7.3	8.4	8.2	12.7	15.2	28.6	33.0	32.2	38.4
Sales (comparison between average annual sales USD per mg at annual exchange rates per 100k population)									
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		0.2	0.7	1.0	1.2	1.0	1.0	2.4	3.7	5.0
Velcade	0.6	1.9	2.3	2.8	4.5	3.6	3.2	3.1	4.0	5.1
Erbitux	1.2	2.2	2.1	1.8	1.0	1.0	1.7	3.1	4.0	4.2
Tarceva		0.3	1.7	2.6	3.6	5.7	5.7	5.3	4.6	4.5
Alimta	0.1	0.5	0.6	0.7	1.0	1.0	2.0	2.7	3.1	3.3

Source: authors' analysis from IMS.

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Table 12 illustrates prices, sales and volumes for the UK in comparison with France. Once again, relative sales in the UK are lower, with UK values representing a maximum of 13% of France values (for Tarceva). Erbitux is once again the medicine with lowest relative prices and the highest relative volumes. It is worth noting that the relative volume for Erbitux in the UK versus France experienced a considerably growth, increasing from 10.7% in 2004 to 878.4% in 2013.

Velcade's relative price in the UK versus France is the highest in our sample – although has suffered a decrease since 2004, from 134.3% to 81.4. Over the same period, relative UK volume for Velcade increased from 6.3% to 63.1%.

Table 12. Bilateral price, sales and volume comparisons between UK and France

Average annual price and volume: UK compared with France (Values presented in percentages)										
Price (comparison between average annual prices USD per mg at annual exchange rates)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		87.7	87.6	87.3	74.9	67.0	69.7	71.9	91.2	87.0
Velcade	70.7	70.2	70.4	70.2	73.2	66.4	70.8	69.9	76.4	73.0
Erbitux	84.2	83.6	83.8	86.8	56.0	57.5	66.3	64.2	69.3	66.3
Tarceva			81.1	90.7	79.3	71.0	73.8	72.9	79.9	76.2
Alimta	66.6	66.1	66.2	81.6	71.1	61.9	64.3	63.5	73.9	70.9
Price (comparison between average annual prices USD per mg fixed at 2004 exchange rates)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		88.4	88.1	88.1	88.1	88.1	88.1	91.9	109.0	109.0
Velcade	70.7	70.8	70.7	70.7	86.0	87.2	89.5	89.4	91.2	91.4
Erbitux	84.2	84.2	84.2	87.5	65.8	75.5	83.8	82.1	82.8	83.0
Tarceva			81.5	91.4	93.2	93.3	93.2	93.2	95.5	95.5
Alimta	66.6	66.6	66.6	82.3	83.6	81.3	81.3	81.3	88.3	88.8
Volume (comparison between average annual volumes mg per 100k population)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		1.0	2.5	3.3	4.0	3.9	3.8	9.5	15.3	21.1
Velcade	6.3	14.6	18.7	22.2	40.4	39.6	37.2	36.8	47.9	63.1
Erbitux	10.7	18.3	17.5	46.5	99.6	179.6	314.2	613.5	775.7	878.4
Tarceva	0.0	1.1	8.3	13.4	21.0	42.7	48.1	46.8	44.8	48.9
Alimta	4.9	7.1	9.4	9.6	16.9	18.3	32.5	38.1	41.3	45.4
Sales (comparison between average annual sales USD per mg at annual exchange rates per 100k population)										
	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
Avastin		4.3	3.6	3.1	1.7	1.6	1.6	4.0	7.6	10.0
Velcade	4.2	3.6	3.9	3.3	6.9	6.9	8.0	9.8	12.3	12.1
Erbitux	5.8	4.0	4.1	2.5	1.3	1.4	2.3	4.2	5.7	5.9
Tarceva		4.1	4.9	4.5	5.7	9.9	11.8	11.8	13.0	13.0
Alimta	0.3	0.5	0.6	0.7	0.9	1.1	2.5	3.2	3.9	4.6

Source: authors' analysis from IMS.

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7.3 Results for individual medicines

This sub-section shows the results for individual medicines, expressed graphically. The first set of figures plot different measures of prices for the three countries: prices in USD per milligram at constant 2004 exchange rates (Figures 17-21); price *indices* (based on Figures 17-21) at constant 2004 exchange rates, where the *US = 100 for all years* (Figures 22-26); *price changes relative to the original price*, where the price of a medicine = 100% in the first quarter for which data are available (Figures 27-31). Figures 27 to 31 show any price fluctuations within each country – but they should not be used to compare price levels or indices across the three countries. It should be noted that one of the primary purposes of analysing the pricing data is to understand whether and how prices change following initial assessment.

The two sets of figures that follow focus on absolute and relative uptake for each medicine per country. First, we show volume usage in milligrams per 100,000 population in the three countries (Figures 32-36). Second, we show volume usage using indices where the US = 100 (Figures 37-41); thus any line above (below) the US horizontal line implies higher (lower) volume usage per 100,000 population relative to the US.

7.3.1 Evolution of the prices between 2004-2013 (price USD per mg)

Figures 17 to 21 show the evolution of prices (USD per mg at 2004 constant exchange rates) from 2004 to 2013 for the five selected medicines. Note that because prices per milligram are significantly different across medicines, the scales used for the vertical axes differ across the figures. Three key findings are apparent consistently across the figures: (1) prices in the UK are relatively stable; (2) UK prices are lower than those in the US (except for the earlier years for Velcade); (3) UK prices are lower than those in France, although by the end of the time period UK prices relative to France are above 90% for Velcade and Tarceva, and higher for Avastin.

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Figure 17 illustrates the case of Avastin. First, we observe that the US price is higher than the prices in France and the UK. The price reduction in France in 2011 stands out – this coincides with the approval of Avastin for the first-line treatment for breast cancer. The US price increases slightly towards the end of the period.

Figure 17. **Avastin price USD per mg, France, UK, US (2004 constant exchange rates)**

Source: authors' analysis from IMS.

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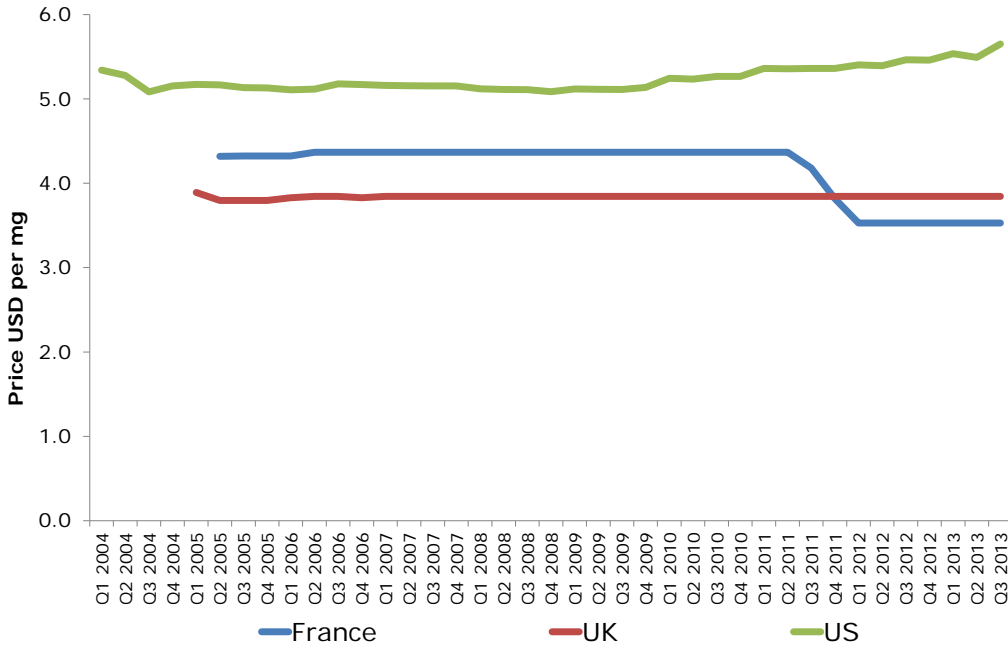
Figure 18 shows the results for Velcade. We observe a relative increase in the US price over time. However, the price in France is consistently higher than in the US (this is the only such case amongst the five medicines). Nevertheless, we observe a substantial reduction in the French price at the beginning of 2008. Similarly, before 2011, the UK price exceeds the US price. It is notable that amongst the five selected products, this is the only example where the UK price is not the lowest of the three countries (at least until 2011).

Figure 18. Velcade price USD per mg, France, UK, US (2004 constant exchange rates)
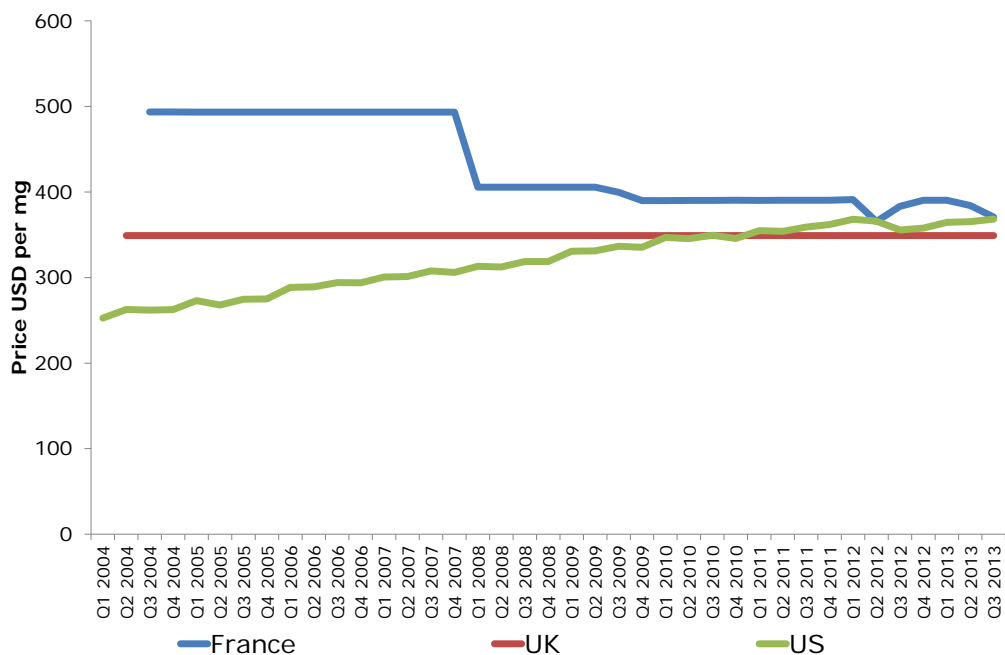
Source: authors' analysis from IMS.

Figure 19 shows the results for Erbitux. The gap between the US and the UK/France level of prices is considerable, with a difference of around $300 per milligram. The French price is relatively stable for most of the period, though we observe a reduction towards the end of 2007. In contrast to Velcade (Figure 18), this reduction in France prices is transitory as the price then increases to a level that is higher than it was before the 2007 reduction. We also a transitory increase in the UK price at the beginning of 2007.

Figure 19. Erbitux price USD per mg, France, UK, US (2004 constant exchange rates)
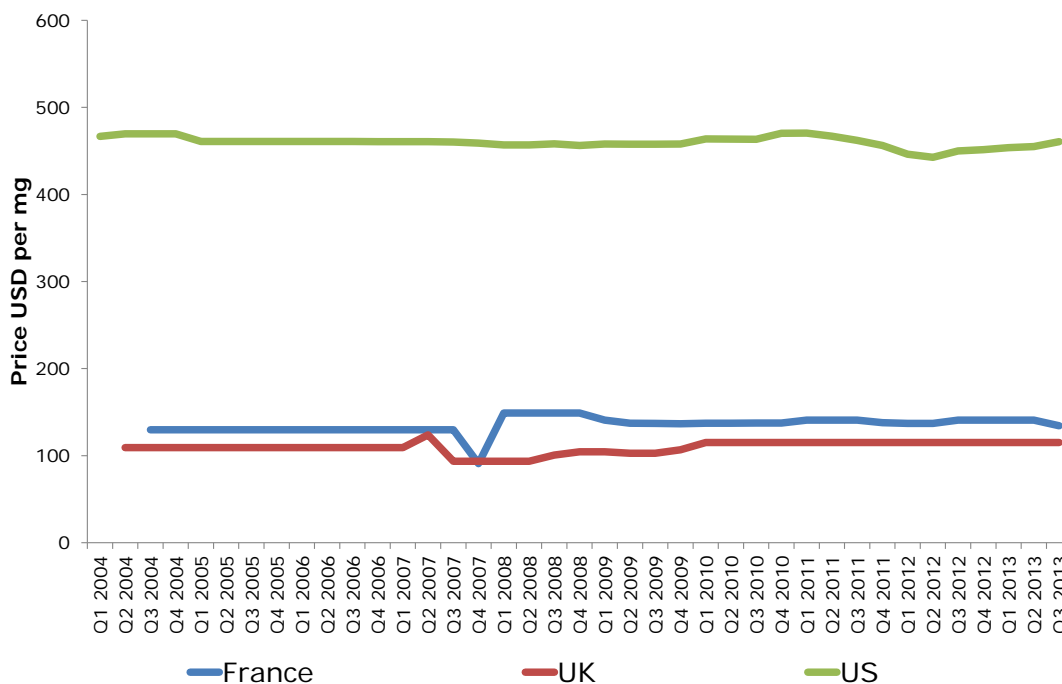
Source: authors' analysis from IMS.

Figure 20 shows the results for Tarceva. Of the five selected medicines, Tarceva has the lowest price per milligram in the three countries. Figure 20 shows three commonly observed patterns: (1) low and stable UK prices; (2) converging of prices in UK and France towards the end of the period; and (3) prices in the US increasing over time. The price in France is relatively stable, with only an important increase after launch. The US price increases at a relatively steady rate over time.

Figure 20. Tarceva price USD per mg, France, UK, US (2004 constant exchange rates)

Source: authors' analysis from IMS.

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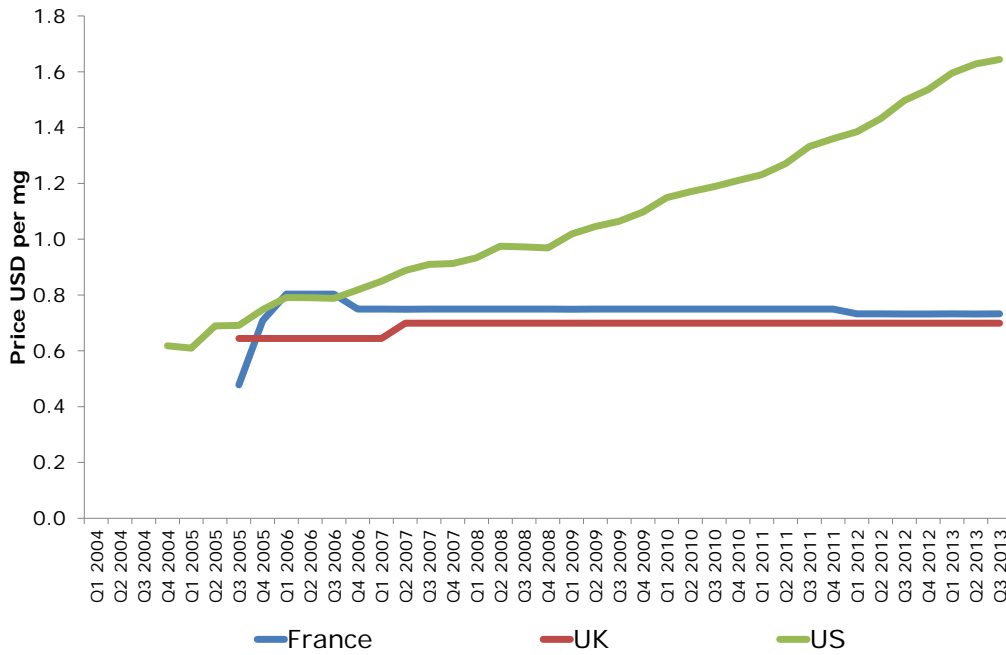
Figure 21 shows the results for Alimta. In common with the other medicines examined, the UK price is the lowest (and most stable). The prices in France and the US are similar at launch, but the French price then declines over the period. In this case, the fall in the price in France occurs in mid-2006, coinciding with the positive recommendation by HAS regarding the use of Alimta for the second-line treatment of patients with multiple myeloma. The US price increases steadily over time, exceeding the price in France at the beginning of 2006. This is similar to the case of Tarceva (Figure 20).

Figure 21. Alimta price USD per mg, France, UK, US (2004 constant exchange rates)
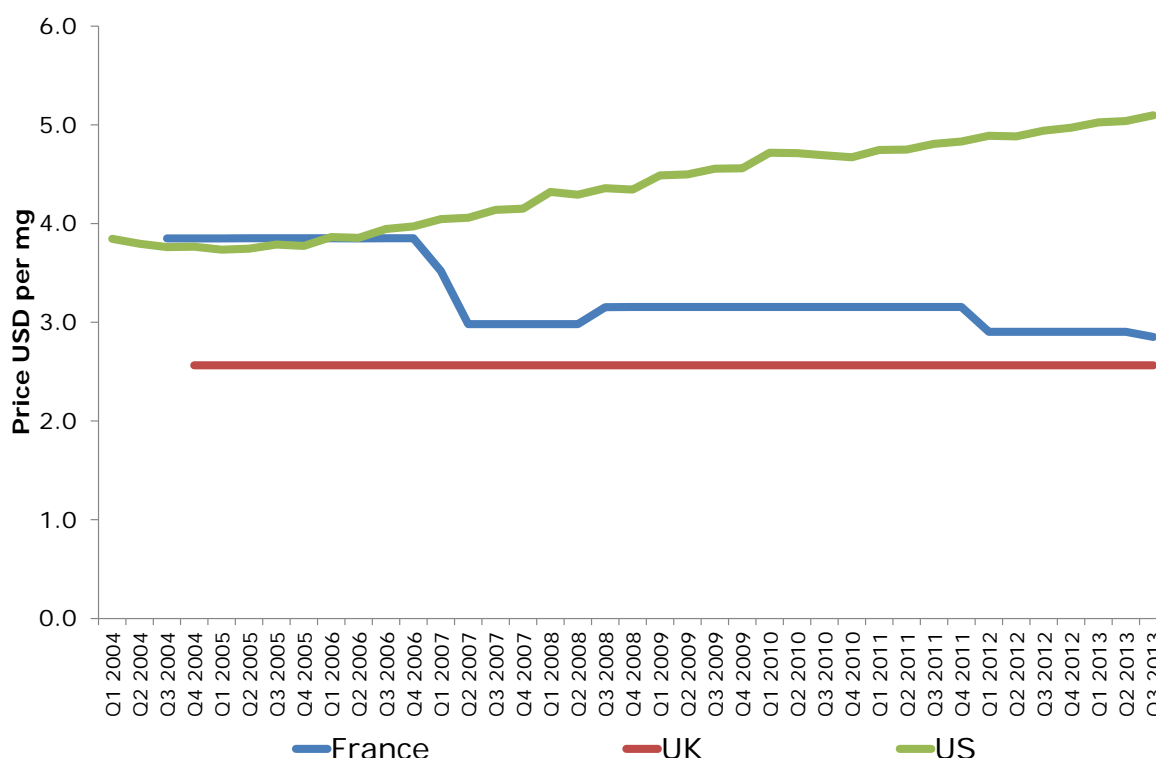
Source: authors' analysis from IMS.

7.3.2 Evolution of the prices USD per mg in France and the UK relative to the US

Figures 22 to 26 present a more intuitive method of price comparisons: relative prices, shown as indices (starting from prices expressed in USD). We compare the prices in the European countries (France and the UK) with those in the US. In all cases, the US price is always set to 100% throughout the entire period. In most cases, the relative prices in France and the UK are distributed between 20% and 103%. Velcade is the outlier, with a relative price of more than 160% prior to 2008. In this sense, is important to remember that the launch price in the US was around USD $253 and in the UK around USD $350 per milligram, while the launch price in France was much higher – around USD $493 per milligram (Figure 18).

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In addition, and in accordance with the results presented in Figures 17 to 21, the relative price in the UK is in four of the five cases lower than 100% during the whole period, with values distributed between 20% (Erbitux) and 133% (Velcade). The case of Erbitux is particularly noteworthy, with prices in France and the UK consistently lower than 35% relative to the US price. Furthermore, Figure 23 (Velcade), Figure 25 (Tarceva) and Figure 26 (Alimta) all show UK prices steadily declining in comparison to US prices. In each case this can be explained by increases in the US price over time, as UK prices tend to be relatively stable.

Figure 22. Avastin Price USD per mg in France and the UK relative to the US (US = 100%) (2004 constant exchange rates)
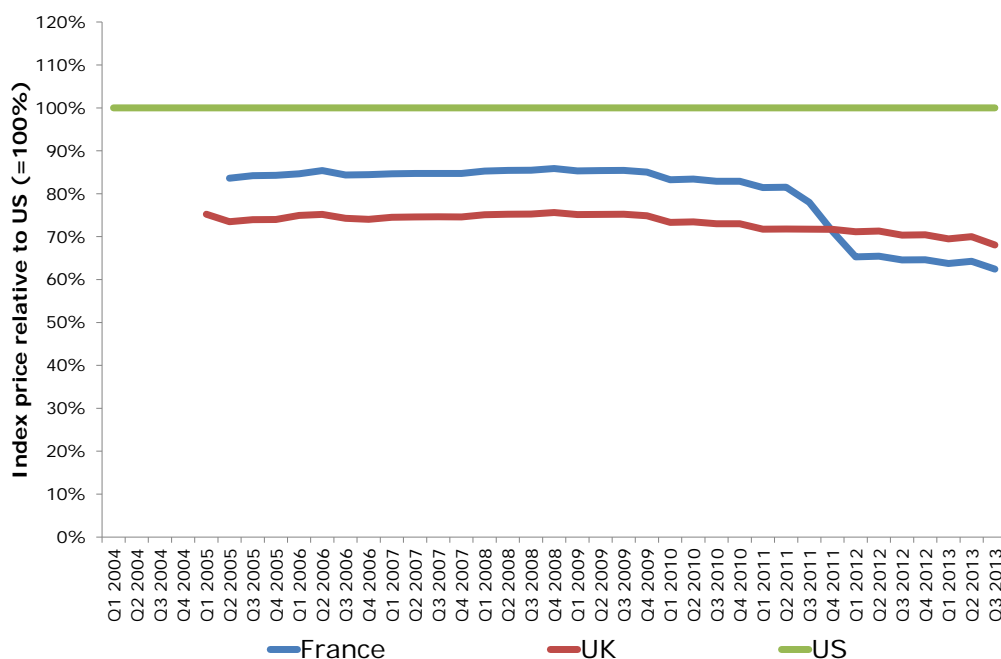
Source: authors' analysis from IMS.

