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Current Perspective

Therapeutic indications in oncology: Emerging features and regulatory dynamics

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ABSTRACT

The regulatory route leading to the definition of therapeutic indications of new compounds as well as extensions of indication (EoI) of already approved ones is a challenging process. If new anticancer drugs reach the market with a lack of complete evidence, this usually leads regulators to request additional data, post approval commitments or restrictions in therapeutic indications.

This study aims at quantifying the time needed for anticancer drugs approved by the EMEA to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) significantly decrease from about 81 months in 1996 to 6 months in 2006. Twenty-four out of 43 approved anticancer medicines (about 56%) have only a single therapeutic indication, 12 of which were approved before 2005.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval (CI): 0.07–1.04). With regard to the type of EoI ($n = 60$), our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour, in 37% of cases the extension consisted in a switch of line within the same therapeutic indication. The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient population (7%).

The analysis of indication restrictions showed that in 20 cases out of 50 (40%) therapeutic indications were restricted by the Committee for Medicinal Products for Human Use (CHMP) during the assessment, with 60% of the restrictions occurring in 2006–2007.

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This study adds three main pieces of information: (i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments.

1. Background

Once a medicinal product is on the market, companies usually perform new clinical studies to extend therapeutic indications.[1] Providing data from new trials is a requirement for expanding the indications, contrarily to the past, when case series or other less robust methods were considered sufficient evidence for this purpose. New indications may also include new patient settings or a switch in the treatment line (e.g. from second to first line). The regulatory route leading to the definition of therapeutic indications of new compounds and extensions of indication (EoI) of already approved ones are challenging processes. This is particularly the case for oncology, where there are many unmet medical needs, and where new therapeutic opportunities are often immediately translated into clinical practice. This process is per definition complicated by the fact that new anticancer drugs reach the market with a lack of complete and sound evidence.[2–5] An uncertain benefit/risk profile of a drug is hard to review for regulators, which usually leads to the requests for additional data, post approval commitments or restrictions in therapeutic indications.[6,7] A restriction of therapeutic indications is a tool with an immediate effect, which aims at identifying the specific patient's population that may benefit most from the medicine. Restrictions may also fuel off-label prescribing instantly, and on the long run, slow down the availability of formally approved indications and the investments in therapeutic innovation in general.

A critical factor is timing of a positive (or negative) decision about an additional and new indication of a medicinal product. When the decision is made (too) fast, patients may be exposed to treatment on the basis of premature, weak or very uncertain data, asking for more and additional evidence to support a new indication. This study aims at quantifying the time needed for an anticancer drug to get an extension, the rates and characteristics of extensions approved, and at exploring the regulatory process leading to the definition of new indications.

2. Methods

Information on regulatory steps leading to the definition of therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Report (EPAR), publicly available on the EMEA website (http://www.emea.europa.eu/htms/human/epar/eparintro.htm).

Documents were surveyed for new applications as well as for later extensions between January 1995, when the EMEA was set up, and December 2008. The analysis includes all the anticancer drugs with a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) through the so-called Centralised Procedure. As the interferon α-2b (INFα-2b) application was aimed at obtaining a European Marketing Authorisation (MA) after earlier authorisations had been granted at the national level, there was not sufficient information for its oncology indications and the drug was therefore excluded from the analysis. Palliative or supportive therapies (such as bisphosphonates, immunoglobulins and anti-emetics), hormone treatments, colony-stimulating factors, chemoprevention treatments, vaccines and generics were also excluded from the analysis.

For the purpose of this analysis, the following parameters were extracted: active compound, date of issue of the European MA, number of therapeutic indications, study characteristics (design, number of patients and primary end-point), indication requested (IR) by the applicant and indication approved (IA) by the CHMP. Only indications for which the IR was clearly stated in the EPAR were considered eligible for the analysis. Then, a comparison between IR and IA was performed in order to find possible restrictions. The analysis of the types of extensions of indication was performed considering the following pre-specified categories: (i) new tumour, (ii) tumour stage, (iii) new population and (iv) switch in the treatment line. We defined *a priori* two common data acquisition forms to be completed. FT and GT independently evaluated all the EPARs and filled the respective forms. The results were then cross-checked, leading to a joint document. In the case of disagreement, the final decision was taken through a consensus process reached following further discussion.

