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Approval probabilities and regulatory review patterns for anticancer drugs in the European Union

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Contents

Abstract

Aim: This article reviews outcomes of marketing authorization applications for anticancer drugs in the EU and outlines factors and hurdles of impact.
Methods: Procedures for initial approval of anticancer and non-cancer drugs were analyzed and compared to anticancer drug approvals in the USA and Japan for the same period.
Results: From 2006 to 2011, the regulatory review of 46 marketing authorization applications resulted in 29 new cancer drug approvals. The overall approval probability (63%) lagged behind the probability for non-cancer drugs (73%). Longer median active review times in line with additional clock-stop and EU Commission decision-making times as well as submission delays contribute to the 7.2 months median time-to-market delay [95% CI 4.7–15.0 months] compared to the USA; Japanese patients had to wait an additional 25.1 months [95% CI 6.2–34.1 months].
Conclusion: Marketing authorization applications for anticancer drugs in the EU are associated with modest approval success. Patients in the USA get access to new products earlier, fostered by the more frequent use of expedited review procedures. So far, both procedures were used in the EU for applications claiming a major public health interest, characterized by pivotal clinical trial hazard ratios below 0.70.

Keywords: Drug approval; Drug evaluation; Approval probability; Anticancer drug approval; European Medicines Agency; Marketing authorization application; Regulatory review pattern; Neoplasms

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1. Introduction

The high failure rate for new products contributes considerably to the enormous development costs for new medicines [1,2]. The reasons behind the astonishingly high attrition rate in pharmaceutical research and development (R&D) have recently become subject of intense discussion; they are considered to comprise intrinsic factors linked to management and R&D methodology issues as well as extrinsic factors related to nature and the biology of humans [3].

The challenge of high attrition rates and the associated decline in the pharmaceutical industry's ability to bring new products to bedside are not only a concern for industry itself but also for patients and regulators who have begun to question the role of drug regulation at the crossroads between safeguarding public health and supporting innovation for the sake of the patient [4–6].

Pharmaceutical R&D is a highly regulated business and the marketing authorization process constitutes a cornerstone in the maturation of each new drug that has made the way from lead generation to confirmatory clinical trials: if the 'new drug' ('medicinal product' in the Europe Union's legal terminology) gains approval, routine clinical use can start.

However, the outcomes of marketing authorization procedures have not been described systematically in the past. In Europe, the existence of parallel regulatory approval pathways has rendered any situation analysis difficult. Negative outcomes were not reported by authorities and have been communicated by applicants predominantly to company stakeholders and investors. New transparency requirements, which entered into force in November 2005, have since allowed to determine approval probabilities and to analyze regulatory review patterns. Since, authorization of all new anticancer drugs has been obtained *via* the centralized procedure, coordinated under the auspices of the European Medicines Agency (EMA).

In the present paper, we examine the outcomes of marketing authorization applications (MAAs) for new anticancer drugs in the EU since 2006. The findings are deemed meaningful to estimate the impact of regulatory decision-making on the overall attrition rates and to identify determinants of risk for successful outcome and for future drug development. For data comparison and interpretation purposes, anticancer drug approval patterns from the USA and Japan were tracked for the same period.

2. Methods

2.1. Sample identification

Information available in the European Public Assessment Reports (EPAR) database (EMA website, http://www.ema.europa.eu) was used for analysis. The final outcomes for MAAs reported between January 2006 and December 2011 were compared and categorized into positive outcomes (positive either after initial CHMP opinion or after re-examination), withdrawal of applications (prior to initial CHMP opinion) and negative outcomes (negative initial CHMP opinion or negative opinion after re-examination, or withdrawal of MAA by the applicant following a negative outcome). Similarly, we searched the EMA EPAR directory to identify all initial MAAs for non-cancer drugs within the same period, applying the same sample identification and data processing rules to this control group.

Relevant characteristics of the initial MAAs were tracked and following information was collected: type of indication, population- and development-specific characteristics (orphan designation {OD}, type of pivotal trial design and primary endpoint), type of medicinal product and the legal basis for approval (new active substance *vs.* significant therapeutic innovation). We also determined regulatory approval times and analyzed restrictions of the authorization (conditional marketing authorization, approval under exceptional circumstances) as well as the regulatory review type (accelerated *vs.* standard).

Our analysis was limited to procedures for medicinal products for treating malignant neoplastic disease, characterized by their assignment to code 'L' in the Anatomical Therapeutic Chemical classification system [7]. Palliative or supportive therapies, cancer vaccines, treatment of chemo-preventive character, diagnostic agents, biosimilars and generic medicinal products were excluded from our analysis as well as hybrid, informed consent or well-established use applications.

2.2. Data processing

Re-submissions and consecutive submissions by different manufacturers for one and the same new active substance (NAS) were counted as duplicate procedures. Complete and independent applications for medicinal products with a known active substance (KAS) claiming 'significant therapeutic, scientific or technical innovation' were assigned to the cohort of initial MAA procedures. The role and function of the EMA in cancer drug regulation has been recently described [8]; EMA regulatory terminology is used accordingly [9].

For CHMP opinions, regulatory review times were calculated as intervals between the start of the centralized procedure (i.e. 'day 0'), the date of the initial CHMP opinion or the withdrawal decision, and the date of the EU Commission decision. Endpoints and trial designs were, in accordance with the literature, classified *via* three denominators for each variable [10].

For data comparison and interpretation purposes, anticancer drug approval patterns from the USA and Japan were tracked for the same period. Publicly available databases and reports from the US Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) were used to identify new drug approvals. Dates of submission and approval were used to analyze