Figure 23. Velcade Price USD per mg in France and the UK relative to the US (US = 100%) (2004 constant exchange rates)
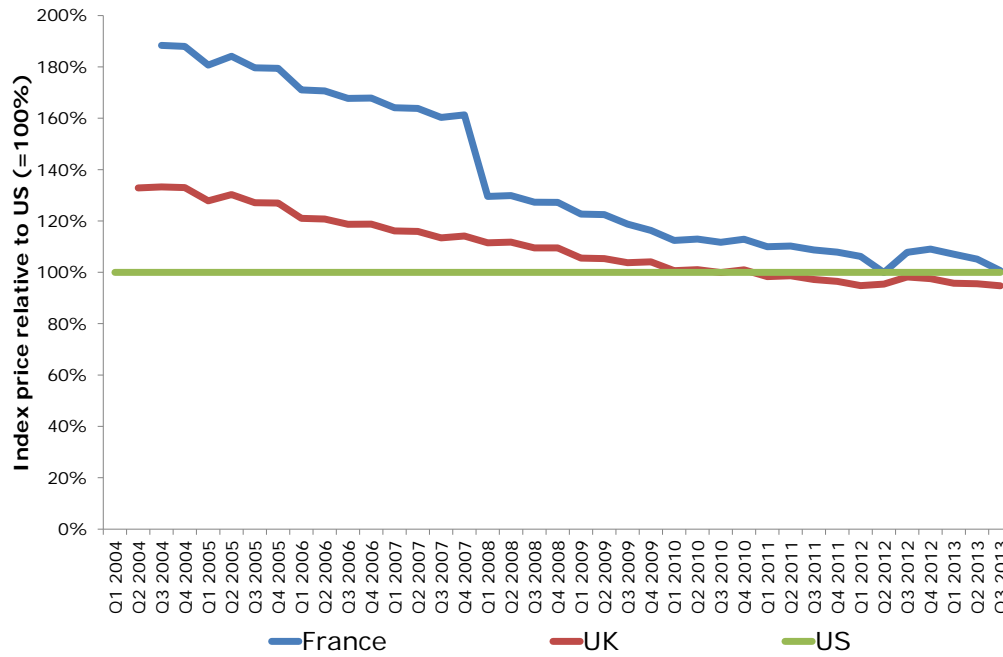
Source: authors' analysis from IMS.

Figure 24. Erbitux Price USD per mg in France and the UK relative to the US (US = 100%) (2004 constant exchange rates)

Source: authors' analysis from IMS.

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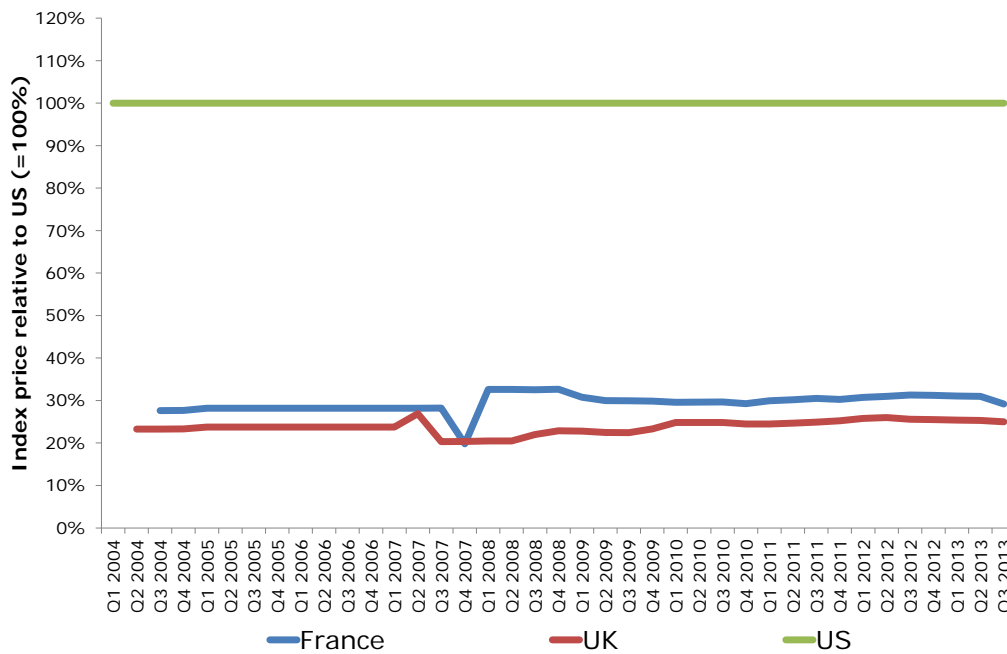
Figure 25. Tarceva Price USD per mg in France and the UK relative to the US (US = 100%) (2004 constant exchange rates)
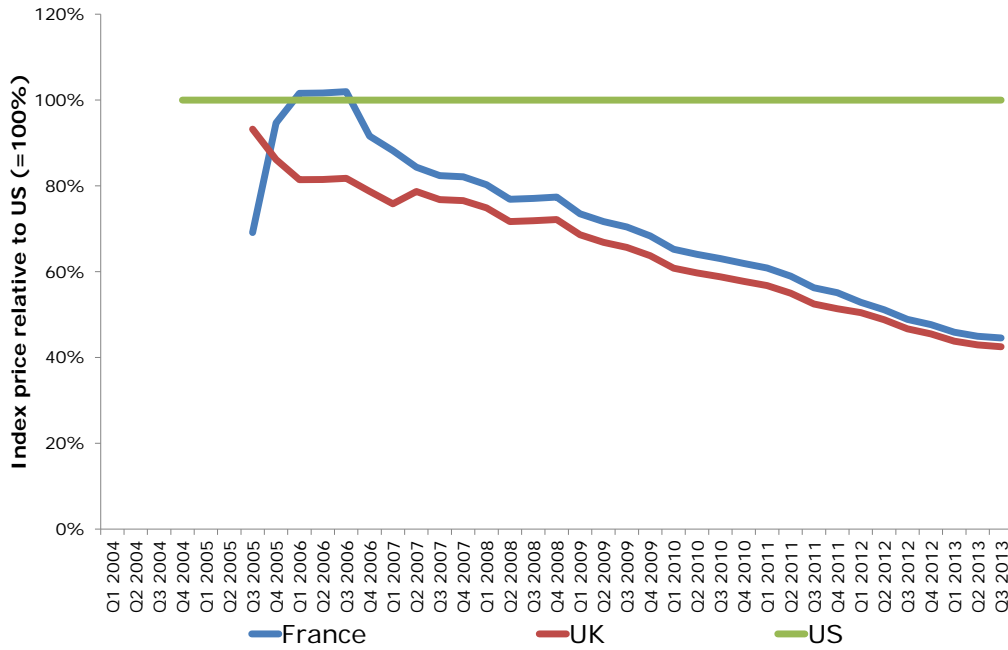
Source: authors' analysis from IMS.

Figure 26. Alimta Price USD per mg in France and the UK relative to the US (US = 100%) (2004 constant exchange rates)

Source: authors' analysis from IMS.

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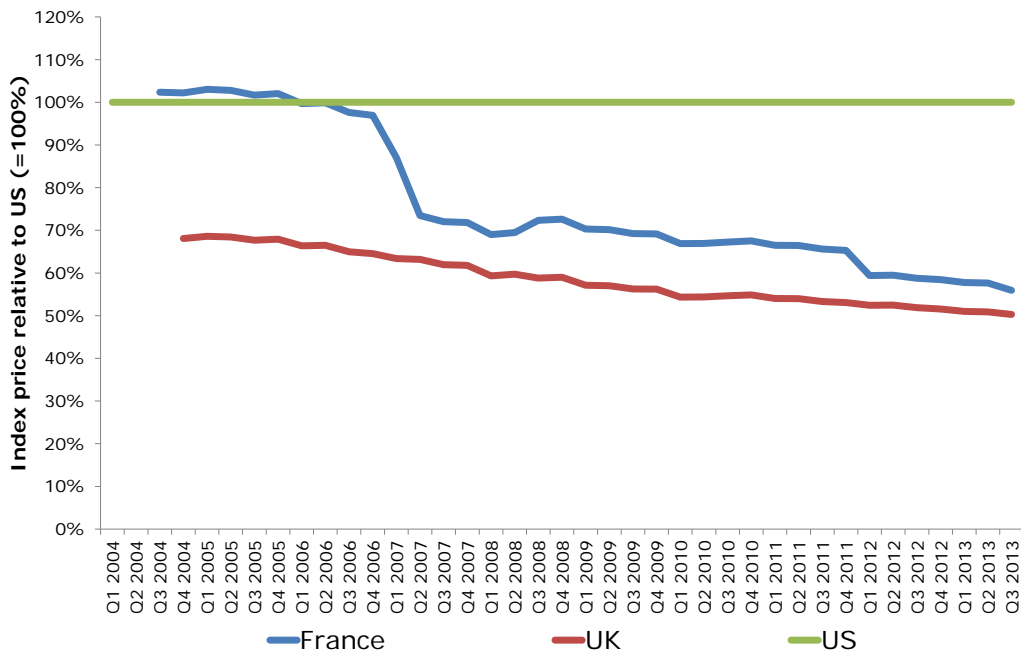
7.3.3 Evolution of price indices in France, UK, US compared with the first quarter price for each country

In this sub-section, we show how price changes relative to the launch price, within each country. For this purpose, we compare the price in each period with the price at the time of launch, i.e. the first quarter for which data are available. Figures 27 to 31 do not show comparisons across countries. All prices start at 100% – any deviation from 100% can be interpreted as a price change for the drug in country X relative to price at launch in country X. In other words, when the figure shows a straight line at the level of 100% across the entire period, this means that the price has remained the same, at a level equal to its launch price. Conversely, when prices increase (fall) after launch the figure will show values above (below) 100%. This allows us to easily identify any price changes. The results are presented in Figures 27 to 31.

For three drugs in France (Avastin, Velcade and Alimta) the upper limit corresponds to the launch price, with reductions in the price observed thereafter. This reduction occurs two and a half years after launch in the case of Alimta; four years after launch for Velcade; and six years after launch for Avastin. This could be related to reviews of the price level by the Economic Committee for Healthcare Products (CEPS) in France. However, we cannot identify the exact dates of the price reviews.

Avastin appears to have the most stable prices across the three countries (Figure 27), with only France seeing a one-off price reduction in 2011. For Erbitux (Figure 29), there are multiple price changes in the UK and France between 2007 and 2009, but we have not been able to identify the exact reasons for these.

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Figure 27. Avastin Price index France, UK, US compared with first quarter price for each country
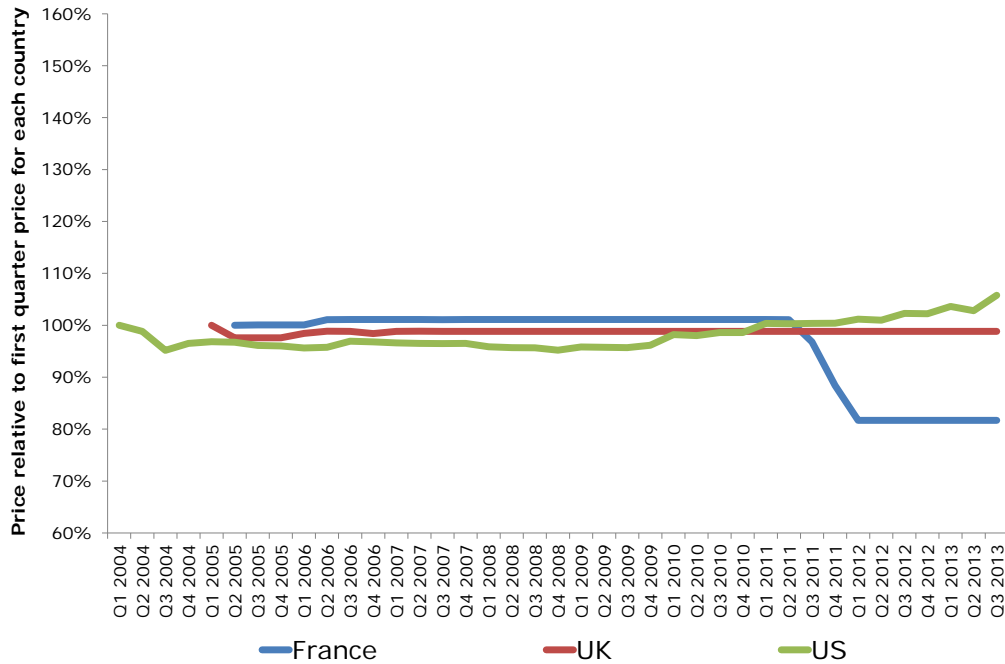
Source: authors' analysis from IMS.

**Figure 28. Velcade Price index France, UK, US compared with first quarter price for each country**

Source: authors' analysis from IMS.

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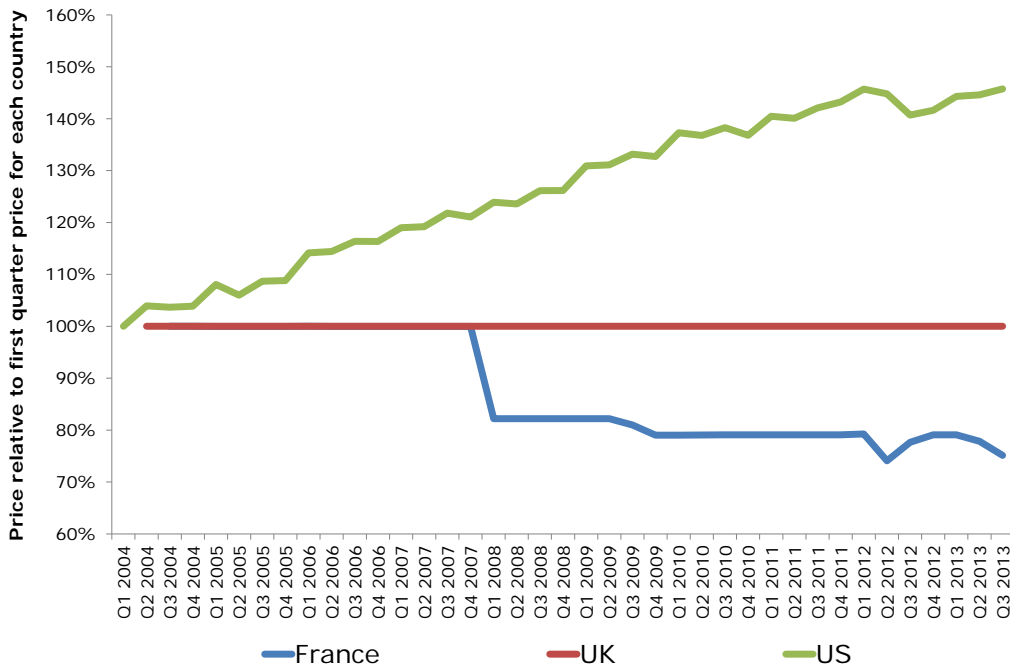
Figure 29. Erbitux Price index France, UK, US compared with first quarter price for each country
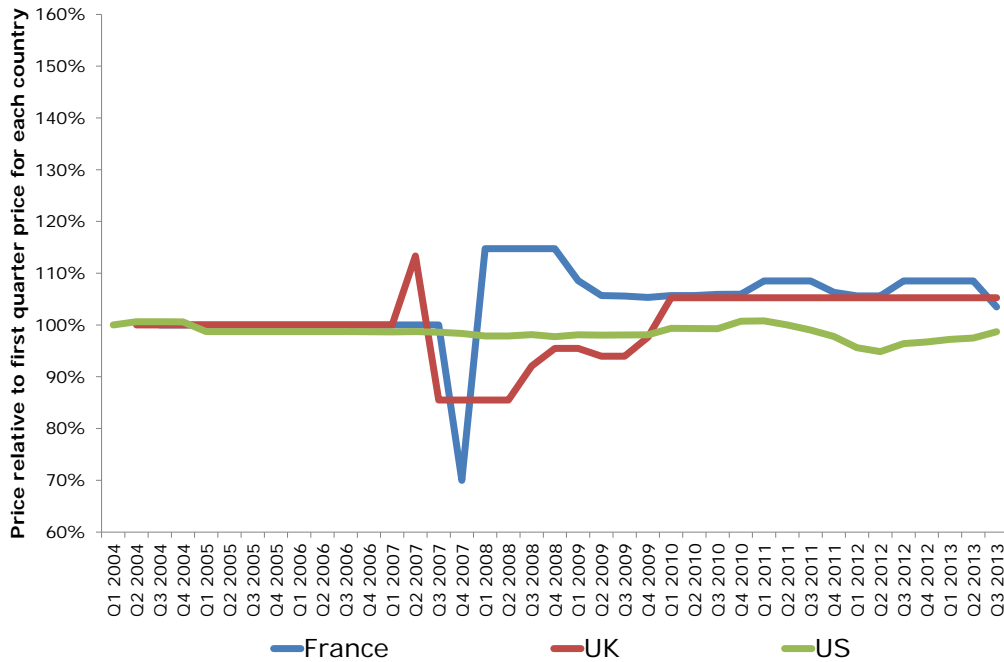
Source: authors' analysis from IMS.

Figure 30. Tarceva Price index France, UK, US compared with first quarter price for each country
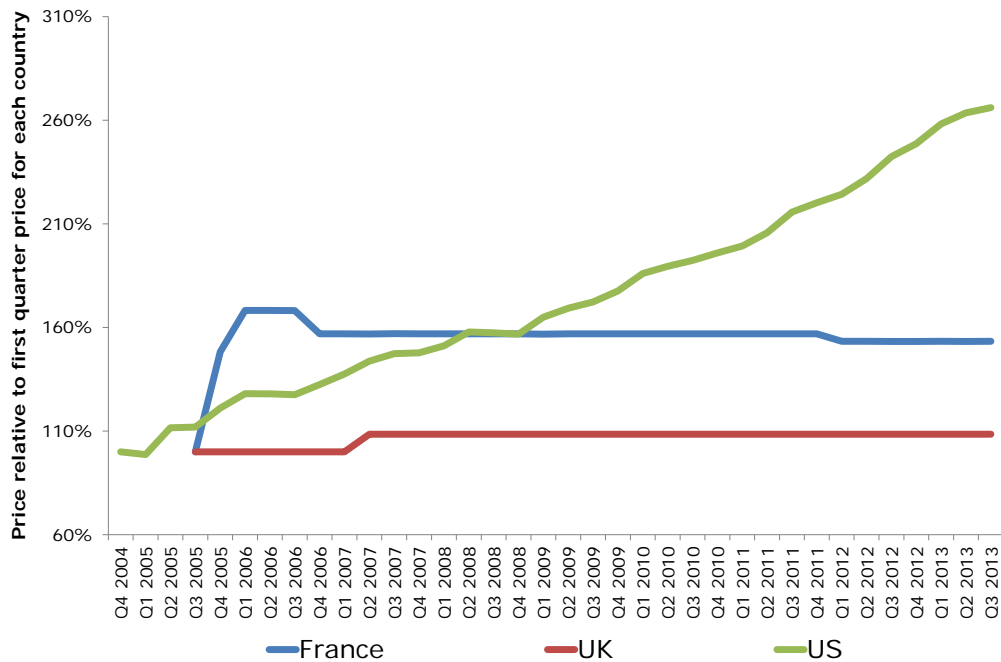
Source: authors' analysis from IMS.

Figure 31. Alimta Price index France, UK, US compared with first quarter price for each country
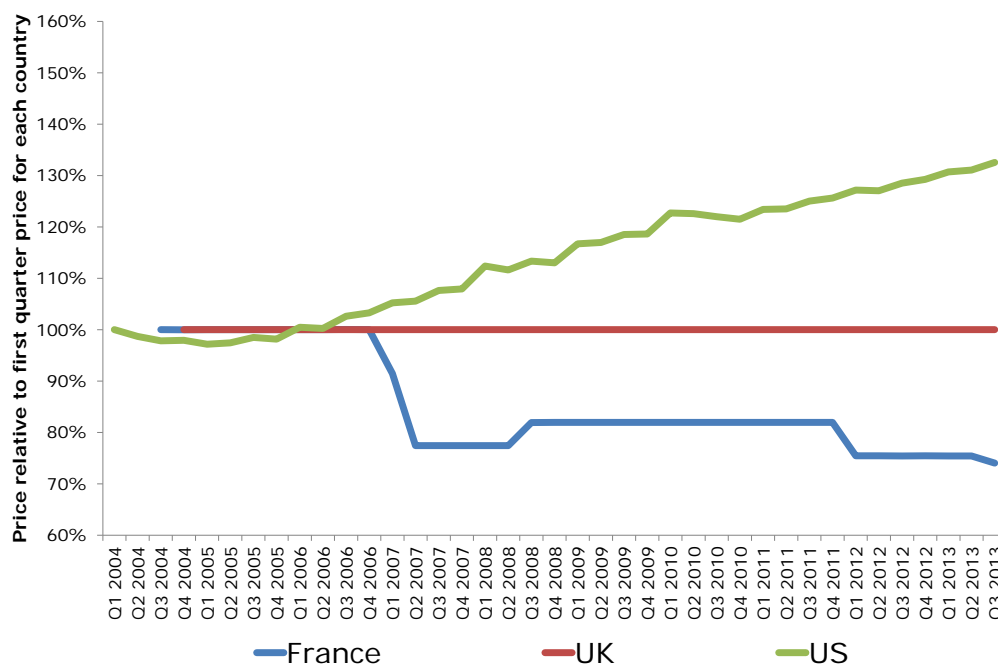
Source: authors' analysis from IMS.

7.3.4 Evolution of the volume usage

Figures 32 to 36 plot absolute uptake for each of the selected drugs. Usage is measured as in terms of milligrams per 100,000 people. Given that the range of volume usage differs greatly across the selected drugs, each figure in this sub-section uses a different scale for the vertical axis. In general, usage in the UK is lower than in France and the US, particularly in the cases of Avastin (Figure 32) and Alimta (Figure 36). The exception is Erbitux, where volume in the UK is the highest among the three countries from 2011 onwards.

As mentioned above, usage of Avastin in the UK is significantly lower than in France and the US. Usage of Avastin in France and the US increases until 2009, after which we observe a decline followed by a relatively flat curve (Figure 32). In the UK, usage increases from 2011 onwards.