3. Results

A total of 103 therapeutic oncological indications, related to a cohort of 43 anticancer drugs, were retrieved between 1995 and 2008. Overall, 60 EoI were approved between 1995 and 2008. An increasing trend in EoI can be observed since 2002, with a median of 8 approved indications per year, while before 2002 only 5 out of 60 EoI (8.3%) were approved. In contrast, the rate of newly approved oncological products remains almost constant within the time frame 1995–2008 with an average of 3.3 per year. The median time occurring between different indications for the same compound (defined as Time to New Extension, TtNE) was also calculated, using the dates of European MA for each indication (Fig. 1).

A significant continuous decline of TtNE has been shown from 1995 up to 2008. For example, this means that for an anticancer medicine approved in 1996, about 81 months were necessary to have a new indication approved for the same drug. While for a product approved in 2006, the time needed was much shorter, i.e. 6 months.

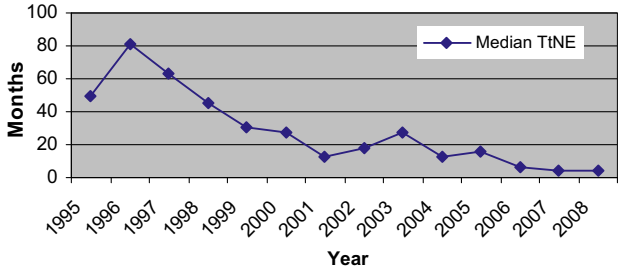

Fig. 1 – Median Time to New Extension (TtNE) defined as the median time (in months) occurring between different indications for the same compound (*n* = 103 indications).

Twenty-four out of 43 approved anticancer medicines (about 56%) have only a single therapeutic indication, 12 of which were approved before 2005 (Table 1). Only 7 products (about 16%) have at least five therapeutic indications (these include capecitabine, imatinib and docetaxel with 6, 9 and 11 indications, respectively). Except for bevacizumab, approved in 2005, the remaining 6 were approved between 1995 and 2001. Three products that, although recently approved present several indications, were identified: sunitinib approved in 2006 with three indications, cetuximab approved in 2004 with four and bevacizumab approved in 2005 with five.

When considering two different cohorts of drugs in relation to the time of approval (1995–2004 versus 2005–2008), although not statistically significant, the older cohort tended to have a decreased probability of having EoI when compared to the new cohort (OR = 0.27; 95% confidence interval (CI): 0.07–1.04).

With regard to the type of EoI, which usually aims at broadening the first indication, our findings showed that in 48% of cases the initially approved indication was extended to treat a different tumour (Fig. 2). For example, erlotinib, initially approved for non-small cell lung cancer, was then granted a new indication for pancreatic cancer. Moreover, in 22 out of 60 EoI (37%), the extension consisted in a switch of

Table 1 – New anticancer drugs approved by the EMEA by number of therapeutic indications and year of approval.

Number of indications	Number of new drugs	Name of compound firstly approved between 1995 and 2004	Name of compound firstly approved between 2005 and 2008
1	24	Imiquimod (2004); tasonermin (1999); cytarabine (2001); toremifene (1996); fulvestrant (2004); temoporfin (2001); cladribine (2004); mitotane (2004); doxorubicin (2000); alitretinoin (2000); bexarotene (2001); arsenic trioxide (2002)	Paclitaxel (as paclitaxel albumin) (2008); nelarabine (2007); clofarabine (2006); lenalidomide (2007); dasatinib (2006); nilotinib (2007); thalidomide (2008); temsirolimus (2007); lapatinib ditosylate monohydrate (2008); panitumumab (2007); azacitidine (2008); trabectedin (2007)
2	5	Busulfan (2003); alemtuzumab (2001); ibritumomab tiuxetan (2004)	Sorafenib (2006); erlotinib (2005)
3	5	Pemetrexed (2004); bortezomib (2004); topotecan (1996); temozolomide (1999)	Sunitinib (2006)
4	2	Doxorubicin hydrochloride (1996); cetuximab (2004)	–
5	4	Paclitaxel (1999); trastuzumab (2000); rituximab (1998)	Bevacizumab (2005)
6	1	Capecitabine (2001)	–
7	0	–	–
8	0	–	–
9	1	Imatinib mesilate (2001)	–
10	0	–	–
11	1	Docetaxel (1995)	–
Total	43	–	–

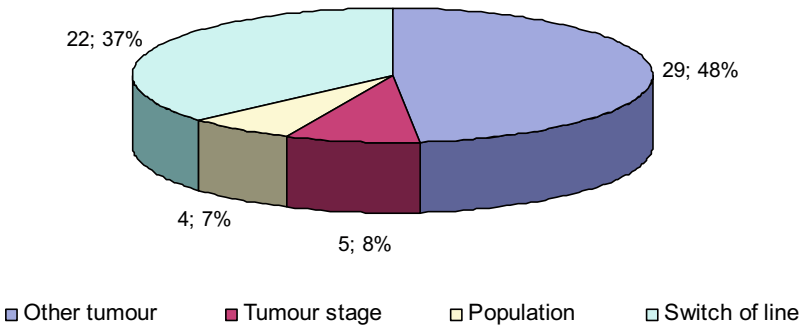

Fig. 2 – Types of broadening of therapeutic indication.