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Figure 32. Avastin volume usage mg per 100,000 population France, UK and US
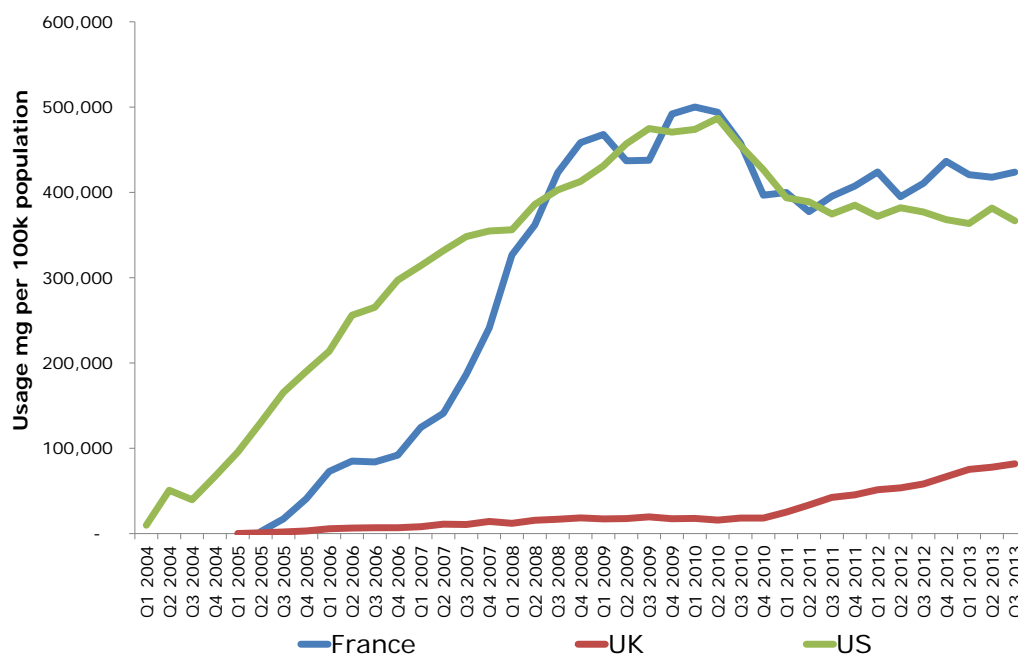
Source: authors' analysis from IMS.

As shown in Figure 33, usage of Velcade increases in the three countries over time, though we observe a marked reduction in the US in 2012. The gap between France and the US increases between 2010 and 2012, then decreases towards the end of the period. Usage in the UK is lower than in the US and France, but the relative gap between the UK and these two countries is the smallest among our cohort of drugs (with the exception of Erbitux).

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Figure 33. Velcade volume usage mg per 100,000 population France, UK and US
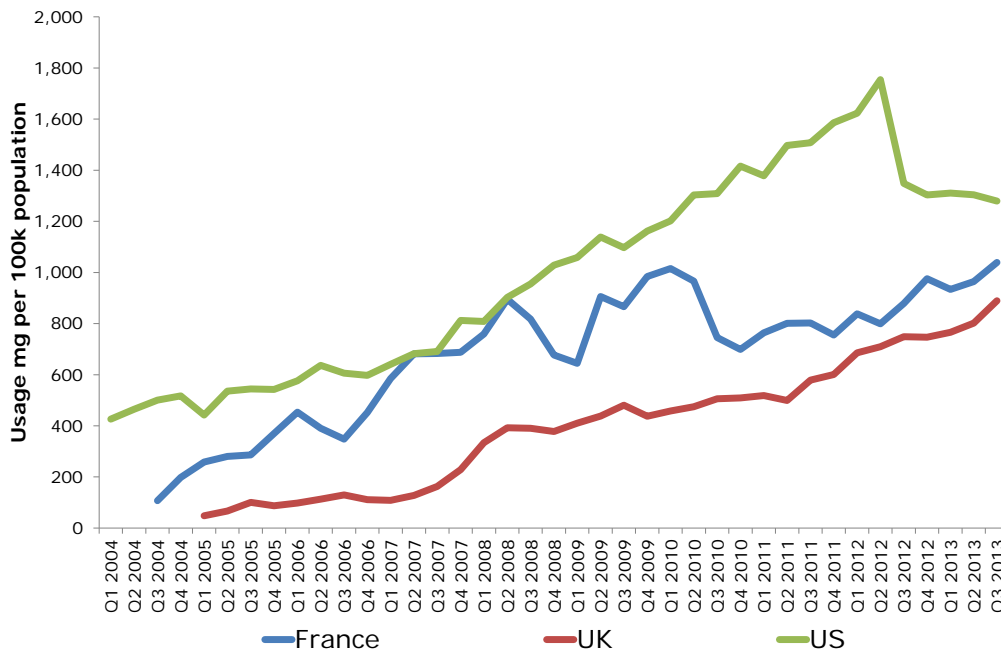
Source: authors' analysis from IMS.

Figure 34 plots the usage of Erbitux. Unlike the other medicines, the UK shows significantly greater usage relative to the US and France, especially after 2011.

Figure 34. Erbitux volume usage mg per 100,000 population France, UK and US

Source: authors' analysis from IMS.

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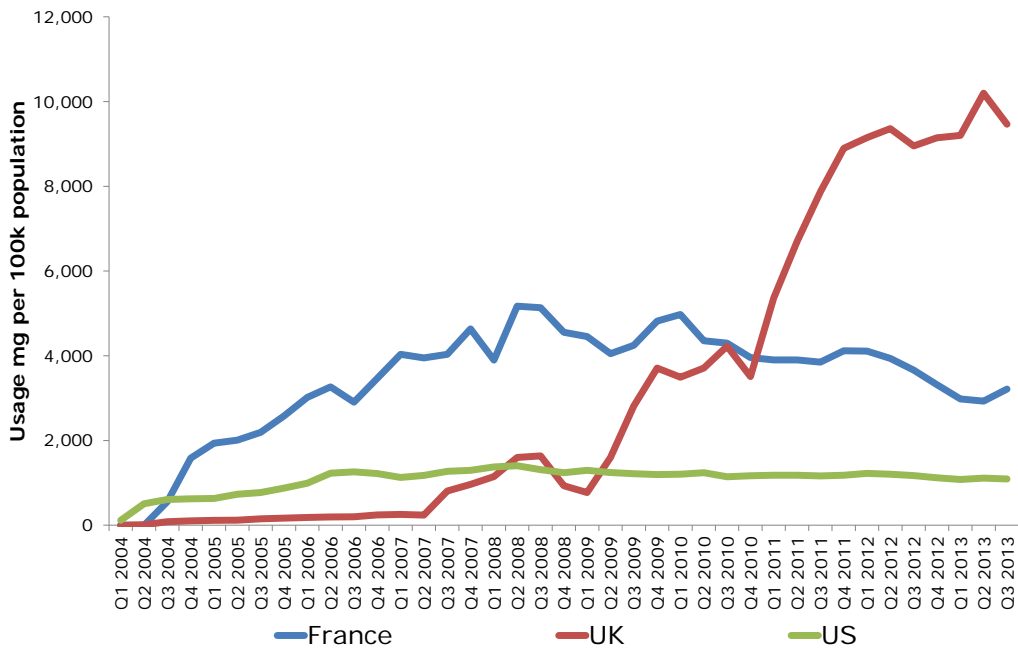
Figure 35 plots the usage of Tarceva. We observe a similar pattern in France and the US, with increases up until 2006/2007, followed by a period of stability and then decreases at the end of the period. By the end of 2006, usage of Tarceva per 100,000 population in France surpasses that in the US. The slight decline in usage for France and the US in the later years could be the result of new entrants into this class of medicines. UK usage is again the lowest among the three countries.

Figure 35. Tarceva volume usage mg per 100,000 population France, UK and US

Source: authors' analysis from IMS.

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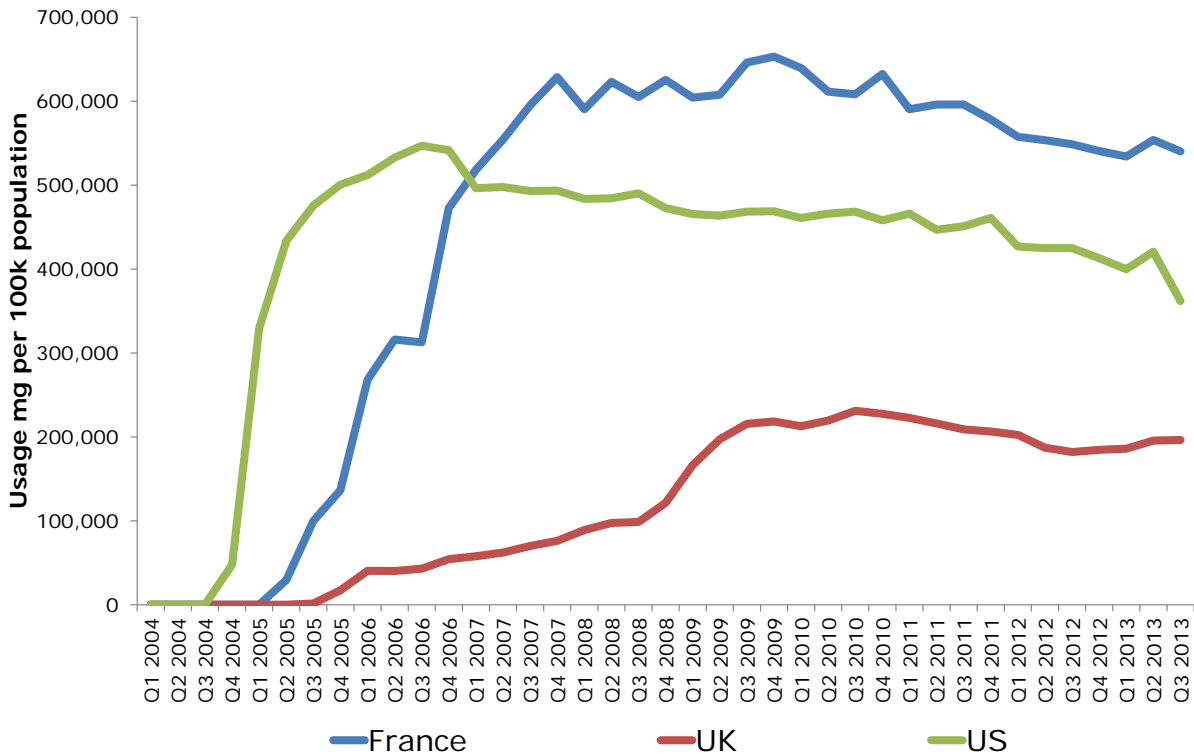
Volume usage for Alimta again shows a similar pattern to the other medicines in the sample: low usage in the UK and comparable levels of usage in France and the US (Figure 36).

Figure 36. Alimta volume usage mg per 100,000 population France, UK and US
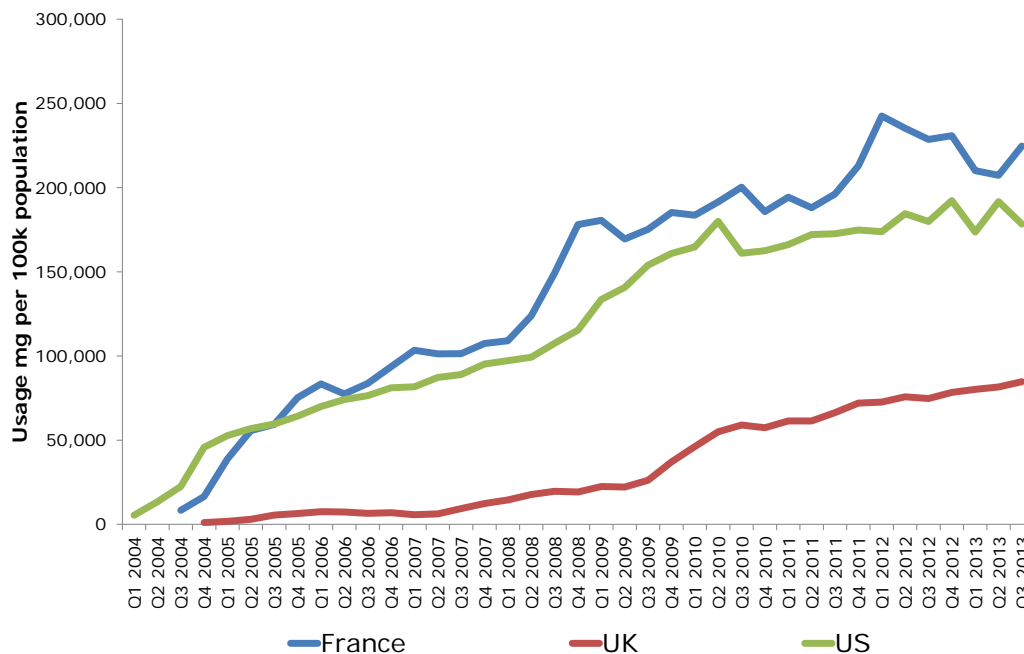
Source: authors' analysis from IMS.

7.3.5 Evolution of the volume usage indices in France and the UK relative to the US

Figures 37 to 41 present volume usage in France and the UK relative to the US. The use of indices reduces the issue of huge differences in scales when examining absolute usage. Most of the selected drugs show relative usage in France and the UK distributed between 0% and 160% relative to the US. However, the increase in the usage of Erbitux in the UK stands out (Figure 39). Starting at a level below 100% in 2009, the relative usage of Erbitux in the UK increases to approximately 900% within five years. In most cases, we observe a rapid increase in relative usage in France fairly early in the period of analysis.

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Figure 37. Avastin volume usage index for France and the UK relative to the US (US = 100%)
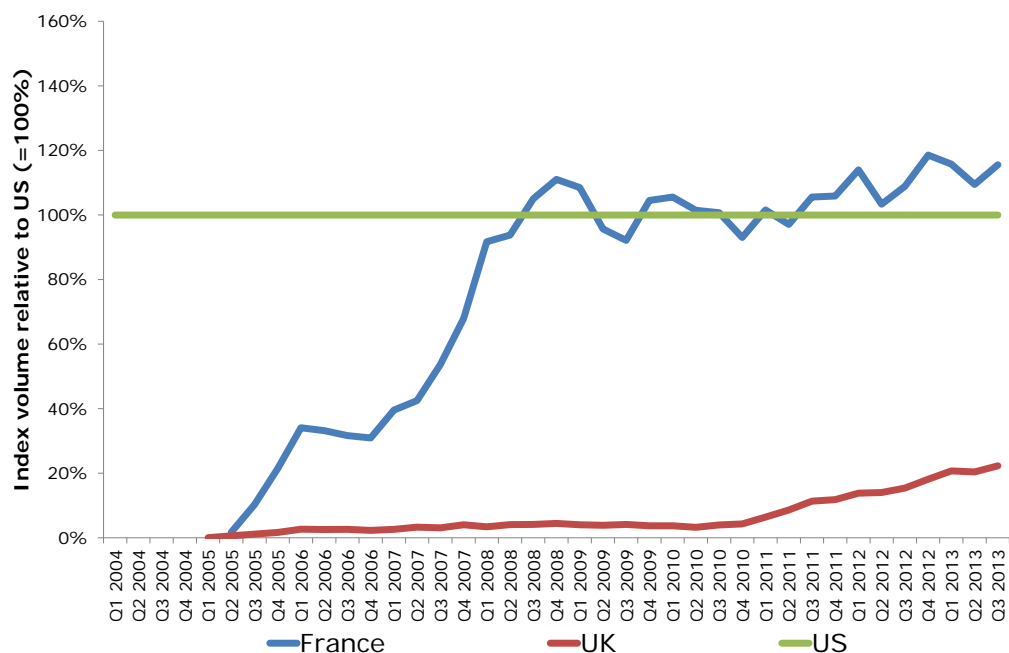
Source: authors' analysis from IMS.

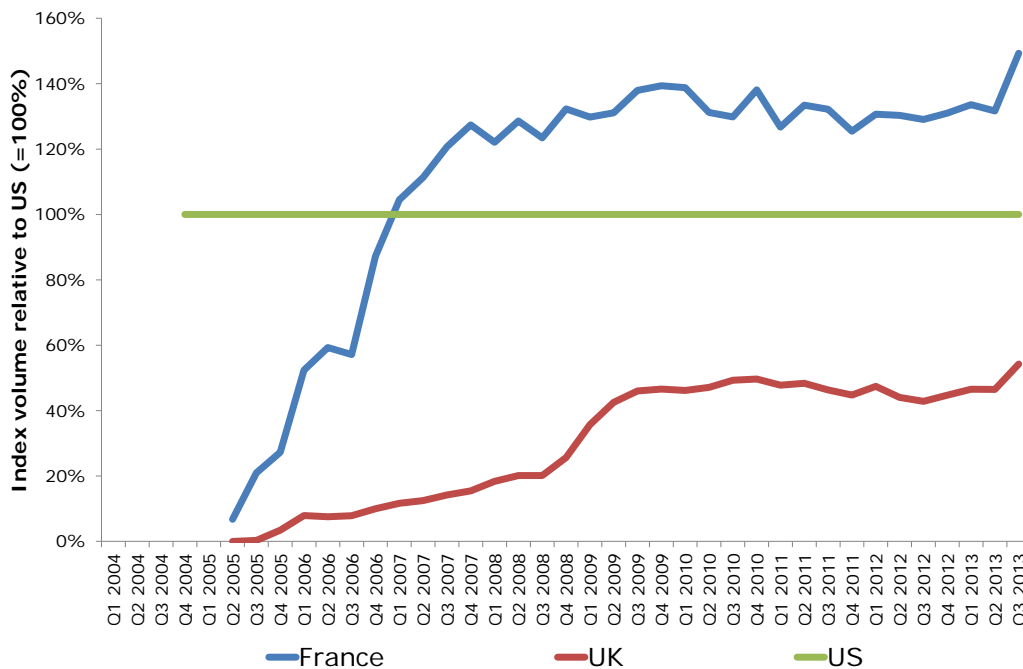**Figure 38. Velcade volume usage index for France and the UK relative to the US (US = 100%)**

Source: authors' analysis from IMS.

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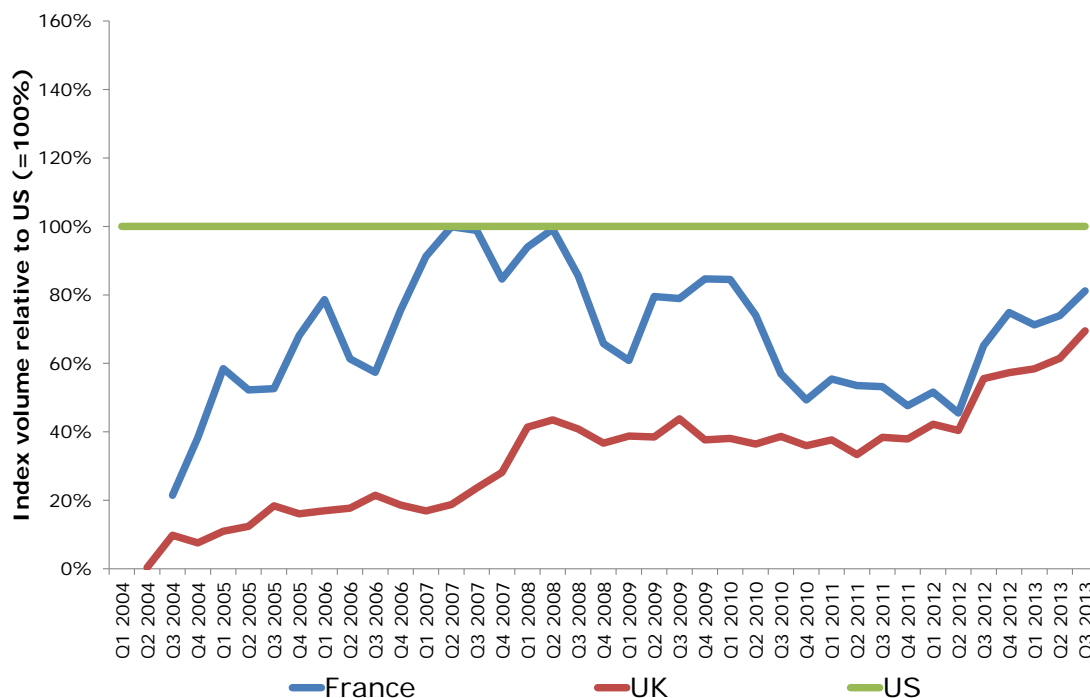
Figure 39. Erbitux volume usage index for France and the UK relative to the US (US = 100%)
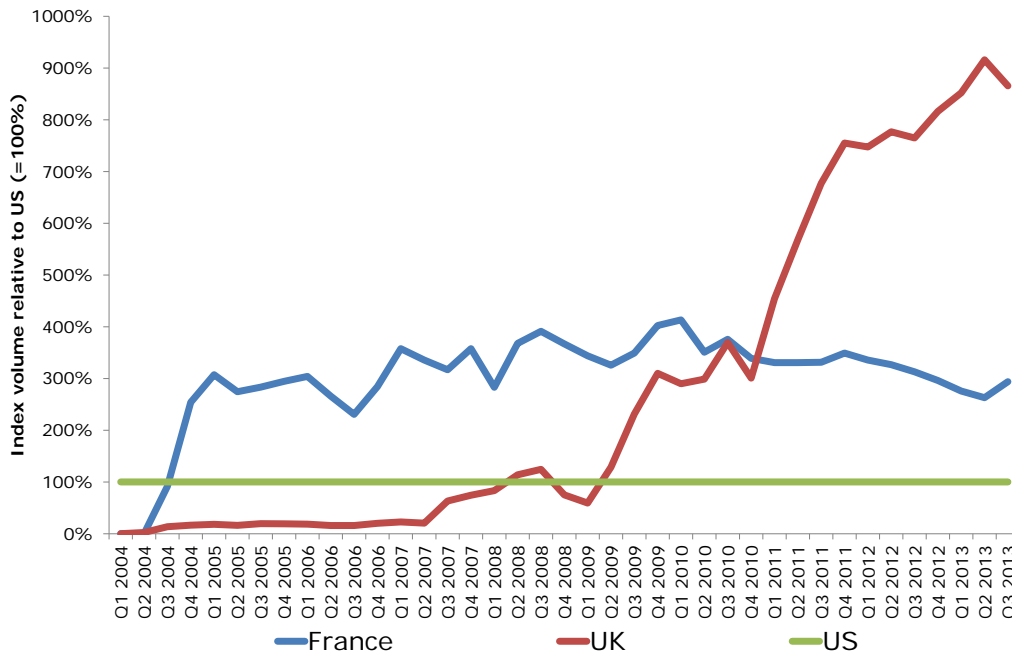
Source: authors' analysis from IMS.

Figure 40. Tarceva volume usage index for France and the UK relative to the US (US = 100%)

Source: authors' analysis from IMS.

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Figure 41. Alimta volume usage index for France and the UK relative to the US (US = 100%)
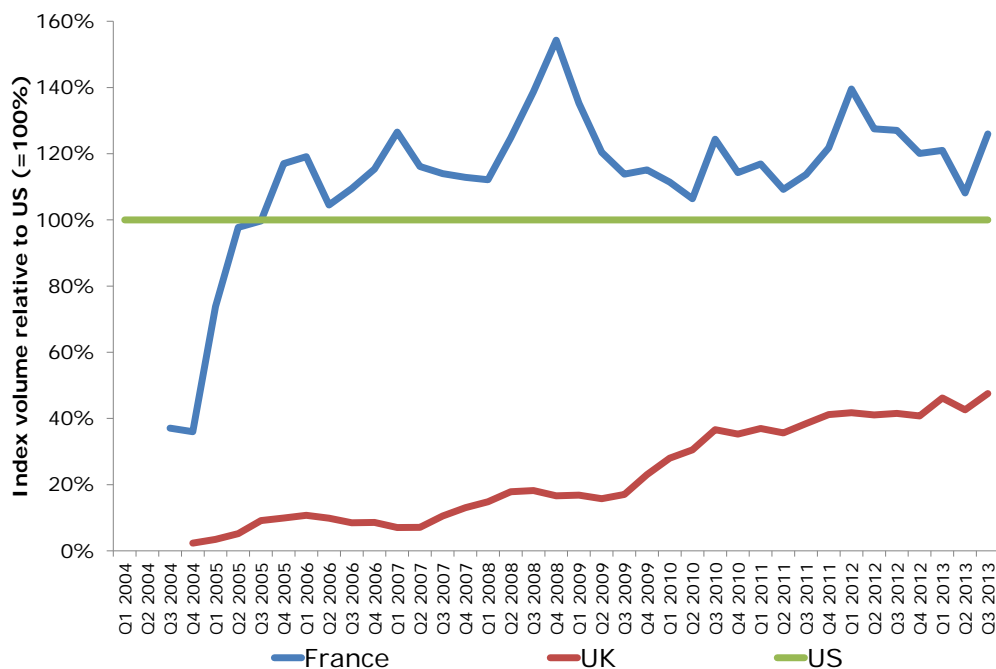
Source: authors' analysis from IMS.

7.4 Drug-by-drug value footprints mapped onto total sales

This sub-section presents total sales in local currency mapped onto the value footprint analyses from Stage 3. It is beyond the scope of this exercise to apply econometric analysis to the data. The figures below plot the value recognition events (by EMA and the relevant HTA agency) against quarterly sales for France and the UK for the five medicines included in the analysis. Note that total EMA licenses equate to the total value of the shaded region. Details of the value recognition method and further information for each medicine can be found in Stage 3.

We thus show two figures per medicine: one mapping France sales and HAS assessments; the other mapping UK sales and NICE assessments. Both figures include EMA authorisations. We first show the five figures for France (Figures 42 to 46) followed by the five for the UK (Figures 47 to 51). Note that we do not have similar figures for the US, given the data issues regarding Aetna assessments.

In the case of France (Figures 42 to 46), quarterly sales are largely distributed between €0 and €35 million. Avastin is the only case outside of this range, with a maximum of around €110 million.

In Figure 42 we observe a sharp increase in the sales of Avastin from the moment of launch in 2005 until the first quarter of 2009. The increase precedes a number of HAS's values recognitions. This could be related to the fact that Avastin appears in the Temporary Authorisations for Use (ATU) list since 2005.[2] The ATU procedure is an exceptional measure implemented in France with the objective of making available new medical products that do not have yet a Marketing Authorisation from the EMA. Avastin received four EMA value recognitions in 2007 (including approved indications for three further cancers) and sales in France increase further immediately after that. It is worth noting that after the first quarter of 2009, when the recognitions of value expansion by HAS are mainly for different treatment regimens for two cancers (plus one indication for a new cancer in 2011), sales of Avastin begin to fall.

Figure 42. Sales (EUR) of Avastin in France compared with EMA authorisations and HAS value recognitions
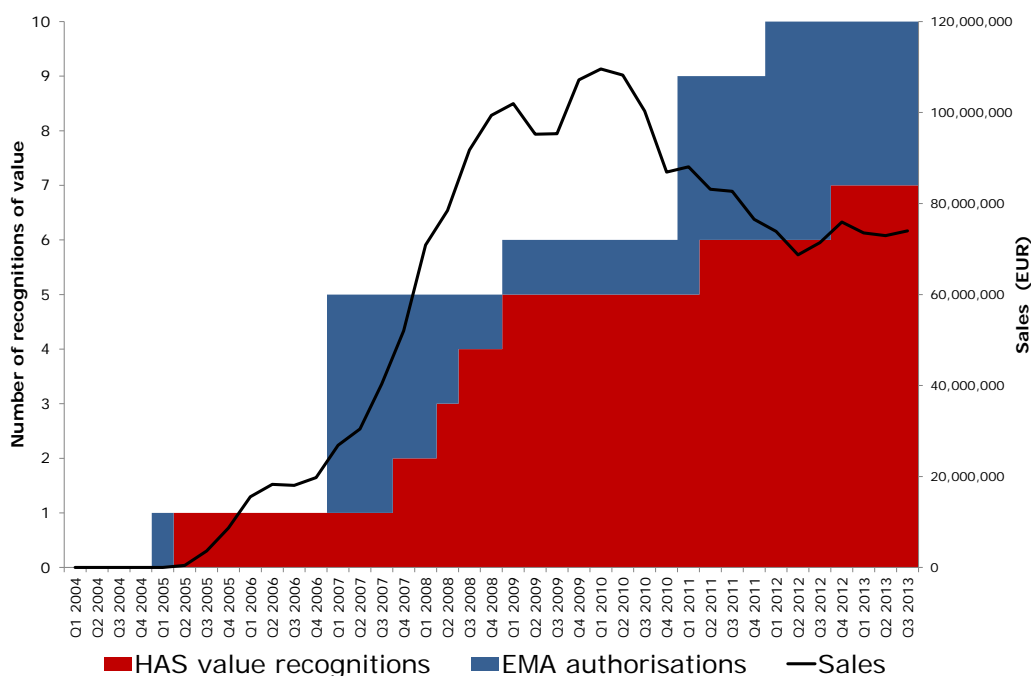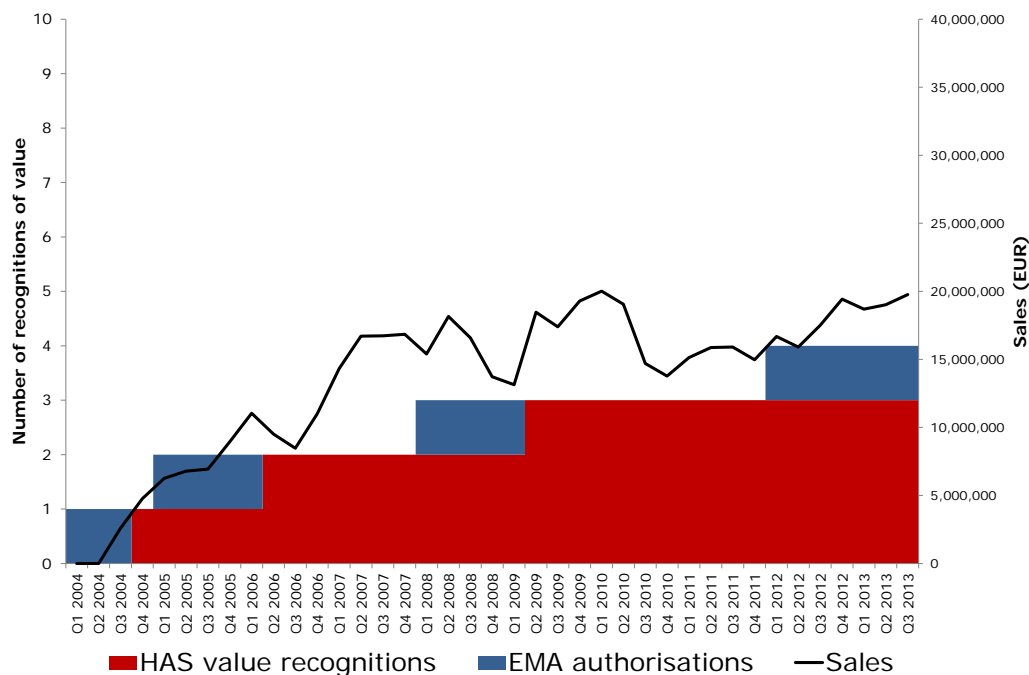

Source: authors' analysis from IMS and Stage 3 of this study.

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[2] List of the Specialties for which nominative ATU were granted between 1 July 2004 and 30 June 2005 can be found in http://ansm.sante.fr/Activites/Autorisations-Temporaires-d-Utilisation-ATU/ATU-nominatives/(offset)/2

Sales for Velcade in France are presented in Figure 43. It is not possible to observe a link between value recognitions and sales by eyeballing the data. Nevertheless, sales appear to exhibit an annual cyclical pattern.
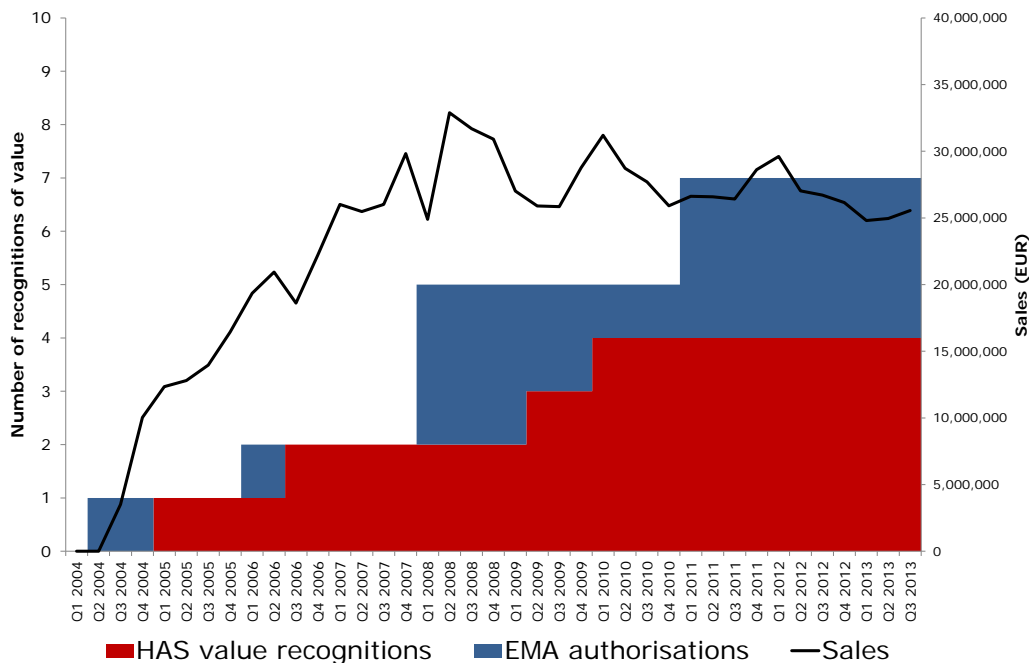
Figure 43. Sales (EUR) of Velcade in France compared with EMA authorisations and HAS value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

In Figure 44, the relationship between sales and recognitions of values for Erbitux is unclear. Nevertheless, during the first four years, a period that also corresponds to two approvals for the different cancer types, quarterly sales of Erbitux increase from €0 to €25 million. After this, during the next six years when there are only two EMA authorisations, quarterly sales fluctuate between €25 million and €35 million. Like Avastin, Erbitux appears in the ATU list of 2004, which could explain the sharp increase in sales that precedes the HAS value recognition.

Figure 44. Sales (EUR) of Erbitux in France compared with EMA authorisations and HAS value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

As with Erbitux, sales of Tarceva in France increase from launch until reaching a point of relative stability (Figure 45). Additionally, sales of Tarceva present less variability during the period of analysis than the other selected drugs. Although there does not appear to be a clear relationship between sales and value expansions, it is important to note that Tarceva was mentioned in the ATU list of 2004.

Figure 45. Sales (EUR) of Tarceva in France compared with EMA authorisations and HAS value recognitions
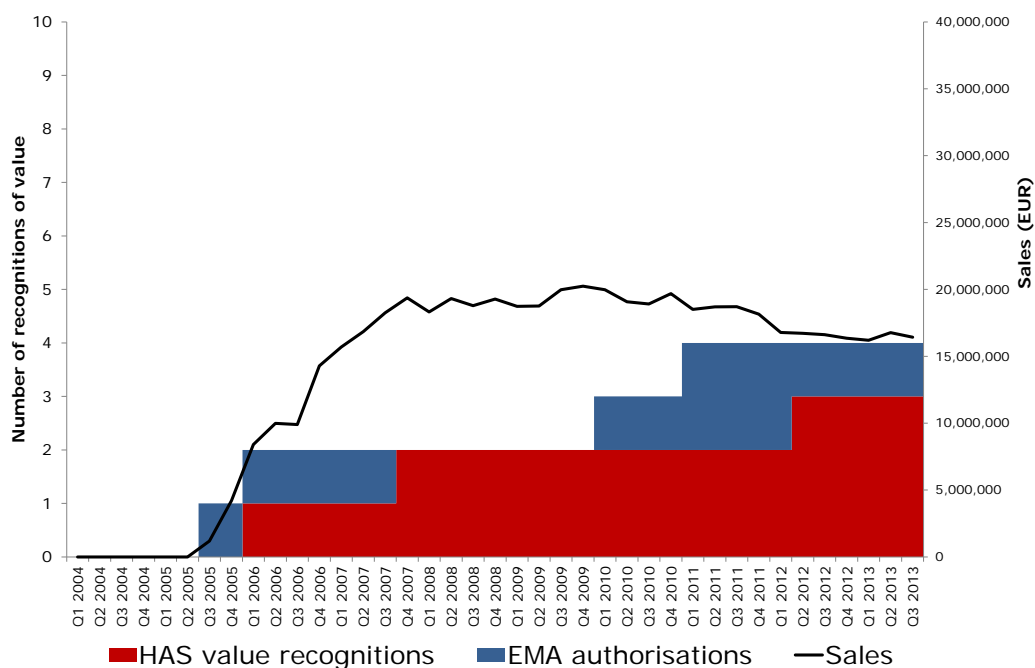
Source: authors' analysis from IMS and Stage 3 of this study.

The final figure for France presents the data for Alimta (Figure 46). Just as with the previous figures, we observe a strong increase in sales after launch – in this case between late 2004 and early 2006. After a period of relative stability, a second sharp growth in sales is observed during 2008. This growth is driven primarily by an increase in usage (Figure 36) rather than a price increase (Figure 21). In addition, the start of the second growth period in sales (2008) coincides with the approval of Alimta as first and second-line treatment for NSCLC. Again, Alimta was one of the specialties for which nominative ATU was granted between 1 July 2004 and 30 June 2005.

Figure 46. Sales (EUR) of Alimta in France compared with EMA authorisations and HAS value recognitions
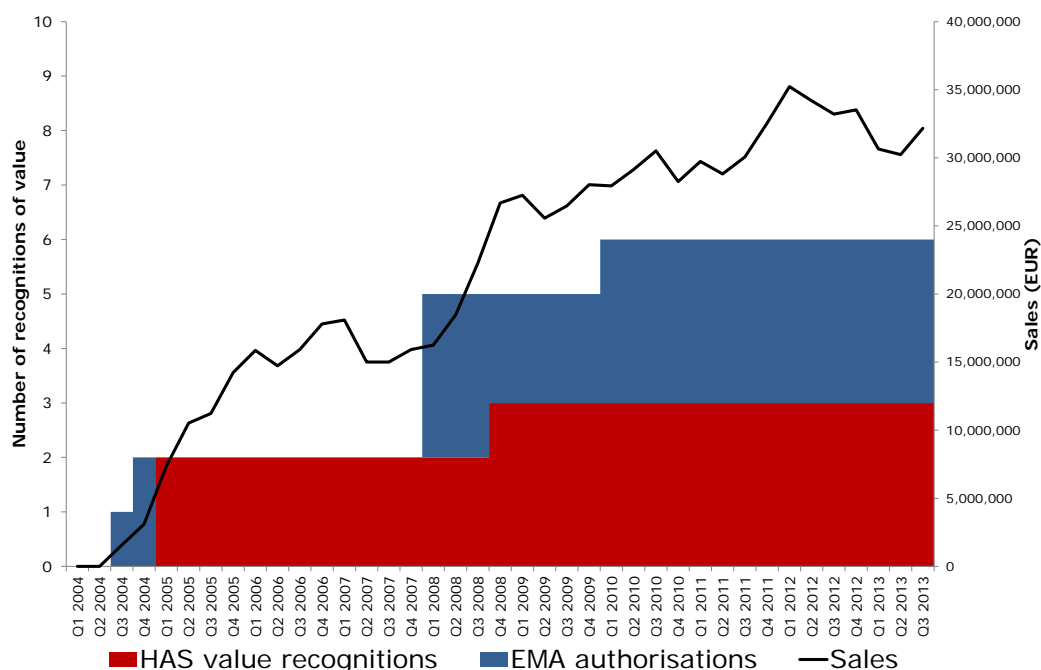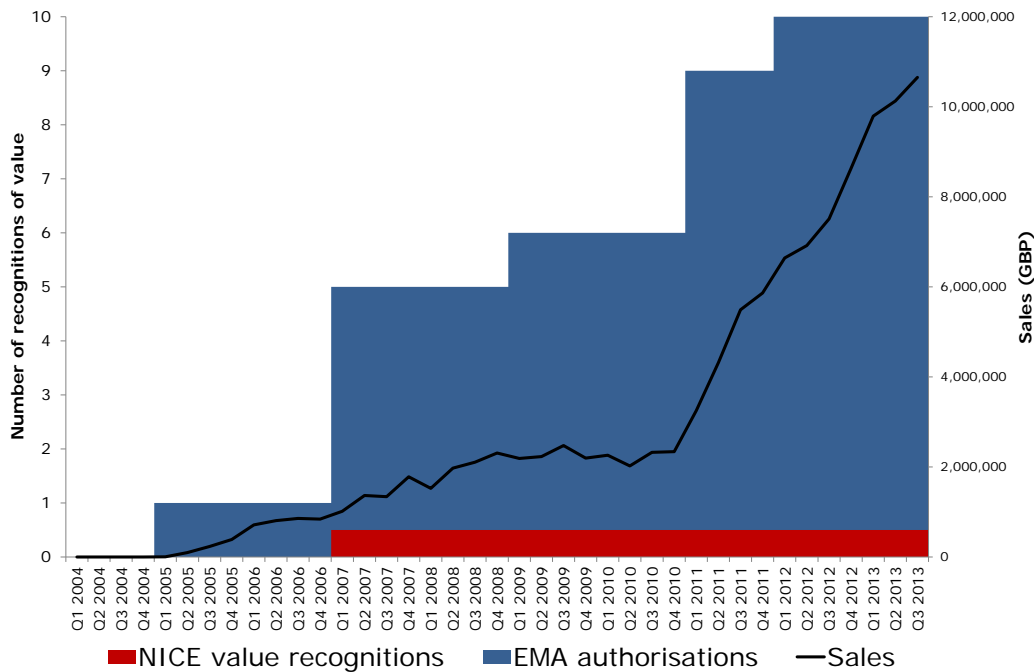

Source: authors' analysis from IMS and Stage 3 of this study.

In the UK (Figures 47 to 51), the level of sales is considerably smaller than in the case of France, with a range between 0 and £11 million per quarter.

Figure 47 presents the data for Avastin. The eight NICE appraisals of the use of Avastin resulted in non-recommendations. However, of our five selected medicines, Avastin displays the strongest increase in UK sales, particularly from 2011 onwards. It is important to note that the Cancer Drugs Fund (CDF) was introduced in England and Wales in 2010, and there are a large number of notifications regarding the use of Avastin under the CDF (see Appendix II for more details). It is possible that the increase in sales for Avastin observed after 2011 is due to the CDF (we cannot tell from IMS data whether that is indeed the case).
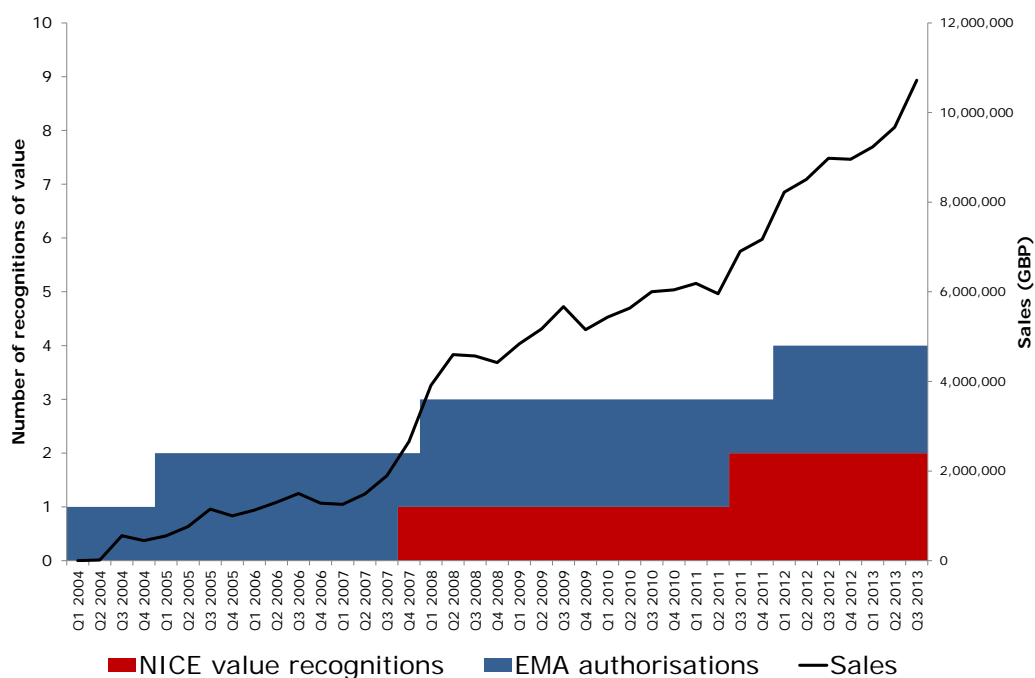
Figure 47. Sales (GBP) of Avastin in the UK compared with EMA authorisations and NICE value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

Sales of Velcade are presented in Figure 48. Just as with Avastin, by the end of the analysis period quarterly sales are close to £11 million. We observe two points of inflexion in the sales curve. The first is in 2007, which coincides with the restricted recommendation by NICE of Velcade for the second-line treatment of multiple myeloma. The second is in 2011, which is when NICE gave a positive (albeit restricted) recommendation to the use of Velcade for the first-line treatment of multiple myeloma. In addition, some of the increase may be due to the CDF as there are also notifications to use this product under the CDF (see Appendix II).