Table 2 – Number of indications restricted during the review process.

Year of approval	Number of indications	Indication requested (IR) available	Indications restricted
1995–2004	32	5	4
2005–2008	71	45	16
Total	103	50	20

line within the same therapeutic indication (e.g. sunitinib, which was switched from second-line to first-line treatment of renal cell carcinoma (RCC)). The other two types of indication broadening refer to a different tumour stage (8%) and to the inclusion of a new patient's population (7%) (e.g. busulfan indication extended to cover paediatric patients).

In order to investigate the regulatory dynamics occurring during the review process, a comparison was performed between the indications initially submitted by companies and those resulting at the end of the CHMP evaluation process. For this analysis, a clear information on the IR was retrieved in the EPARs for 50 out of the total sample of 103 indications (Table 2).

For example, sorafenib was granted the first indication in July 2006. The indication initially proposed by the applicant was the treatment of patients with advanced RCC as a first-line therapy. However, during the CHMP review process, it was acknowledged that the assessment of the full potential of sorafenib in terms of survival benefit in the treatment of advanced RCC was not possible due to the early unblinding of study results and subsequent cross-over. Therefore, due to the availability of other authorised treatments for the first-line treatment of advanced RCC, the indication was restricted to use in the second line.

A consistent retrieval on EPARs of the information about the IR was only possible since the year 2004. In fact, 45 out of 50 IR (90%) were available in the EPARs issued between 2004 and 2008.

The analysis of indication restrictions occurring during the EMEA review showed that in 20 cases out of 50 (40%) therapeutic indications were restricted by the CHMP during the assessment, with 60% of the restrictions occurring in 2006–2007.

4. Discussion

Our analysis confirms that, while the rate of newly approved drugs is constant over the years, there is an increase in the rate of EoI per year (91.7% of EoI occurred after 2002). Although this finding reflects the 'young age' of the EMEA (set up in 1995), it is also in line with the current awareness of the lack of original pharmaceutical products which leads drug companies to make the most out of already existing drugs.[8] The indicator (TtNE), considered to analyse how fast a new indication was developed and eventually approved during the last 13 years, showed a continuous decline. This reflects a shorter clinical development process and reduced regulatory delays. It also shows how quickly new treatments become available to patients. Furthermore, the shortened TtNE and the increased number of granted EoI suggest that companies set up wide clinical development plans, testing a compound in different oncological areas.

Contrary to common belief, most anticancer drugs (about 56%) present only a single therapeutic indication. It seems that drugs approved earlier do not have more EoI than newest compounds. There are very few examples of drugs having a large number of EoI and in most cases these are widely recognised as breakthrough drugs (e.g. imatinib, approved in 2001, holding nine indications; trastuzumab, approved in 2000, holding five indications). Other anticancer drugs with many indications are old cytotoxic compounds, such as paclitaxel, capecitabine and docetaxel, whose use is very well established and which still represent the basis of several therapeutic strategies. However, we identified three medicines, presenting multiple indications, with an uncommon accelerated development process: (i) sunitinib (approved in 2006 with three indications); (ii) cetuximab (approved in 2004 with four) and (iii) bevacizumab (approved in 2005 with five). On average, at least one indication per year was approved. Can this decrease of time between two subsequent indications ensure an adequate provision and assessment of clinical and safety data? Moreover, the two latter drugs, although examples of 'targeted drugs', were always approved in combination therapy with classical cytotoxic agents, showing their efficacy in this setting. This raises questions as to the real efficacy of such targeted compounds when used alone.