Figure 48. Sales (GBP) of Velcade in the UK compared with EMA authorisations and NICE value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

In the case of Erbitux (Figure 49), there appear to be two inflexion points corresponding to increases in sales. The first is in 2009, which is when NICE approved the restricted use of Erbitux for the first-line treatment of colorectal cancer. The second is in 2011, which coincides with the implementation of the CDF in England and Wales.
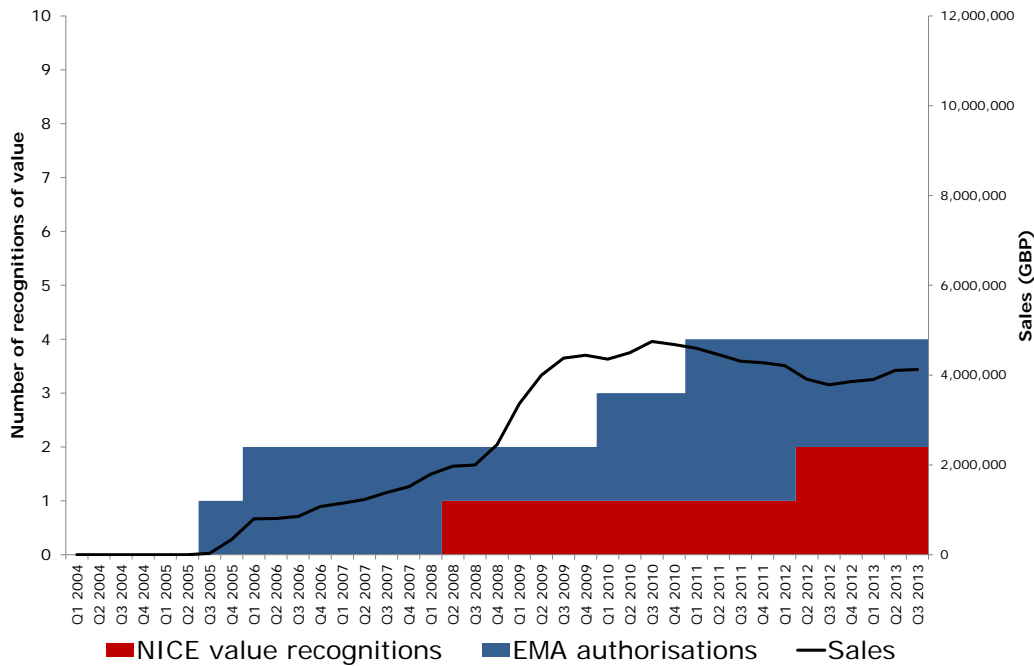
Figure 49: Sales (GBP) of Erbitux in the UK compared with EMA authorisations and NICE value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

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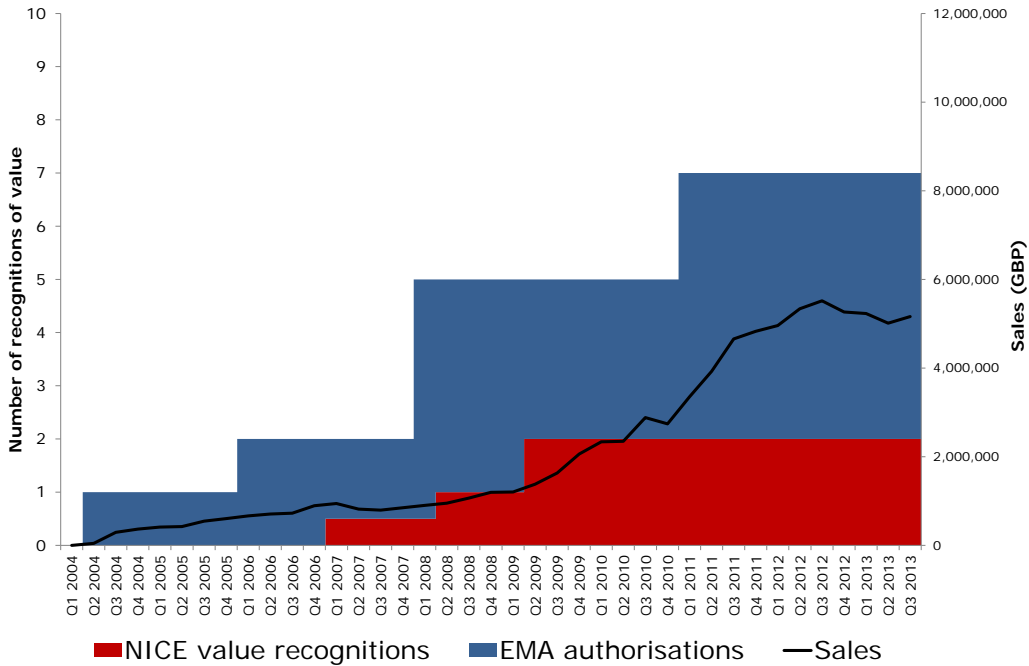
Of the selected drugs, we observe the lowest level of UK sales for Tarceva, with a maximum of approximately £5 million per quarter (Figure 50). We observe four different periods in the evolution of sales. First, there is a steady increase in sales until mid-2008. This is followed by a faster growth in sales lasting for one year, a slight decline until late 2012, and a slight increase thereafter. The increase in sales during the second period occurs just after NICE recommended (with restrictions) the use of Tarceva for the second-line treatment of NSCLC. The third period, when sales decline, coincides with the introduction of the CDF.

Figure 50. Sales (GBP) of Tarceva in the UK compared with EMA authorisations and NICE value recognitions

Source: authors' analysis from IMS and Stage 3 of this study.

Sales of Alimta in the UK increase throughout the period of analysis (Figure 51). Between 2004 and mid-2009, we observe a relatively slow growth in sales. After this, sales of Alimta increase at a faster rate, for a period of about one year. From mid-2010 onwards, the growth in sales reverts to a steadier pace. The two main inflexion points occur around three quarters following positive assessments by NICE.

Figure 51. Sales (GBP) of Alimta in the UK compared with EMA authorisations and NICE value recognitions
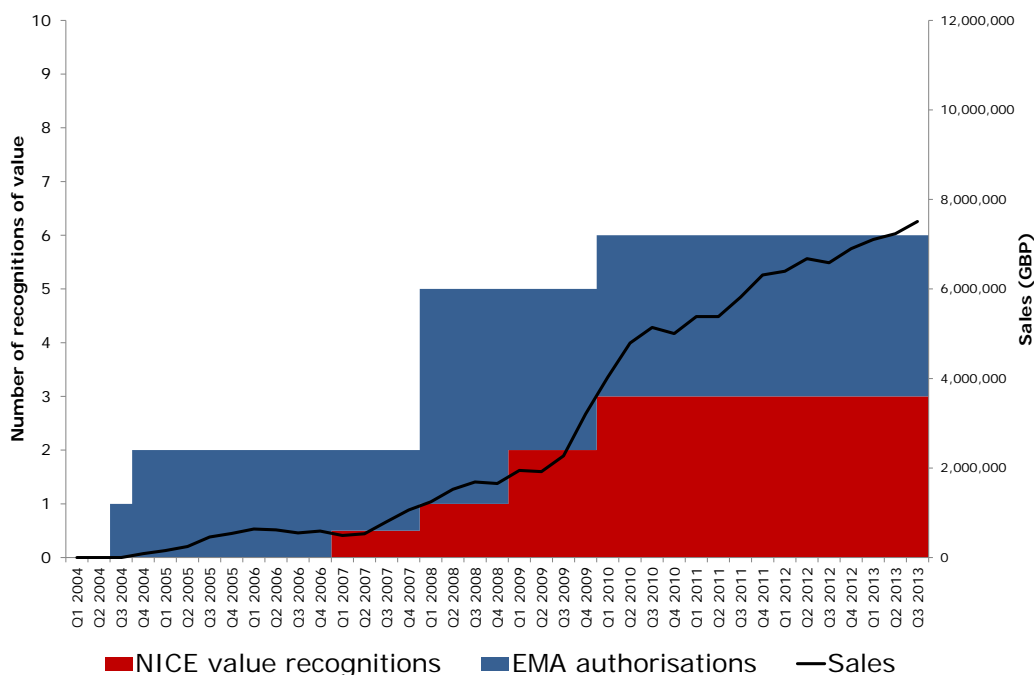
Source: authors' analysis from IMS and Stage 3 of this study.

Overall, and based on Figures 42 to 51, there is mixed picture in terms of the links between recommendations by NICE/HAS and sales in the UK/France. In France, there are cases where uptake has taken off in advance of HAS decisions. This typically occurred when the drug in question was made available via the ATU system, which allows medicines to be available prior to marketing authorisation. For the UK, two points are worth raising. First, there are cases where sales increased after the introduction of the CDF (Avastin, Velcade and Erbitux). Second, for Velcade, Erbitux, Tarceva and Alimta there is an upward inflexion at or soon after the time of a positive (albeit restricted) NICE recommendation. Unsurprisingly, there is a *prima facie* link between expansions in licensed indications and increases in sales. In a number of cases, we observe strong growth in use as the first post-launch label expansions occur, followed by a flattening or reduction in usage. We have not explored the impact of the availability of competing products for our cohort of drugs. Increased competition or changes in treatment patterns for the first approvals could lead to reductions in usage in later years. This effect might offset the increased opportunity of further expansions of value.

8. STAGE 5: CHARACTERISING THE HTA ENVIRONMENT

8.1 Understanding "value"

In this sub-section, we first set out a framework to discuss "value" in general terms. We then apply this framework to explore how value is characterised and assessed in our countries of interest.

8.1.1 What is value?

Broadly speaking, countries' HTA systems can be divided into two groups depending on whether they focus on:

1. Clinical effectiveness/added therapeutic value, based upon clinical trials or surveys of clinical practice, combined with budget impact; or

2. Cost-effectiveness criteria, with or without some threshold for the cost per QALY.

Both systems involve a comparison with other drugs or the standard of care to link price to value. Price (P) can therefore be thought of as a function of the decision maker's perception of value (V), and algebraically this could be expressed as:

$P = f(V)$

Algebraically, we could define value as a function of four different attributes:

$V = g(B, C, k, U)$

where value (V) is the additional benefit (B) minus additional cost (C). Across different systems, all benefits are not expressed in a common currency (e.g. money or a cost-per-QALY ICER). When this explicit common currency does not exist, then B becomes a key attribute in the decision making process.

In addition, we have k representing the opportunity cost of resources. Referring back to our original typology of HTA systems, there could be two different interpretations for k. Under cost-effectiveness analysis (group 2), k involves an implicit or explicit threshold. With the therapeutic added value (group 1), there is no formal cost-effectiveness analysis, so the price is set by a mix of rules and negotiation. Finally, U is the uncertainty around the value.

We could categorise the HTA system in France as falling within group (1), whereas the HTA system in England and Wales falls within group (2). France may, however, be moving towards group (2): HAS recently published a "Methodological Guide" to economic evaluation in which it states that QALYs are to be measured in cost-utility analyses in cases where it is possible to obtain QALY data at reasonable cost (HAS,

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2012). The use of QALYs as an outcome measure could be a precursor to the use of a cost-per-QALY threshold.

In addition, HAS could be deemed as a decision maker, as ultimately HAS ratings will be reflected in the price of medicines in France when they are negotiated between HAS and the manufacturer. NICE, on the other hand, offers recommendations about whether or not to use a medicine, under what conditions and for what patient sub-populations. NICE does not negotiate prices with manufacturers. Appendix II contains further details on the two systems. The differences between HAS and NICE should be considered when we try to compare their decisions; it is difficult to make "like-for-like" comparisons. Given the limited information, we have not been able to find the explicit — or revealed implicit — criteria used by Aetna, so it is unclear which group Aetna would fall within.
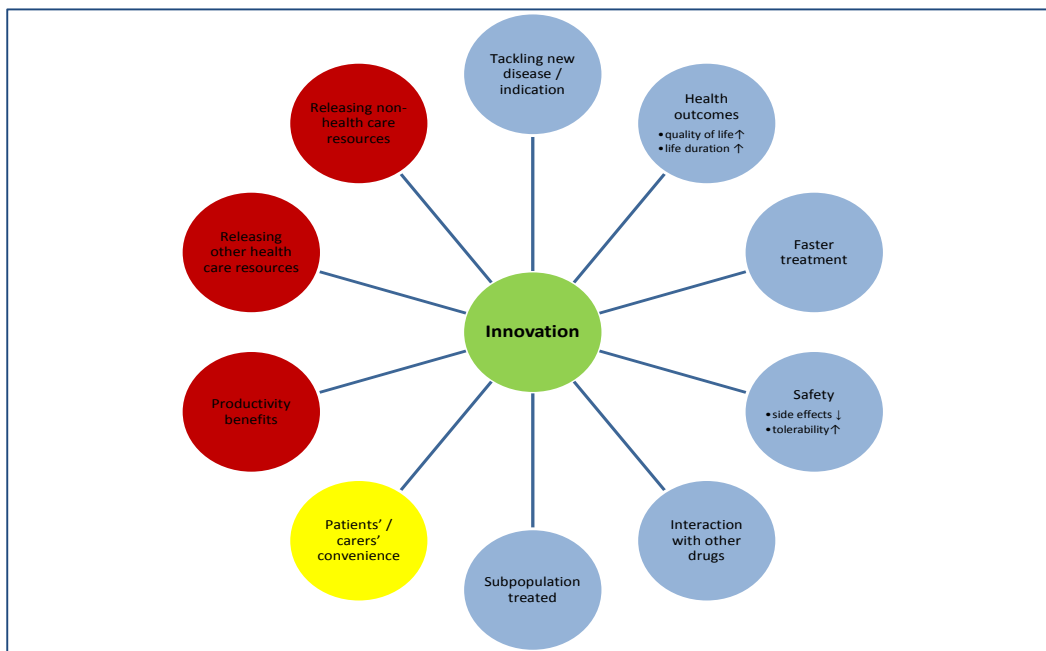
Elements of value

A number of elements could be used to define value. "Health effect" is usually the single most important benefit, followed by cost-offsets within the health care system. We then have elements of benefit to the patient that are not necessarily captured in the measure of health gain, including:

- Health-related quality of life aspects not well captured by a generic measure
- Health care process-related aspects such as being treated with dignity, at a convenient time and location, and after only a short wait
- Information for the patient which, for example, enables lifestyle choices to be made, independent of any health effects

There are also other costs and benefits beyond those to patients and the health care system, as well as innovative attributes of a technology that may be deemed to confer value independent of the health gain generated. Figure 52 illustrates diagrammatically all of these possible elements of value.

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Figure 52. Elements of value of medicines

Source: Mestre-Ferrandiz, Sussex and Towse (2012).

However, not all elements are recognised in assessments of value of new medicines. Figure 53 illustrates those elements that are usually recognised, and those which are recognised less frequently or consistently.

Figure 53. Elements of value recognised in value assessments
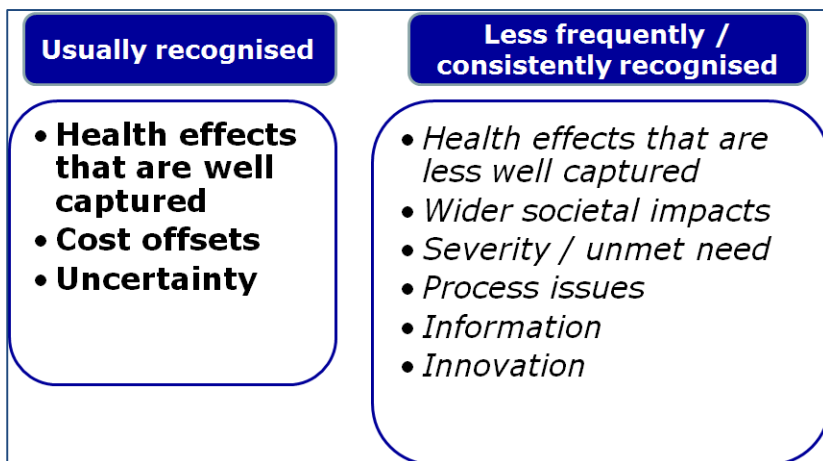
Source: Authors' interpretation from publicly available information.

The next step to consider is how these elements are measured and supported with evidence. The health effect is usually measured by the use of QALYs, clinical outcomes, patient-reported outcomes and disease-specific measures. These effects are supported

by evidence from different sources, such as randomised clinical trials (RCTs), observational studies, patient testimony and expert clinical opinion.

For health gain in particular, we can also observe that the "value" of the health gain to society may be higher or lower depending on who gets it. For example, some countries recognise additional value when target segments of the population experience the gain, such as disadvantaged groups, the sickest patients, caregivers or children. Following this rationale, it can also be the case that the type of illness also matters, such as for "end of life" conditions.

A critical component of the assessment of value, and in particular health gain, is the comparator used to assess the value of a new medicine. Thus, the choice of comparator is key. The comparator is usually defined as "standard of care", but this term is used inconsistently, and different operational definitions tend to be used by the same stakeholder at different times. Figure 54 shows the different definitions of standard of care used in practice.

Figure 54. Definitions of "standard of care"
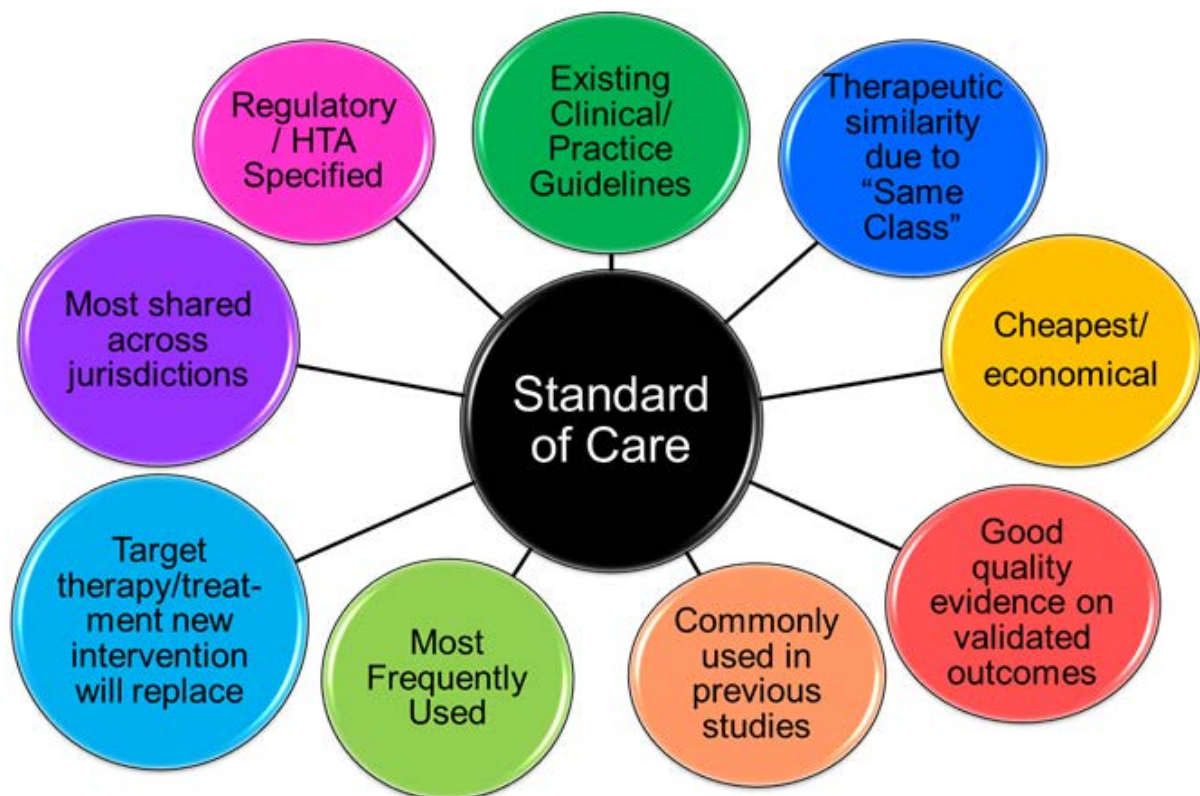
Source: DeLozier et al. (2013).

A key challenge when assessing the value of new medicines is the volatility that can exist around the standard of care. For instance, the standard of care used during a Phase

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III trial can actually change, because of market withdrawals, the emergence of innovative products and/or generic entrants and changing practice. Moreover, there are inter-country variations as the standard of care in one country can be different from the standard of care in another country. And regulators and payers/HTA bodies might differ in terms of what they deem to be an appropriate comparator, as these two stakeholders have different remits when assessing the "value" of new medicines.

We now apply our general conceptual framework to describe in detail how our countries of interest assess the value of new medicines.

8.2 Differences in how evidence has interpreted by different agencies

In this sub-section we briefly examine how NICE and HAS often reached different conclusions about the same product/indication, focusing on Alimta as an illustrative example (similar issues arise for the other drugs with multiple value expansions).

Alimta for the second-line treatment of malignant pleural mesothelioma

HAS approved Alimta for this indication and gave it an SMR of II (important) and an ASMR of III (significant improvement). This shows the picture of a therapy that is regarded by HAS as highly valuable and that is seen as showing significant added value compared to other therapies already available in the market for that indication. This valuable addition that Alimta brings to the therapeutic arsenal available in the market is reflected in the price for which the French health care system reimburses the drug. However, NICE recommends Alimta for this indication with some restrictions in the treatment population for which it is recommended (i.e. only recommended for patients with WHO performance status 0 or 1; not recommended for patients with WHO performance status >1). This is an example of HAS recommending the reimbursement of a drug at a high price for the indication that the EMA previously authorised it for, and NICE recommending it only for a restricted patient sub population.

Alimta in combination with cisplatin for the first-line treatment of NSCLC other than predominantly squamous histology

HAS recommended the use of Alimta in this indication for the same patient population as the EMA's authorisation. HAS awarded the drug an SMR rating of II (important) and an ASMR rating V (no improvement). In this case, Alimta was regarded by HAS as having important benefits for the indication authorised by the EMA, but having no added value when compared with the therapeutic alternatives already available in the market. However, NICE recommended the use of Alimta, restricting it to patients with histology of adenocarcinoma or large-cell carcinoma. In this example, HAS recommended reimbursing the drug for the appraised indication with a very low price, and NICE recommended it for a subgroup of population and deemed it to be appropriate use of

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NHS resources considering the price suggested by the manufacturer in the cost-effectiveness analysis.

Alimta as monotherapy after prior chemotherapy for the treatment of NSCLC

This is an example of a drug indication that was recommended by HAS and not recommended by NICE. In 2005 HAS assessed this indication, authorised by the EMA in 2004, and awarded it a SMR of II (important) and an ASMR of V (no improvement). NICE appraised the use of Alimta for the same indication in 2007 and did not recommend it, stating that it would not be cost-effective use of NHS resources. In this case, HAS recommended the reimbursement of the drug for the appraised indication at a very low price, while NICE recommended not reimbursing it at all.

8.3 Contractions of patient populations and personalised medicine

The value expansions derived from changes in the patient sub-population present a particular paradigm. As described in the section on Stage 2, this expansion refers to changes that: (1) expand the use of the drug to new populations; and (2) restrict the use of the treatment to a patient sub-population that is more likely to benefit from it. Treating new patient populations represents a benefit to the patients that become eligible to receive a treatment and to the manufacturer of the drug that see an increase in the volume of sales for that drug. However, the reward to the manufacturer is less clear when their treatment is approved for a small patient sub-population. Targeting patient sub-populations is aimed at treating patients more likely to benefit and prevent unnecessary adverse events in patients for whom the treatment would not be effective enough to justify the risks. On the other hand, the consequence for the manufacturer is a reduction of volume of sales due to the reduction in the number of patients treated with that drug. This could pose a market disincentive for manufacturers to pursue the approval of their therapies for specific patient sub-populations (Reid, Bin Yameen and Parker, 2013).

The data relating to our cohort of drugs and the time period studied contained little information about companion diagnostics, so we have not been able to explore in great detail the challenges that personalised medicine and companion diagnostics bring to HTA for oncology drugs. Nevertheless, Garau et al. (2013) argue that current pricing and reimbursement systems for diagnostics are not efficient because prices for diagnostics are often driven by administrative practices and expected production costs. The authors suggest a potential two-part approach to improving the value assessment process for molecular diagnostics. Companion diagnostics introduced at drug launch should be assessed through new drug assessment processes considering a broad range of value elements and a balanced analysis of diagnostic impacts. A separate diagnostic-dedicated committee using value-based pricing principles should review other diagnostics lying outside the companion diagnostics-and-drug 'at-launch' situation.

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Towse and Garrison (2013) summarise the critical economic issues in developing evidence of value for drugs and diagnostics that are part of personalised medicine – sometimes called "stratified" medicine. They argue that that progress in personalised medicine has been slower than many had hoped for several reasons – the scientific challenges particularly, but perhaps also the poor incentives for rewarding value and evidence generation related to diagnostics. They also suggest offering appropriate economic incentives, particularly in terms of flexible pricing based on value, to encourage more rapid progress in the development and availability of drugs and diagnostics. This would require adjustments to existing pricing, evidence, and intellectual property approaches.

## 8.4 Recognition of the value of health outcome improvements

Most of the value expansions analysed in Stages 2 and 3 are supported by evidence of gains in overall survival offered by the drug under assessment relative to an appropriate comparator. Figures 55 through 58 examine the relationship between the estimated gain in overall survival reported for a particular drug/indication against its comparator, and the way in which the added value of the drug/indication was interpreted by the HTA agencies (as in Figures 7 through 16, we focus on ASMR level for HAS and recommendation/decision for NICE). We have expressed gain in overall survival (relative to the comparator) both in terms of absolute gains and in percentage terms. The rationale for the latter was to examine whether a gain of a certain size was perceived as having a different value depending on the starting point (i.e. is an extra month of survival in addition to a baseline survival of five months valued the same as an extra month in additional to a baseline of 10 months). The figures are based on the four drugs for which most data are available: Alimta, Avastin, Erbitux and Tarceva.

The analysis is crude and approximate, and some limitations should be noted. Overall survival estimates are not always reported in the assessment reports – for example, due to uncertainty or because the benefits were reported in terms of a different measure such as progression-free survival. In such cases, the data would not be captured by the figures. Furthermore, Figures 55 through 58 do not indicate whether or not the reported gains in overall survival were statistically significant (though this information is captured explicitly in the Stage 3 database). Furthermore, NICE often reports multiple overall survival estimates within a given appraisal, particularly when distinguishing between different patient subgroups. For this basic analysis we have taken the mid-point of the range or the average of the estimates reported, when applicable.

Notwithstanding these caveats, we see that the higher the estimated gains in overall survival (expressed in absolute terms), the more likely HAS is to award a higher ASMR level (II or III) rather than a lower ASMR level (IV or V). In the two cases of no ASMR rating being given (due to an SMR rating of level V, i.e. insufficient; Tarceva in both instances), the estimated gains in overall survival were no greater than one month.

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At a high level, we can observe similar patterns when gains in overall survival are expressed as in percentage terms, but one interesting result emerges. Percentage gains in overall survival can be higher for some ASMR level IV and V decisions for the only ASMR level II decision; in absolute terms, this was never the case.

Figure 55. Relationship between estimated absolute gain in overall survival and HAS ASMR rating
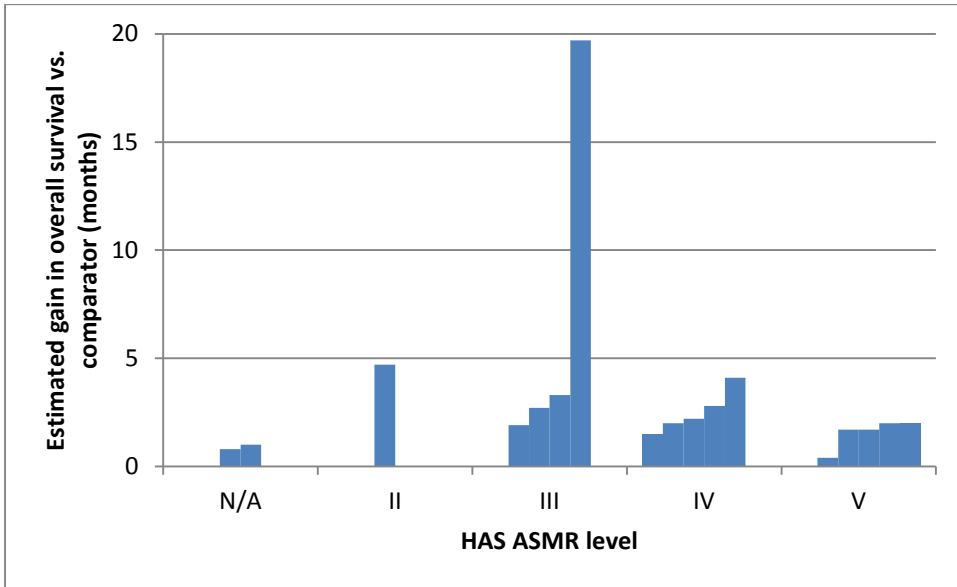
Source: Stage 3 database.

Figure 56. Relationship between estimated percentage gain in overall survival and HAS ASMR rating
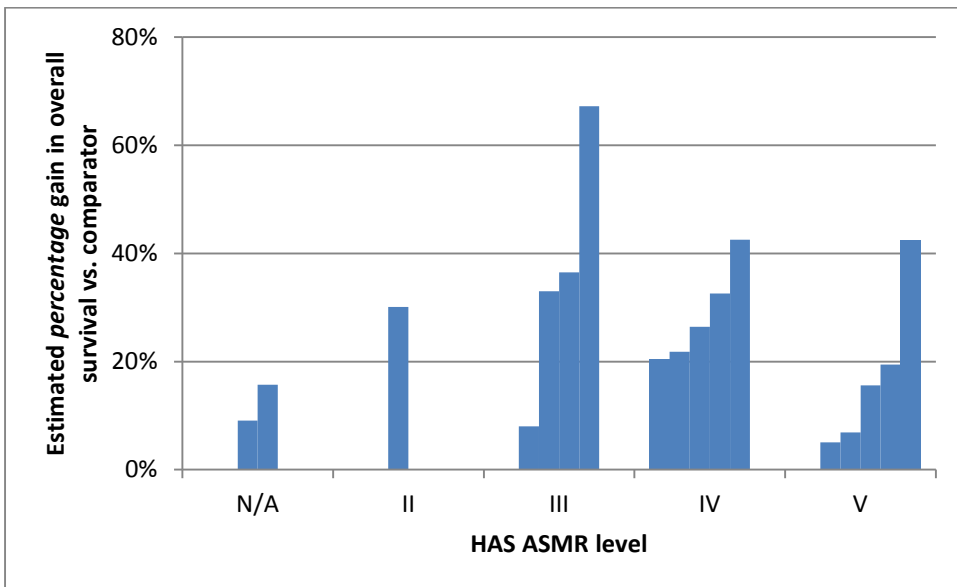
Source: Stage 3 database.

The results for NICE also seem to suggest a positive association between gains in overall survival and recommendation decision; although there are a number of "Recommended with restrictions" decisions with lower gains relative to those reported for "Not recommended" decisions. This reinforces the point that a key element in NICE decision process is the ICER (rather than survival gains alone). A similar association is apparent when gains are expressed as a percentage.

Figure 57. Relationship between estimated absolute gain in overall survival and NICE decision
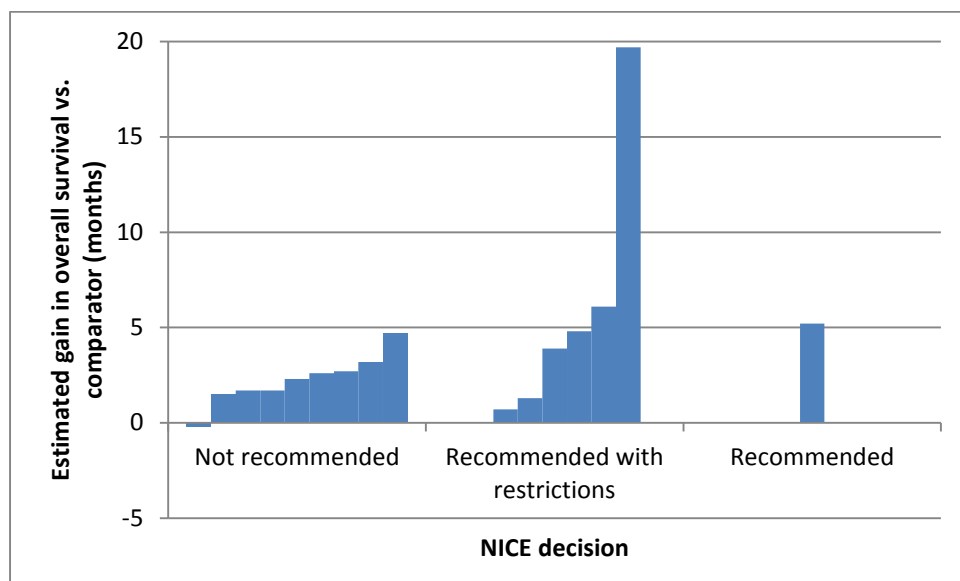
Source: Stage 3 database.

Figure 58. Relationship between estimated percentage gain in overall survival and NICE decision
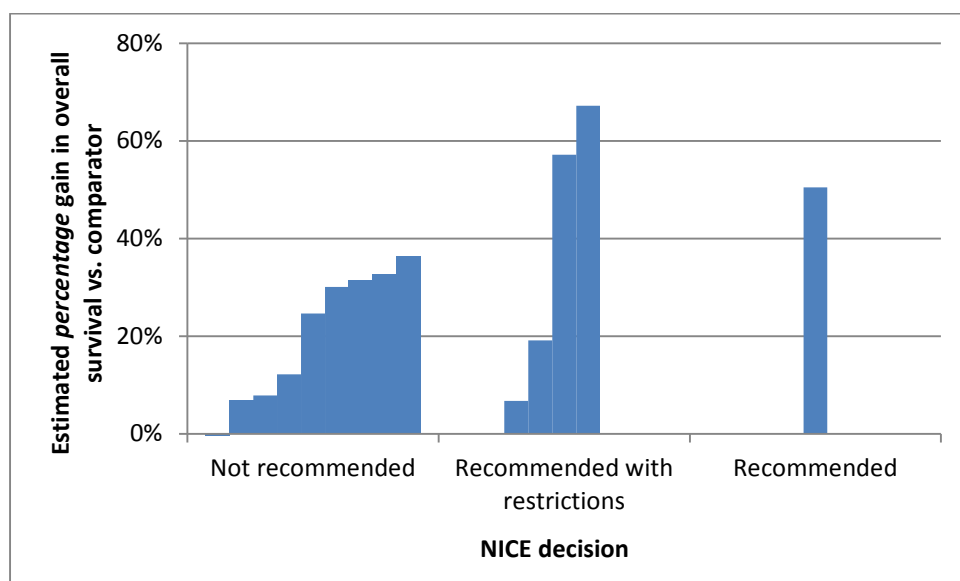

Source: Stage 3 database.

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Although we acknowledge that any conclusions made from such a small sample should be treated with a great deal of caution, the data presented here suggest that HAS and NICE differ in terms of the value they place on an overall survival gain of a given size, with HAS being more likely to value the gain differently depending on the baseline level of survival.

The clear outlier in these figures refers to the case of Erbitux for the treatment of locally advanced squamous cell cancer of the head and neck. Both HAS and NICE reported in their assessments that Erbitux plus radiotherapy offered a large and statistically significant improvement in overall survival compared to radiotherapy alone – indeed, the largest incremental improvement, both in absolute (19.7 months) and relative (67%) terms, of any of the indications covered in this study. Yet NICE still placed restrictions on its recommendation – the use of Erbitux was not recommended for certain patient subgroups due to unfavourable ICERs. Furthermore, although the HAS assessment of this indication was the only one we identified as resulting in the award of an SMR level I (representing the highest level of health benefit), the ASMR level awarded (III) was lower than that achieved by another drug (Avastin for first-line treatment of metastatic colorectal cancer) which offered smaller absolute and relative gains in overall survival. This shows that whilst gain in overall survival gains is a fairly good predictor of a favourable assessment, it is clearly not the only element of value that matters.

The data collected in Stage 3 also allow us to examine how incremental improvements in health outcomes over time (for a given drug and cancer type) are recognised by HAS and NICE in their technology assessments. For example, Tables 8 and 9 summarise the HAS and NICE assessments of Alimta for the treatment of locally advanced/metastatic NSCLC. When the agencies assessed the drug for the first of its EMA authorised indications (second-line monotherapy; indication 2 in Table 2), the reported gains in overall survival compared to its comparator docetaxel were very small/non-existent. As a result, low value was attributed to the use of Alimta for this indication – HAS awarded it an ASMR rating of V (no improvement) and NICE did not recommend its use.

By contrast, when the agencies assessed Alimta for a more recently approved EMA indication (monotherapy maintenance treatment in patients whose disease has not progressed immediately following platinum-based chemotherapy with gemcitabine, paclitaxel or docetaxel; indication 5 in Table 2), the reported gains in overall survival were larger. This led to greater recognition of the product's value in the agencies' assessments – HAS awarded it an ASMR rating of IV (minor improvement) and NICE recommended its use (albeit after applying QALY multipliers as the drug was considered to meet the criteria for being appraised as a life-extending end of life treatment).

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Table 13. HAS assessments of Alimta for the treatment of locally advanced/metastatic NSCLC

Date	EMA indication (cf. Table 2)	Estimated gain in OS (months)	Decision	HAS SMR	HAS ASMR
Mar 2005	2	0.4	Recommended	II	V
Nov 2008	3	0.0	Recommended	II	V
Nov 2008	4	1.7	Recommended	II	V
May 2010	5	2.8	Recommended	II	IV

Source: Stage 3 database.

Table 14. NICE appraisals of Alimta for the treatment of locally advanced/metastatic NSCLC

Date	EMA indication (cf. Table 2)	Estimated gain in OS (months)	Decision	NICE ICER (£/QALY gained)
Aug 2007	2	-0.18	Not recommended	450,000
Sep 2009	3	0.0 - 1.4	Recommended with restrictions	17,162 - 30,142
Jun 2010	5	5.2	Recommended	47,000

Source: Stage 3 database.

In the case of Erbitux for the treatment of cancer of the head and neck, the initial EMA authorised indication (in combination with radiotherapy, for locally advanced epidermoid carcinoma; indication 20 in Table 2) was associated with an extremely large improvement in overall survival for certain patient groups. It was awarded by HAS an SMR rating of I (high; the only such case in our study) and an ASMR rating of III (significant improvement); and was recommended for use in selected patient subgroups by NICE.

However, the more recent EMA authorisation for Erbitux for this cancer type (in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic squamous cell disease; indication 22 in Table 2) was associated with much smaller health gains. For this indication, HAS gave the drug a lower SMR rating of II, and NICE did not recommend its use as the high ICER suggested that it would not be a cost-effective use of NHS resources.

Table 15. HAS assessments of Erbitux for the treatment of cancer of the head and neck

Date	EMA indication (cf. Table 2)	Estimated gain in OS (months)	Decision	HAS SMR	HAS ASMR
Oct 2006	20	19.7	Recommended	I	III
Feb 2010	22	2.7	Recommended	II	III

Source: Stage 3 database.

Table 16. NICE appraisals of Erbtiux for the treatment of cancer of the head and neck

Date	EMA indication (cf. Table 2)	Estimated gain in OS (months)	Decision	NICE ICER (£/QALY gained)
Jun 2008	20	19.7	Recommended with restrictions	4,467 - 58,200
Jun 2009	22	2.7	Not recommended	166,307

Source: Stage 3 database.

8.4.1 Factors beyond health outcomes

The preceding sub-section describes the relationship between the estimated gains in survival offered by cancer medicines and the extent to which the value of the medicines were recognised by HAS and NICE. However, a number of other factors are taken into account by payers and HTA agencies when evaluating drugs and making reimbursement decisions.

For example, NICE's decision-making is guided by a several factors beyond cost-effectiveness alone, such as considerations about equity or the severity of the underlying illness (Rawlins, Barnett and Stevens, 2010; Shah et al., 2013; see Appendix II for further details). However, although budget impact does not play an explicit role in NICE's decision making processes, it has been shown to have an effect on its recommendations. Mauskopf et al. (2013) estimate the correlation between the degree of restriction on NICE recommendations for each new drug indication and the potential budget impact of those recommendations, controlling for clinical and cost-effectiveness. They show that budget impact did not predict overall recommendations by NICE but was certainly associated with the application of restrictions on the recommendations.

8.5 Appropriateness of the methods for assessing and appraising oncology treatments

Although like-for-like comparisons are difficult, the Stage 3 analysis clearly shows that NICE is much more likely *not* to recommend the use of a given oncology product than is HAS. However, the UK Government introduced in 2010 (but only for England) the CDF, with the objective of providing a means of improving patient access to cancer drugs not approved by NICE (amongst other criteria). Although originally announced to run only until the end of March 2014, it was announced in 2013 that the CDF will now run until 2016 (NICE, 2013c). Appendix II contains further details on the CDF. One interpretation of the introduction of the CDF is that the standard NICE approach, which compares the ICER of the drug under appraisal with a cost-effectiveness threshold, is not always appropriate for oncology treatments. The ICERs of oncology drugs frequently exceed NICE's threshold of £20,000 to £30,000 per QALY gains (Trowman et al., 2011).

Analysis by O'Neill (unpublished) [for full details see Appendix II] shows how the proportion of "not recommended" decisions for oncology medicines has more than doubled since the introduction of the CDF (58% post-CDF vs. 24% pre-CDF), while the proportion of "restricted" decisions has fallen significantly, from 41% to 9%. The proportion of positive recommendations has fallen slightly, from 26% to 24%. We do not know the reasons for this shift from "restricted" to "not recommended", so we cannot necessarily conclude that the increased likelihood of negative decisions is associated with the fact that access to the rejected drugs may still be possible via the CDF. However, it is certainly possible that the existence of the CDF reduces the willingness of NICE and the company to compromise as both parties know that the CDF offers an alternative route for patients to access the treatment and companies to obtain sales revenue. We could also interpret the CDF as a sign that in England there is a willingness to pay a price premium (over and above the usual threshold) for cancer drugs. Indeed, 11 of our 15 "not recommended" decisions were associated with ICERs greater than £30,000 per QALY gained (no ICERs were reported for the remaining four decisions), and some of rejected drugs were later covered by the CDF.

A further point to note is that QALYs do not always capture well the benefits of cancer treatments. In a recent review, Garau et al. (2011) found that the QALY shows important limitations in terms of its ability to accurately capture the value of health gains deemed important by cancer patients. The limitations include:

- generic instruments used to measure health-related quality of life, such as the EuroQol Group's EQ-5D, have been found to be relatively insensitive to changes in the health status of cancer patients;
- methods for estimating the value of health states, such as the time trade-off, involve making assumptions that are likely to be violated in end-of-life scenarios;
- the practice of using valuations of members of the general population, as is commonly recommended by HTA agencies such as NICE, is problematic because such individuals typically display a misunderstanding of what it is really like for patients to live with cancer.

In the extreme, agencies could treat cancer drugs similarly to orphan drugs, where the processes for assessing orphan drugs differ from those used for non-orphans (Garau and Mestre-Ferrandiz, 2009). In the Netherlands, for example, manufacturers of orphan drugs are exempt from submitting full economic dossiers (but in exchange there is a commitment to collect post-launch data). NICE does not assess orphan drugs on a regular basis (and ultra-orphan drugs are assessed separately). Indeed, the three orphan drugs – Busilvex, Litak and Lysodren – in our cohort sample have not been assessed by NICE.

8.6 Developing dynamic multi-indication, life-cycle value assessments of the drugs

To this point, our study has defined and tracked the value footprint of 10 compounds in a largely descriptive manner. The expansions of value described can be both dynamic – i.e. changing over time – and for multiple indications for a given product. This raises the obvious question of how much value, in monetary terms, do these expansions actually represent – both in the aggregate and for specific components of the expansion? While a precise estimate may not be feasible for a number of theoretical and practical reasons, it may be possible to produce some approximate magnitudes that are useful for policy discussions. We briefly outline a framework and approach here.

The foundation of economic value determination is rooted in basic microeconomics. The value of an economic good, such as a new medicine, is what a consumer would be willing to pay for it if fully informed about its features. For a particular good, some consumers would be willing to pay more and some less, and in competitive markets, some consumers actually pay less than they would be willing to pay (the difference being "consumer surplus"). Thus, the actual sales would represent a lower bound on the value transacted.

As is well appreciated, the medical care marketplace is unique in terms of the distance of the purchaser from the final consumption decision, since the ultimate purchases are goods that are often prepaid via insurance systems (including public tax-based systems). Still, at a health system level, public and private payers sometimes state – but certainly reveal through their decisions – what they are willing to pay for health gains. NICE's threshold of £20,000 to £30,000 per QALY gained effectively constitutes a willingness to pay (WTP) for health gains, and coverage decisions in the US have often demonstrated a WTP of over $100,000 (as can be observed in the analyses on the Tufts Medical Center Cost Effectiveness Analysis Registry; https://research.tufts-nemc.org/cear4/ [Accessed 6 December 2013]). These estimates provide an approximate range of societal WTP that can be used in an aggregate calculation.

The aggregate net value created or generated by the consumption of a medicine in a given year in a country and given indication can be thought of and measured as the multiplicative product of: (1) the number of patients initiating treatment with the medicine; (2) the expected health gain over the lifetimes of the patients; and (3) the societal WTP for health gains (net of cost). It is important to note that this is a "cohort" or incidence approach rather than an annual prevalence approach. The former estimates the projected value for the cohort initiating treatment in a given year, while the latter would attempt to estimate the value generated in a given year for all patients who are using or have used the product previously. Both could be useful for particular purposes, but the former is more straightforward to estimate as a projection exercise.

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To implement the annual cohort-based approach, two key elements are needed for each year: (1) an estimate of the actual initiation of use for patients by indication; and (2) estimates of the mean ICER for each indication or line of treatment. Estimating the first element can be the more challenging of the two in that few health systems track national volume of use for specific products by disease indication. An alternative approach is to begin with a national-level demographic/epidemiological estimate of the incidence of a condition, and then make assumptions about medicine uptake to develop an estimate of annual use. The mean ICER estimates are by necessity projections based on pharmacoeconomic models, as few, if any, medicines have ICER estimates based on long-term, real-world follow-up.

Garrison and Veenstra (2009) have carried out such a calculation for trastuzumab (Herceptin) over a projected life cycle for two indications – HER2-positive metastatic and early breast cancer – in the US. The product was launched in 1998 for metastatic breast cancer and in 2006 for early breast cancer. They project the potential value creation out to a horizon of the year 2016. To do so required an assumed range of WTP for each indication, demographic/epidemiological projections of annual metastatic and early breast cancer new cases, and assumptions about uptake, use and health gain. Figure 59 shows actual (as of 2006) and projected use of Herceptin for these two indications until 2016. The authors projected that aggregate net value creation (in 2006 USD discounted to 1998) was in the range from $6.2 billion to $49.5 billion, with the variability being driven mainly by the value of a QALY, which was allowed to vary from $50,000 to $150,000.