With regard to the broadening of indication, the practice of the switch of line is quite common and reflects companies' efforts to reach an earlier treatment line in an unidirectional way. This seems also to be the result of a precautionary regulatory approach, which often tends to restrict the indications proposed by the industry and then, as evidence is provided, relax these initial restrictions. About half of the EoI consist of the utilisation of the product for other tumours. This fulfils the industry expectations after the product reaches the market and it is generally favourable from a public health perspective. In fact, stimulating further research on already approved drugs mainly contributes to limit the off-label use of drugs. Unfortunately, the broadening of indications including special populations such as children or the elderly is still highly neglected due to difficulties of generalising evidence in these special groups.

The analysis of restrictions of indications during the regulatory review process showed that, 50% of the indications could be included into our sample size due to a lack of sufficient information in part of the EPARs. A cut-off date for the improvement of EPARs quality could be traced in 2004, since before this year only 10% of reviewed EPARs explicitly reported the IR information. This improvement might be attributable to the effect of the EU Regulation (EC) No. 726/2004 (issued on 31 March 2004), which provided a clear and understandable information on medicinal products to be reported in the EPAR.[9] However, since useful information such as the IR is often still missing, more transparency on the regulatory dynamics leading to the conclusion of the assessment procedure is needed.

Our data highlighted that restricting the indications is quite a common and a recent 'practice', used by regulators. A graphical description of the regulatory dynamics over time for a general indication is provided in Fig. 3. In several cases,

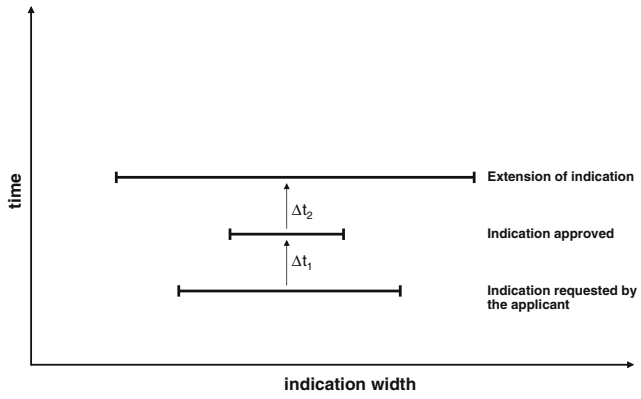

Fig. 3 – Graphical description of the regulatory dynamics over time for a general indication.

the indications requested at the time of the dossier submission tend to be wider than those eventually approved by regulators. Afterwards, the indications are widened again during subsequent extensions, in a time period that, as previously reported, is gradually declining (Δt_2).

Our findings show an interesting association between the time needed for an indication extension and the rate of indication restrictions: in fact during the time period 2006–2007, when restrictions reach a peak, there is an evident decline in the time needed to obtain a new extension, TtNE. This leads to hypothesise a relationship between a faster clinical development and the chance of receiving an indication restriction from regulators. The fact that restrictions of indication occurred because of an incomplete clinical data package can then be easily assumed. It seems that in case of immature efficacy and safety data, regulators often tend to shift towards the terminal treatment lines in order to restrict the drug use only to patients with no alternatives. The consequence is a subsequent request by companies for getting earlier treatment lines approved, resulting in a *continuum* in terms of EoI for a single compound.

5. Conclusions

While companies can benefit from the extensions given the enlarged market and patent protection, extending therapeutic indications is also very positive from a public health perspective to better define drug benefit/risk profiles, to monitor safety issues and to reduce the off-label use.

From a regulatory point of view, the practice of restring or broadening indications is of pivotal interest given the challenge of finding the right balance between acquiring as much evidence as possible to support a new application of an existing product and risking widespread off-label use.

Submitting a drug dossier to regulatory authorities containing immature data could be risky for the industry itself as unexpected costs and delays could occur. The progressive shortening of the clinical development may result in an uncertain drug benefit/risk profile, which is hard to review for regulators and may result in harming the patient. As a consequence, the risk of restrictions in therapeutic indications, requests for additional data, and post approval commitments (such as further confirmatory trials) are increased, with a possibly negative impact on industry's resources.

In conclusion, this study adds three main pieces of information: (i) the majority of anticancer drugs still have a single indication regardless of the year of approval; (ii) the time needed to obtain an extension of indication has decreased significantly over the last decade and (iii) a highest rate of regulatory restrictions is matched to shorter clinical developments. Lots still remain to be done in terms of continuing broadening therapeutic indications. This would potentially determine a reduction of the off-label use of drugs, through an increase of labelled indications, with positive implications for therapeutic decision makers (e.g. clinical guideline committees and reimbursement authorities) and, most importantly, for patients, provided that the creation of new therapeutic indications is based on robust clinical evidence.

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Conflict of interest statement

None declared.

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