Figure 59. Estimated and project use of Herceptin over product life cycle for metastatic and early breast cancer
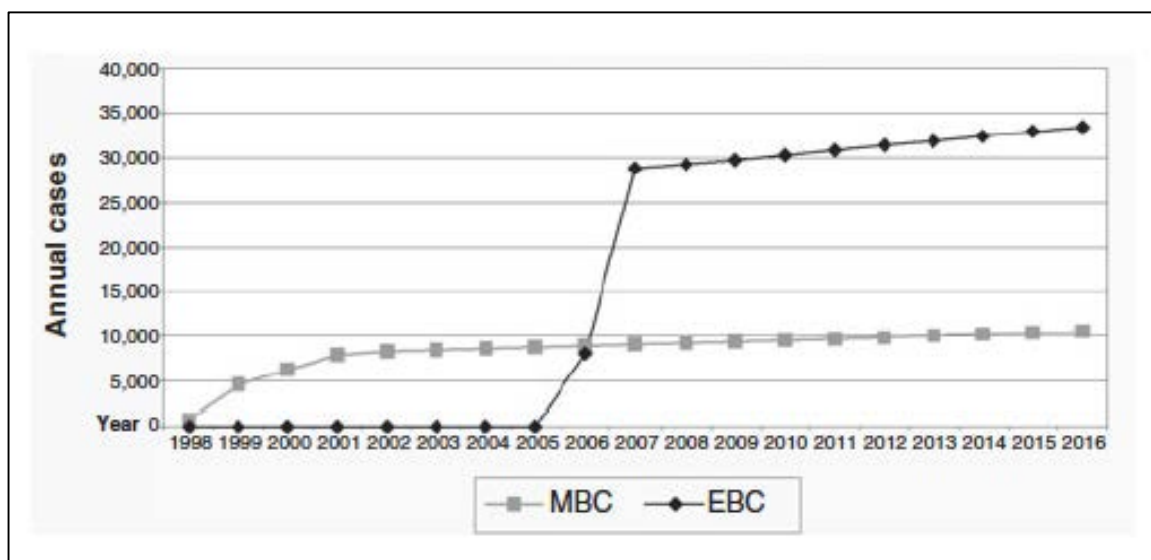
Source: Garrison and Veenstra (2009).

The per-patient Herceptin cost differs somewhat between the two indications (though the price per vial of is constant, and the projected QALY gains differ substantially (0.56 for metastatic and 1.70 for early breast cancer): hence their projected ICERs also differed greatly – $85,700 for metastatic and $26,400 for early breast cancer, respectively (Figure 60). NICE's original recommendation was against coverage in the initial indication of metastatic breast cancer, but this was later reversed based on a re-assessment of the cost-effectiveness. The first published US cost-effectiveness analysis projected the ICER at about $125,000, suggesting that it was on the high side (Elkin et al., 2004). But from a life cycle perspective the combined value of $35,600 would be considered to be cost-effective in most high-income developed countries. This combined value is estimated by projecting between 1998 and 2016 the cumulative net cost of Herceptin ($154bn) and the cumulative QALYs gained (432,547), and then dividing the former by the latter.

Figure 60. Indication-specific and overall life-cycle ICERs for Herceptin
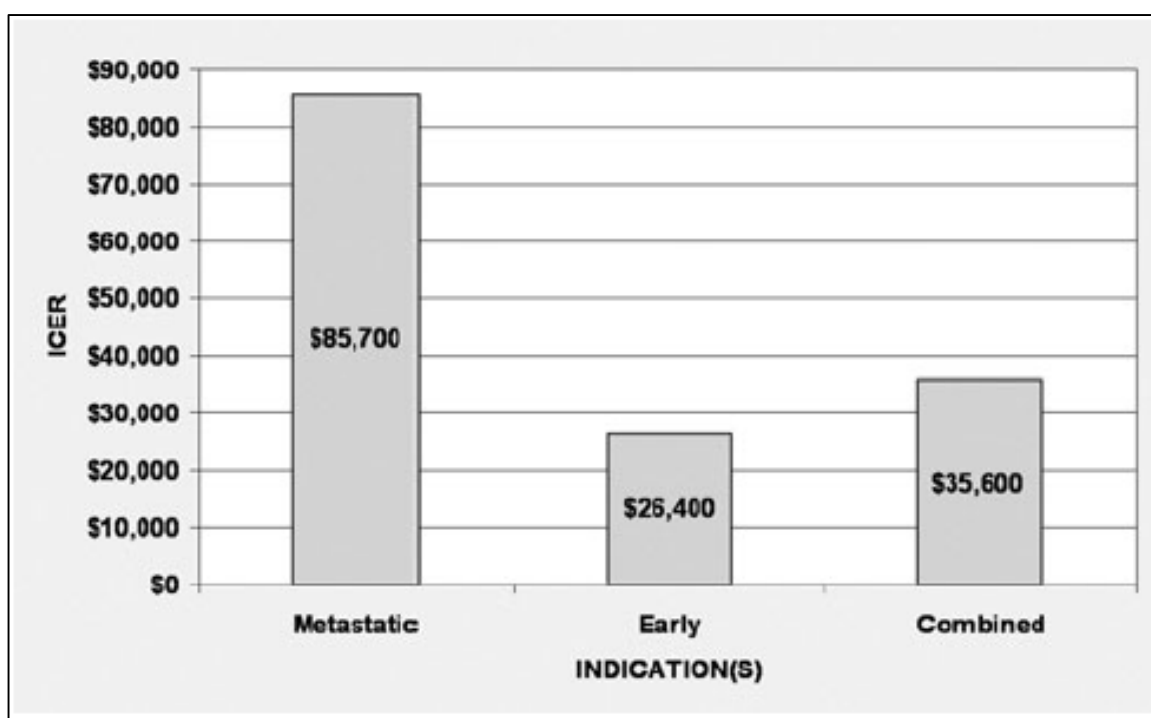
Source: Garrison and Veenstra (2009).

A similar analysis, reported in Garrison (2010), was conducted for the five major European countries (France, Germany, Italy, Spain and the UK). The projected ICER was €42,900 for metastatic breast cancer, and €14,900 for early breast cancer, and the combined estimate over the product life cycle would be €17,300 per QALY. It is clear, in both the US and the major European countries, that the company in this example is receiving less that 50% of the social surplus created (though it should be noted that the value of gains in cancer survival accruing to manufacturers is often reported to be less than 2% – see Lakdawalla et al., 2010; Yin et al., 2012). In other words, if the societal

WTP is over $100,000 per QALY in the US, and around $50,000 in Europe, cost-effectiveness ratios that are less than half of these amounts indicate that the manufacturers are getting less than half of the economic value created over the product life cycle during the period of patent protection. Similarly, Lu et al. (2012) found that ICERs declined substantially over the life cycle for paclitaxel and docetaxel, but they also accounted for price changes after patent expiry, which is important to consider from a long-term societal perspective (Garrison et al., 2010). Of course, it is not necessarily the case that the average ICER across all indications will fall as use is expanded to new indications or lines of treatments. Still, it would be useful to understand the overall value and the contribution by indication.

Jena and Philipson (2013) further emphasise that given the use of ICERs as a basis for value-based pricing, as is being proposed in the UK, the cost-effectiveness ratios for new medicines become endogenous. The real issue then becomes dynamic efficiency: what is the optimal reward (i.e. the share of value given to the company as proportion of total value created) necessary to elicit the optimal amount of R&D. The evidence on the elasticity of efficient R&D levels with respect to the award amount is very limited. One study (Dubois et al., 2011) provides a clue by comparing market size across therapeutic areas: their results imply a 1% greater market size is related to a 0.25% increase in the number of new molecular entities launched. This may or may not be the optimal response. Nonetheless, it can be assumed that more rewards will elicit a greater supply of innovation in new medicines.

An alternative view is put forward by Danzon, Towse and Mestre-Ferrandiz (2013), who suggest that payers effectively send out a signal to manufacturers about the optimal level of R&D through the setting of cost-effectiveness thresholds that are informed by their (or their citizens') willingness to pay for health gains.

For public policymakers to understand how these value expansions occur and how the aggregate amount grows and is shared, it would be helpful to be able to provide some concrete quantitative examples. This section has illustrated how this has and can be done. Of course, if databases on use by indication become more available, the precision of the estimates could increase dramatically. Towse and Garrison (2013) have argued for flexible (including indication-specific) pricing for new medicines as well as their companion diagnostics. This implies, according to these authors, a greater willingness on the part of payers to accept prices that reflect value (for both drugs and diagnostics) and thus allowing price flexibility for drugs as evidence of their value for different groups of patients emerges over time.[3] A greater appreciation of the value expansion of new medicines may be needed for policymakers to embrace such changes. To our knowledge, only the UK allows for "flexible pricing" schemes, which were introduced in the 2009

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[3] The concept of differential pricing is also used to allow for different prices for the same drug across different market segments. Segments are differentiated according to their price elasticity of demand, which can be proxied by their income levels or willingness to pay. Differential pricing is also being raised in the general HTA/pricing literature in regard to differential pricing between and within countries (see for example, Danzon, Towse and Mestre-Ferrandiz, 2013).

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Pharmaceutical Price Regulation Scheme (DH and ABPI, 2008). These flexible pricing schemes enable a company to increase or reduce the original list price of its product in light of new evidence or a different indication being developed. However, as of February 2014 we believe no proposals for price changes have been submitted under the flexible pricing provisions. While the trastuzumab example is noteworthy, policy makers may certainly question how typical it is; having a large set of quantified examples would be both informative and illustrative for such discussions.

8.7 Earlier recognition of future value expansion

Figure 6 shows that, with the exception of the orphan drugs in our study, the value of oncology products is dynamic in nature, with many expansions of value being observed over time. In Figures 7 through 16 we observe that HAS and NICE have restricted access to EMA-approved value expansions in a number of ways:

- Delaying decisions (through timing of the assessments)
- Not recommending the use of the drug
- Making restrictions to the patient population relative to EMA-approved value expansion
- Giving low values to expansions of indication approved by the EMA which ultimately excludes the possibility of new drugs receiving price premiums versus comparators

The EMA and HTA agencies can make different decisions/recommendations for the same medicine, but this is partly due to the fact that these agencies have a different role: HTA agencies are asking question that is different from those being asked by the regulator. Broadly speaking, the EMA will act as a guardian to guarantee minimum levels of safety, quality and efficacy of drugs before they are approved for different uses, while HTA agencies will decide which of those uses represent an appropriate use of limited resources, and their assessments will often inform future pricing negotiations. However, it is worthwhile considering the possible unintended consequences of negative decisions by both regulatory and HTA agencies too, and how earlier collaboration between the two levels could improve current practice.

At a regulatory level, key members of the EMA are leading discussions about the different types of errors and unintended consequences in regulatory decision making (Eichler et al., 2013). One of the consequences raised was the opportunity cost associated with unwillingness to accept some uncertainty. Eichler et al. (2013) conclude that the opportunity cost of risk aversion in drug regulation comes at a twofold price for patients: delay in accessing therapeutics and lost therapeutic options owing to the absence of new drugs.

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Similarly, Cook et al. (2011) discussed the particularities of drug development in oncology, referring to the concept of the option value – that is, the "option to extend the innovation in technology to another innovation or a major innovation with more dramatic curative effects". Similarly to how Eichler et al. (2013) reflected on the opportunity cost of negative regulatory decisions, Cook and colleagues discuss how evaluating drugs only on the basis of the value at launch may fail to capture the importance of the drug for future developments (defined as "path-dependency"). Many of the oncology drugs in our cohort did indeed have multiple additional value expansions following the first indication. Cook et al. (2011) argue that, especially for oncology drugs, incremental innovation often proceeds in steps towards the development of major innovations. Adoption at each step stage speeds up the overall process of expanding value meaning that, in using a drug, payers are increasing the speed and likelihood of getting additional benefit. They are buying both the current value of the drug and an option for additional value. Cook et al. conclude that when a drug has an option value that is not rewarded adequately by payers, this will result in suboptimal R&D spending from a societal welfare economic perspective. The key element in their reasoning is that there are interdependencies between indications; if future follow-on indications are independent, then earlier HTA decisions (whether negative or positive) will not have an impact on the development of future indications. The manufacturer will be in the best position to ascertain whether there are interdependencies or not. The case of Avastin could be used as an example where negative decisions have not curtailed the development of future indications. Potentially, however, some of the drugs in our cohort might have had an even greater number of value expansions if better incentives for R&D spending had been in place early on in the development process.

We have shown how the path of innovation toward better cancer treatment outcomes may often move through different treatment scenarios, involving changes such as the use of new treatment regimens or the targeting of certain patient populations. This reinforces Cook et al.'s point about incremental innovation. HTA systems that focus only on direct and immediate benefits, neglecting any future health gains, may not capture the real value over time of medical innovation. However, we are aware that exploring interdependencies is not straightforward and using "option value" might not always be possible when assessing new medicines at launch. At a recent forum discussing the extent, importance and tractability of problems arising from innovation path dependency in health technologies, one of the conclusions was that changing HTA processes might not be most appropriate policy response (Sussex, 2010). Rather, it could be more fruitful to investigate other demand side and supply side interventions to support and encourage the areas of innovation that are being unduly thwarted by path dependency problems.

Thus, Eichler et al.'s (2013) argument that risk aversion at the regulatory level comes at a price for patients also applies at the HTA level when access to medicines is restricted because of a failure to capture appropriately the value of cancer medicines. In the case of NICE, oncology has traditionally been a controversial field (Littlejohns et al., 2009). NICE has often been seen as a *rara avis* because it has been seen as an entrepreneurial agency in the way that it has integrated QALYs into HTA and decision making. Its decisions become immediately effective in England and Wales, but the scope of its

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influence goes beyond the borders of those nations (Hawkes, 2009). The global interest in NICE and its decisions, particularly in emerging markets that lack developed decision support units, should be seen as an opportunity for other countries to see the strengths but also the limitations of NICE's approach.

Nevertheless, we wonder if earlier engagement between regulatory and HTA agencies to discuss the potential value expansions (and the interdependencies, if any) of the products under assessment would have led to more positive HTA decisions. There are arguments both against and in favour of at least considering the "value option". The arguments against are twofold: (1) in the early stages of product development, there is a high degree of uncertainty around the potential value expansions that may or may not emerge along the drug's entire life cycle; (2) commercial-in-confidence information about future development plans of any one company might be made public. In favour, overly conservative regulatory and HTA environments can lead to suboptimal levels of future R&D investment, resulting in the aforementioned opportunity losses being incurred by patients.

We have observed some initiatives whereby manufacturers can seek advice from health authorities before making reimbursement submissions (van Nooten et al.,, 2012). Some health authorities have established consulting arms to provide guidance to manufacturers about the type of evidence needed for optimal reimbursement outcomes.

In the UK, NICE encourages product developers to engage in open and contestable processes during decision making (Chalkidou, 2010). To support such discussions, NICE initiated a consultancy service in 2009 (called NICE Scientific Advice) whereby manufacturers can pay for scientific advice on clinical trial design and other matters. The NICE Scientific Advice service seeks to help technology developers to demonstrate the value of their product – for example, by using appropriate comparators or collecting quality of life and cost data. In addition, manufacturers can seek scientific advice from the EMA, as well as requesting a joint scientific advice meeting with the Medicines and Healthcare Products Regulatory Agency (MHRA) and NICE to discuss their plans for the Phase III development of their product. In Sweden, it is similarly possible for manufacturers to seek joint advice from the HTA agency (The Dental and Pharmaceutical Benefits Agency; TLV) and the regulatory agency (Medical Products Agency; MPA) (Tapestry Networks, 2010; 2011).

Addressing the question of whether earlier engagement between regulatory and HTA authorities would lead to more appropriate recognition of the real value of oncology therapies earlier in their life cycles becomes imperative. This could be the case for drugs with development plans that present a high likelihood of delivering expanded value. Since clinical trial programs are more transparent than in the past (due to clinicaltrials.gov, for example), manufacturers can argue more convincingly that they are willing to place bets (i.e. make substantial investments) on the value of additional indications. They could argue that, in return, payers should be willing to be transparent about the size of the rewards. Flexible, value-based pricing (e.g. different prices for the

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same drug across different indications in any one country) could be one way forward to deal with the uncertainty around future expansions of value. In essence, prices would reflect the different cost-effectiveness ratios across different indications, as we have seen that the health gains offered by a given medicine differ across indications. If flexible pricing is not permitted, a situation may arise whereby the (uniform) price is driven towards one that reflects the low value indication, for example if the low value use comes first and the price cannot be changed when higher value uses are launched. A combination of factors – HTA practices failing to capture the full value of oncology treatments, the dependent nature of innovations in this disease area, overly risk averse regulatory environments, and suboptimal investment in innovation – may have negative consequences for innovation and ultimately for social welfare.

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9. CONCLUSIONS AND POLICY RECOMMENDATIONS

This report demonstrates the need for health systems and policy makers to consider how product life-cycle considerations affect the value of medicines, and in particular, oncology medicines. The findings of this study support those of previous analyses: seven of the cohort sample of 10 medicines have additional value expansions following initial indication. Only one of the seven non-orphan drugs is yet to experience a value expansion. Many of the drugs are now used for indications that are very different from the indication for which they were first approved.

At a crude level, we find some evidence that the higher the estimated gains in overall survival, the more likely HAS is to award a higher ASMR level; likewise with NICE, higher overall survival leads to a greater chance of positive recommendations. However, it is clear that both agencies take into account factors other than survival benefits when making decisions. The differing remits of HAS and NICE are important to note: HAS adopts a more clinical perspective and has historically not used ICERs, whereas NICE has an explicit ICER threshold that plays a key role in its decision making process.

In England/Wales, NICE's supplementary policy for appraising life-extending end of life treatments appears to be leading to more positive decisions for cancer products, and the CDF provides access for medicines not recommended by NICE. Based on our analysis of sales data, it seems that the CDF has had an impact in increasing usage of oncology medicines in the UK. One interpretation of this is that the UK Government acknowledges that the existing HTA approach is not appropriate for the assessment and appraisal the value of oncology treatments and has therefore set up an alternative route to ensure access to these medicines. The CDF will now run until 2016, so a key issue going forward is what will happen when the new value-based assessment process (to be implemented in 2014) and the CDF coincide. If the CDF is abolished post-2016, will that imply the end of reimbursement for medicines currently included under it? Will NICE be more likely to recommend new cancer medicines in the absence of the CDF? Will NICE change its processes for oncology treatments? It is important to keep in mind the global attention on NICE, particularly from emerging markets, when estimating the relevance and impact of changes in England and Wales (Hawkes, 2009).

Thus, one issue to explore further is whether HTA systems based on both clinical and cost-effectiveness should treat oncology treatments differently from non-oncology treatments in their assessments, in the same way that we have observed for orphan drugs. We can think of (at least) two exemptions. First, there could be an exemption from submitting a full cost-effectiveness dossier at launch, but with a proviso that further post-launch data should be collected, particularly if there are high levels of uncertainty at launch. Second, a higher threshold could be used for oncology treatments, reflecting a higher societal WTP for oncology drugs (if that is true).

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A further issue to explore is whether – and if so, how – HTA processes could take into account explicitly the issue of path dependency when assessing new medicines at launch. One option would be for early dialogue between the HTA agency and the manufacturer to discuss any future value expansions that depend on the success of a new indication. The manufacturer is clearly best placed to understand these interdependencies, if any. There are advantages and disadvantages of having this early dialogue, but the issue merits further research.

It is also important to address whether systems should move away from "one price across all indications" approach towards more "flexible pricing" approaches. This can entail differential pricing by indication and/or by patient subgroup (and ultimately, across markets and across income groups within the same market). Currently, this is not possible, with the exceptions of: (a) the US system (where price confidentiality is kept although the Veteran Affairs tender price list is in the public domain (Federal Supply Schedule) but companies can opt to have products excluded); and (b) the UK system (where, as described above, flexible pricing schemes exist in principle but not in practice). One of the stumbling blocks to progress in regard to dynamic recognition and reward of value is the failure to incorporate flexible and dynamic pricing into existing pricing systems. Manufacturers are, somewhat understandably, hesitant about engaging in early, transparent discussions (as described above) in the absence of credible signals that HTA agencies and payers are willing to implement flexible pricing approaches.

We have seen that a number of oncology treatments have multiple indications and the health gains obtained are different across them. A one-price approach could drive prices down to make the lowest value indication cost-effective, leaving cost-effectiveness ratios lower for high value indications at that single price. Most of the consumer surplus rewards for high value uses during the patent will then be reaped by the health care payers and patients, rather than manufacturers. There is a need to ensure that these rewards are shared between the health systems, patients and manufacturers. Nevertheless, understanding the relative value across indications (e.g. in terms of ICERs) could enable an approach that modulates prices across indications to optimise the sharing of the surplus between payer and manufacturer, while maximising access to oncology drugs in their different indications at different prices according to the value they offer to patients in each indication. We believe that using the low-value uses of any one drug as the benchmark to set a price would not provide the correct incentives.

A more detailed analysis of the impact of HTA decisions on uptake and use of oncology medicines might be useful. As part of this analysis, it would be important to disentangle the various factors driving the use of oncology medicines across the three countries. For instance, is the low uptake observed in the UK the result of NICE restrictions or GP conservatism, or both? An important caveat to any analysis based on sales data is that it is not possible to differentiate sales by indication for those medicines with multiple indications.

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Given the findings of this study, a further area of research would be to examine the extent to which the issues identified regarding oncology treatments – value expansions, path dependency and multiple indications – are also applicable to non-oncology treatments.

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APPENDIX I: LIST OF ACRONYMS AND ABBREVIATIONS

ASMR – improvement in medical service (*amelioration du service medical rendu*) rating

CDF – Cancer Drugs Fund

CEPS – Economic Committee of Health Products

CHMP – Committee of Human Medicinal Products

EPAR – European Public Assessment Report

EMA – European Medicines Agency

FDA – Food and Drug Administration

HAS – *Haute Autorité de Santé*

HTA – health technology assessment

ICER – incremental cost-effectiveness ratio

ITR – *Index Thérapeutique Relatif*

MHRA – Medicines and Healthcare Products Regulatory Agency

MPA – Medical Products Agency

NICE – National Institute for Health and Care Excellence

NSCLC – non-small-cell lung cancer

PSARC – Commission and Economic Assessment of Health Public

QALY – quality-adjusted life year

RCT – randomised clinical trial

SMR – medical value (*service medical rendu*) rating

TLV – *Tandvårds- & läkemedelsförmånsverket* (The Dental and Pharmaceutical Benefits Agency)

WTP – willingness to pay

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APPENDIX II: DESCRIPTION OF THE HTA ENVIRONMENTS IN FRANCE AND ENGLAND/WALES

In Europe, Canada and Australia, HTA has been gaining relevance since the 1990s, to varying extents in the different countries. Based on the high-level typology set out in the "What is value?" sub-section, we could categorise the HTA systems in France, Germany, Italy and Spain as falling within group (1); whereas Australia, Canada and UK fall within group (2). France may be moving towards group (2), as discussed below. Indeed, Drummond et al. (2014) note that there is evidence of convergence between the approaches to HTA in France and the UK, "with the movement in France towards producing cost-effectiveness estimates and the movement in the UK towards negotiated prices".

France

In France, the Haute Autorité de Santé (HAS) makes recommendations to the Minister of Health based on an assessment of the "medical value" (service medical rendu; SMR) and "improvement in medical service" (amelioration du service medical rendu; ASMR) offered by the medicine under appraisal. This is a two-stage process. The evaluation of medicines is the responsibility of the Transparency Committee of HAS.

First, the SMR level reflects the extent to which the medicine provides health benefits, and is based on a number of factors: efficacy/tolerance; severity of the disease; existence of therapeutic alternatives; place in the therapeutic strategy (first-line, second-line, etc.); and public health impact. The SMR rating and the disease severity determine the co-payment level. Only when the medicine is given an SMR rating of "insufficient" is there no public reimbursement (i.e. co-payment is equal to 100%). Under all other ratings, there is some level of public reimbursement (either 35% or 65%).

The ASMR level is the result of a comparative assessment of the new product with existing products or therapies. Unless the product is first in its class, the evaluation is done in comparison to products of the same pharmaco-therapeutic class that are already listed. In essence, the ASMR reflects the degree of innovation offered by the medicine relative to the treatments already available, as deemed by HAS. The eventual price paid for a technology is in part determined by its ASMR rating (Shah et al., 2013). Disease severity is taken into account in the SMR assessment, but not in the ASMR assessment (ISPOR, 2009). Figure 61 presents these ASMR ratings, and describes the criteria used to the rating of a given product.

In addition, there are no special criteria in France for orphan medicines (or ultra-orphans), but there is some flexibility on the quality of evidence accepted, e.g. based on Phase II trials (Garau and Mestre-Ferrandiz, 2009). HAS, however, can award Authorisations for Temporary Use to provide early access to medicines prior to their

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marketing authorisations when the disease is severe and there is no alternative treatment. This will be the case for many medicines for very rare diseases.

Figure 61. ASMR ratings
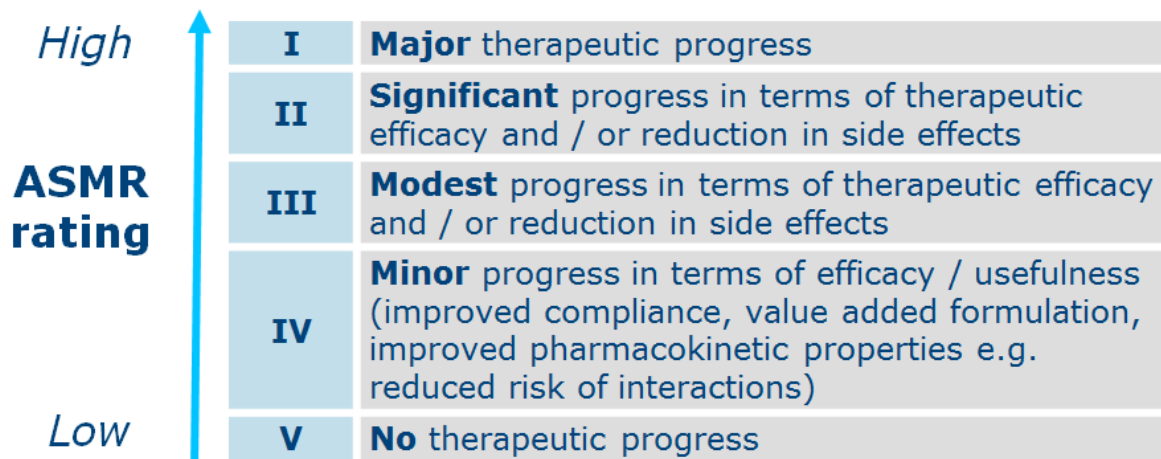
Source: authors' analysis from publicly available information.

In addition to the initial assessment, the manufacturer may request additional assessments for additional indications, whilst medicines are required to undergo reassessment every five years at the cost of the manufacturer.

The latest information we identified which summarises SMR/ASMR ratings granted refers to the year 2008. Figure 62 shows these ratings for the products and indications assessed by HAS in that year.

Figure 62. SMR and ASMR ratings, 2008

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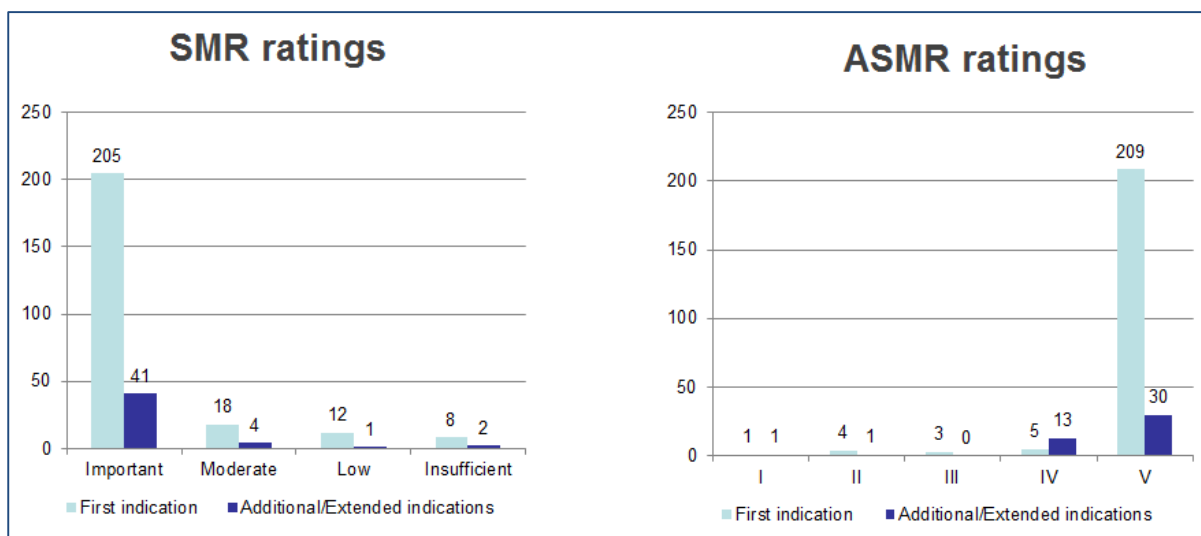
Note: Each decision can include more than one SMR/ASMR rating.

Source: HAS (2008).

Figure 62 shows two key results:

- the proportion of decisions granting important SMR rating was very high;
- but the proportion of decisions granting important ASMR ratings (I, II or III) was very low; indeed most ASMR ratings in 2008 for a first indication were a 'V' (indicating no therapeutic progress).

In addition, we understand that recently there has been a trend of increasing strictness in the application of the SMR and ASMR rating; in particular, the proportion of decisions giving an SMR of "insufficient" has increased.

There are two principal medicines lists:

1. Reimbursable medicines dispensed by retail pharmacists (*Liste des Spécialités remboursables aux Assurés Sociaux*)

2. Hospital medicines (*Liste des Spécialités agréées aux collectivités*), which are further classified as:

    - medicines delivered to out-patients (*Liste Retrocession*)

    - costly medicines that are charged to health insurance in addition to hospital stay fees (*Liste T2A*)

In November 2010, the *Conseil de l'Hospitalisation* issued a recommendation calling for an overhaul of the management of the T2A list (*Secretariat d'etat a la Sante*, 2010). The *Conseil* made a number of specific proposals, including:

- Technologies with an insufficient SMR rating should not be added to the list
- Technologies with an ASMR of IV or V should not be eligible for addition to the list
- The ASMR rating should be considered for each indication

There are important current reforms to the medicines approval and pricing and reimbursement system in France (under the Loi Bertrand Bill), mainly focusing on pharmacovigilance and regulation. This Bill also includes a decree that changes the comparator requirements. Prior to the Loi Bertrand Bill, indirect comparisons of a new medicine with an established therapy were accepted. However, post-Loi Bertrand, a direct comparison with an active comparator, where there is one in use in standard clinical practice, is mandatory. However, given that this requirement has been implemented recently, it is still relatively uncertain whether indirect comparisons with active comparators will be accepted. Furthermore, the requirement for direct comparisons will likely affect both the SMR and the ASMR ratings, although it is not yet clear precisely how. Overall, it is currently unclear which of the decrees outlined in the

Loi Bertrand will be implemented and the timeline for a final decision on formal implementation is unknown.

During a recent interview on health policy (Nile Consulting, 2012), Jean-Luc Harouseau (the President of HAS) proposed changes to the evaluation of medicines in France. The changes, which form part of a change in law (Bill Financing Social Security – Le Projet de Loi de Financement de la Sécurité Sociale 2013), will encompass new drug applications and marketed medicines. The economic evaluation of medicines will be the responsibility of the Commission and Economic Assessment of Health Public (PSARC), whilst the decision on reimbursement will be the responsibility of the Economic Committee of Health Products (CEPS). As such there could be two separate groups, PSARC for evaluation and CEPS for decision making.

In addition, it is expected that cost-effectiveness will play a more prominent role in the near future, under the expected integration of both SMR and ASMR ratings into a single scale – the "Index Thérapeutique Relatif" (ITR) (de Pouvourville, 2013). This is still under consideration. It appears that the Transparency Committee will be responsible for granting the ITR rating. It is expected that the ITR will replace the SMR and the ASMR ratings, though this will require a change to the PLFSS. It is anticipated that the ITR will be a comparative indicator used to compare the treatment under assessment to the best alternative treatment based on assessment criteria provided in advance. The generation of the ITR will be a sequential, semi-quantitative process.

The Transparency Committee will first validate the primary and secondary efficacy endpoints and the comparator used by the sponsor, followed by an assessment of relative efficacy, based principally on the product's primary clinical endpoint, and on secondary criteria if needed (Nile Consulting, 2012). The product's tolerance and its administration will then be considered in setting the ITR to one of the five classes: inferior, identical, slightly superior, moderately superior, very superior.

HAS will then recommend to the Ministry of Health that reimbursement and pricing should be applied as follows:

- Inferior: No reimbursement
- Identical: No reimbursement or reimbursement at a reduced price (vs. comparator)
- Slightly superior: Reimbursement at same price of comparator
- Moderately superior: Reimbursement at a negotiated price
- Very superior: European price

By law, an economic assessment will be required for products that are either viewed as having a significant health economic impact or likely to change the management of the disease. This will apply to drugs with a high ITR and those with high prescription volume potential.

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Under these circumstances, it is expected that at least two assessments will be conducted. First, there will be a "flash study" performed by reviewing the sponsor's submission to verify validity and compliance with the HAS's guidelines and to estimate the preliminary drug's cost/efficacy ratio – this will be based on clinical data. A study will then be designed and agreed with the company to collect "real world" data and to determine the incremental cost-effectiveness of the product versus the comparator that is most representative of standard practice. Timelines between the two assessments are currently unclear but are expected to be two to three years. Such cost-effectiveness assessment will lead to review and, if required, to revision of reimbursement, conditions of use and pricing of the drug.

QALYs are not yet used systematically in France but may be used increasingly in the future. Health gain has hitherto been measured within the context of a certain disease area, so HAS uses disease-specific clinical measures rather than generic measures (ISPOR, 2009). In 2012, HAS published a "Methodological Guide" to economic evaluation in which it states that QALYs are to be measured in cost-utility analyses in cases when it is possible to obtain QALY data at reasonable cost (HAS, 2012). As far as we are aware, such economic evaluations are not yet part of the medicines pricing and reimbursement process in France.

England and Wales

In England and Wales, cost-effectiveness is assessed according to a prescribed set of methods (NICE, 2013a) that links the prices of technologies to the health benefits that they confer, and the resulting ICER estimates are compared to a threshold range that represents what is considered acceptable and affordable for the NHS. This explicit ICER range is between £20,000 and £30,000 per QALY gained, but other factors are taken into account as part of the NICE Appraisal Committees' deliberative process (NICE, 2008; Rawlins, Barnett and Stevens, 2010; Dakin et al, 2013). For instance, Dakin et al. (2013) estimate that cost-effectiveness alone correctly predicted 82% of NICE's past decisions; few other variables were significant.

Additional criteria considered by NICE include:

1. Severity of underlying illness: more generous consideration is given to the acceptability of an ICER for serious conditions, reflecting society's priorities (Rawlins, Barnett and Stevens, 2010)

2. Stakeholder persuasion: Insights provided by stakeholders (e.g. on the adequacy of measures used in trials to reflect symptoms and quality of life) (Rawlins, Barnett and Stevens, 2010; NICE, 2008)

3. End of life treatments: society is considered to place special value on treatments that prolong life at the end of life, providing that the life extension is of reasonable quality (Rawlins, Barnett and Stevens, 2010; NICE, 2009)

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4. Disadvantaged populations: special priority is given to improving the health of the most disadvantaged members of the population (Rawlins, Barnett and Stevens, 2010; NICE, 2008)

5. Children: given methodological challenges in assessing quality of life in children, society would prefer to give "the benefit of the doubt" (Rawlins, Barnett and Stevens, 2010)

In sum, the sources of value deemed important by NICE are: health gains, measured in terms of QALYs; the cost versus that of the comparator; some aspects of severity; and other factors such as equity. Value is summarised by an ICER to be compared to the threshold range, with some additional issues taken into account, such as whether the drug is considered to be an end of life treatment, or whether it is indicated for paediatric or orphan patient populations. The ICER is estimated based on RCT data against the comparator and the incremental cost per QALY is based on an economic model, in which end of life and orphan patients are identified explicitly, and other evidence of patient disadvantage are considered implicitly. Decisions are heavily influenced, but not exclusively dictated, by the comparison of ICERs with the threshold range (£20,000 to £30,000 per QALY gained). When certain criteria are met, NICE's Appraisal Committees are asked to consider the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases (NICE, 2009). Other considerations are weighed deliberatively by NICE's advisory committees.

In November 2013, NICE issued a press release shortly after publishing its 300th appraisal (NICE, 2013b). The Institute argued that it has said "yes" to around 80% of the technologies that it has appraised; 61% in line with their indicated use, and a further 19% of technologies are recommended for optimised use under specific conditions, such as in certain patient groups. A further 5% of technologies were recommended for research purposes, which means that they are recommended for use only in the context of a research study, such as a clinical trial. This can happen, particularly in the case of promising new technologies, because sufficient clinical evidence has not been collected at the time of the appraisal and so the Appraisal Committee is unable to recommend the technology for use in the NHS until further evidence of its effectiveness is available for re-appraisal. In such cases NICE will recommend further research to investigate whether the promise of the technology can be realised (NICE, 2013b).

NICE claims to have said "no" to only 15% of appraised technologies. In most instances, a drug is not recommended because there is a lack of evidence for its clinical effectiveness or because the treatment is not considered to be a cost-effective use of NHS resources, compared with current NHS practice.

O'Neill (unpublished) has undertaken an analysis of all NICE decisions since its inception, up to Q3 2013. The results show that by Q3 2013, 17% if all decisions can be summarised as "not recommended" (similar to the 15% mentioned above), 31% of decisions were positive recommendations and 49% were "restricted" recommendations.

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The remaining 3% refer to appraisals that were terminated. Thus, according to O'Neill (unpublished), 80% of NICE's decisions have been "yes" – identical to NICE's quoted acceptance rate mentioned above. However, the difference between NICE's own analysis and that of O'Neill is the way in which "restricted" or "optimised" decisions (the latter being NICE's terminology) have been classified.

For oncology medicines specifically, a "Cancer Drugs Fund" (CDF) was introduced in England in 2010. Originally announced to run until 2014, in 2013 it was announced it will be extended until 2016 (NICE, 2013c). The CDF provides a means of improving patient access to cancer drugs, and is used to fund drug treatments, including radiopharmaceuticals, for patients who have been unable to access a drug recommended by their oncologist. This includes drugs that are either not routinely available on the NHS or have not been approved or appraised by NICE. It also provides fast track access to cancer drugs that are awaiting NICE guidance as well as access to drugs for less common cancers. O'Neill (unpublished) shows trends in NICE decisions for oncology drugs pre- and post-CDF. Figure 63 shows this analysis.

Figure 63. Trends in NICE decisions for oncology drugs pre- and post-CDF (Q4 2010 to Q1 2013)
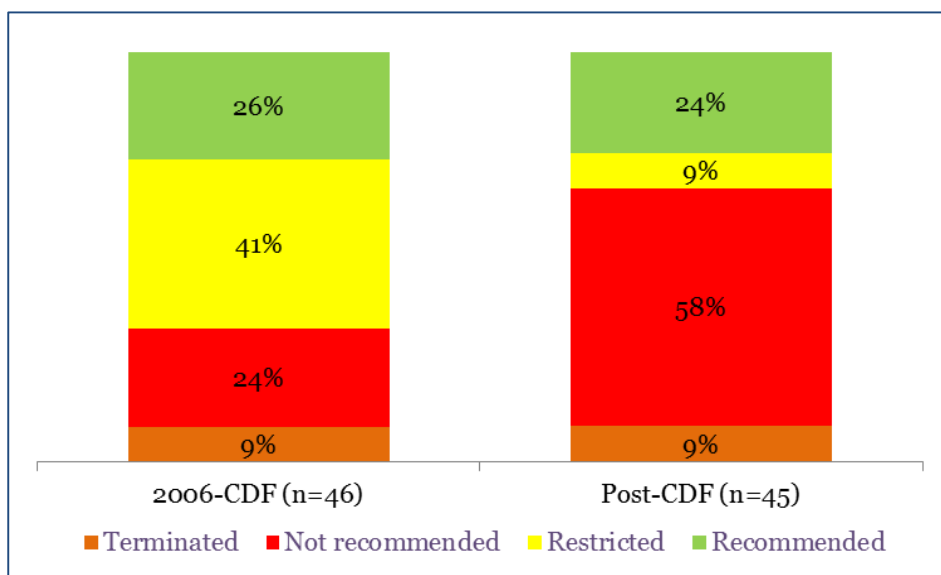
Source: O'Neill (unpublished).

Figure 63 shows how the proportion of "not recommended" decisions for oncology medicines has more than doubled since the introduction of CDF (58% post-CDF vs. 24% pre-CDF), while the proportion of "restricted" decisions has fallen significantly, from 41% to 9%. The proportion of positive recommendations has fallen slightly, from 26% to 24%.

According to the Department of Health, there have been notifications for 31 medicines under the CDF (DH, 2013). Four of our selected medicines are included in the CDF, for the following indications:

- Alimta, for:
    - Second-line treatment of patients with locally advanced or metastatic nonsmall cell lung cancer other than predominantly squamous cell histology in patients who did not receive first-line pemetrexed e.g. first-line clinical trial.
    - Maintenance treatment of stage IIIB/IV non-squamous non-small cell lung cancer after response to pemetrexed-containing first-line therapy
- Avastin for:
    - Treatment of patients with triple negative metastatic breast cancer and/or prior taxane therapy
    - First-line treatment of advanced colorectal cancer with a single agent fluoropyramidine in patients assessed as unfit to receive combination oxaliplatin- or irinotecan-based combination chemotherapy
    - First-line treatment of metastatic colorectal cancer. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy
    - Second-line treatment of metastatic colorectal cancer in combination with standard chemotherapy in patients who have not previously received bevacizumab. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy
    - Third-line treatment of metastatic colorectal cancer in combination with standard chemotherapy in patients who have not previously received bevacizumab. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy
    - First-line treatment of advanced (stage IIIc/IV) ovarian cancer, suboptimally debulked either at primary or delayed primary (interval) surgery (including peritoneal and fallopian tube cancer) OR unsuitable for debulking surgery
    - Second-line treatment of platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer (6 or more months after completion of first-line chemotherapy)
- Erbitux for:
    - First-line treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck
    - Treatment of KRAS wild-type metastatic colorectal cancer in any indication outside of NICE TA176, in patients who have not previously received cetuximab up to progression
- Velcade for:
    - Treatment of relapsed or refractory multiple myeloma at second and subsequent relapse in patients who are bortezomib naïve and where the patient unable to access bortezomib at first relapse
    - Treatment of relapsed or refractory multiple myeloma at second and subsequent relapse in patients with previous good response to bortezomib

- o Treatment of second or subsequent relapse in Refractory Mantle cell Lymphoma, in patients not fit for transplant
- o Treatment of relapsed Waldenstrom's macroglobulinaemia after previous treatment with standard chemotherapy

A number of the indications listed above were not included in our study and no NICE appraisal was identified relating to that indication (for example, Velcade for the treatment of refractory mantle cell lymphoma). In other cases, the CDF inclusion covers an indication that was appraised and ultimately not recommended by NICE. Alimta, Avastin, Erbitux and Velcade have had in total (up to June 2013) 116, 941, 342 and 95 notifications, respectively.

The UK Government is implementing a "new value-based approach to the pricing of branded medicines" in 2014. The new pricing and reimbursement structure has been informed by consultation processes. The Government's public consultation establishes which attributes of a medicine deliver value to society (DH, 2010, paragraph 4.10):

1. Improving health across the NHS – measured as the number of incremental QALYs produced relative to the comparator treatment or current standard of care;

2. Tackling diseases where there is greater "burden of illness" (whether the medicine treats diseases with unmet medical need or for patients suffering particularly severe conditions);

3. Demonstrating greater therapeutic innovation and improvements compared with other products; and

4. Demonstrating wider societal benefits, such as the ability to get patients and/or their carers back to work sooner.

In principle, the new elements to be incorporated in the future system that are currently not explicitly taken into account are (2), (3) and (4). The new system has not been formally implemented, so the practical application of its principles has not been set out yet. But at a high level, we understand that the Government will set a cost-effectiveness threshold structure that applies weights to the different benefits provided by new medicines that reflect the value of a new drug. It was announced by the Department of Health in November 2013 that the current cost-effectiveness threshold will remain unchanged until the end of 2018 (DH and ABPI, 2013).

Thus, in the UK, we could argue that the on-going reforms is about the weighting given to the evidence and the social value of a drug; for instance, does a drug fulfil an unmet need or is there a high burden of illness associated with this particular disease?

Table 17 summarises the key similarities and differences between England/Wales and France in terms methods for assessing health technologies.

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Table 17. Methods for assessing health technologies – England/Wales vs. France

	England and Wales	France
Analytical method	Cost-effectiveness (cost utility analysis preferred)	Efficacy and relative efficacy; no formal requirement for cost-effectiveness analysis at this stage (expected to be incorporated within P&R system in the near future)
Health outcomes	QALYs	Final outcomes preferred: mortality, morbidity and quality of life; in a cost utility analysis, the health outcome used is QALYs
Evidence considered	Strong preference for head to head RCTs; but others accepted (non-RCTs; indirect comparisons; mixed treatment comparison; meta-analysis)	Clinical studies (head-to-head RCT versus active comparator required when possible); systematic literature review and synthesis
Perspective (Outcomes)	All health effects on individuals	French health system perspective
Comparator	Therapies routinely used (including current best practice)	Approved, listed pharmaceuticals of same therapeutic category that fall into the following categories: •used most regularly •cheapest treatment cost •included in positive list most recently
Uncertainty	Full account of assumptions and data inputs; sensitivity analysis required	Full account of assumptions, parameters, model and methodological choices; sensitivity analysis required
Who provides the evidence	Academic groups; manufacturers and sponsors; patient and carer groups; health care professionals and clinical experts	Manufacturer

Source: Moloney et al. (unpublished).

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