How to assess assessments?

The main principle of regulatory drug evaluation is relatively simple: the marketing authorisation of a medicinal product relies on the demonstrated efficacy, safety and quality of the product. To reach a positive opinion for marketing authorisation, the applicant has to provide evidence that the benefits of the product in question outweigh the risks in the proposed indication. Although the procedures and legal basis may differ across the regulatory agencies such as the US Food and Drug Administration (FDA), Health Canada (HC) and European Union’s European Medicines Agency (EMA), all the Western countries follow the principle of ‘positive benefit-risk ratio’ for drug approval and utilise harmonised Internal Conference of Harmonisation guidelines.

From 2001 through 2010, 186 applications for novel therapeutic agents have been reported to have been approved by the EMA, 99 by HC and 225 by the FDA, respectively [1]. Specifically for anti-cancer products, 42 approvals, corresponding to 100 indications, were granted by the EMA between 1995 and 2008 [2]. Along with increasing scientific and financial interests in the field of anti-cancer products, these numbers are expected to rise in the near future—highlighted by the fact that oncology is the therapeutic area with the highest number of scientific advice requests received by the EMA [3]. Considering the impact that marketing authorisations and other regulatory decisions have, not only on the clinical practice but also on the conduct of clinical trials, they are quite infrequently analysed or reviewed in the scientific literature. To be provocative, they may often be criticised, but not that often systematically studied. Several papers have been recently published, but they are mostly descriptive in nature or focus on procedural issues or legal framework. For instance, the review timelines have been quite thoroughly analysed [1, 2, 4], but few of the papers attempt to analyse the reasons behind the review times—that are often seen as too long and to delay the clinical use of novel agents. Many of the studies appear to be comparative, i.e. they seek to find differences between the decisions of the regulatory agencies, such as EMA and FDA. Notably though, Trotta et al. [2] have recently analysed differences in the indications of novel anti-cancer products as approved by the EMA and FDA. More importantly, they went further in their analysis by considering the clinical implications of these differences— which, interestingly, were found to be clinically relevant in 10 cases of 100 [2].

In this issue of *Annals of Oncology*, Ito et al. provide a critical review of regulatory approvals based on the so-called ‘Public domain applications’ in Japan, with a focus on anti-cancer drugs [5]. ‘Public domain application’ is a flexible regulatory process, by which a currently off-label use of a well-known drug can be approved without further clinical trials. In this process, the approval may be granted by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), if either sufficient data of usage experience outside Japan is provided, if scientific literature demonstrates the safety and efficacy or if the existing results of clinical trials otherwise show sufficient data. The process appears to share some analogy with the Article 505b(2) applications of FDA, as well as with the application based on ‘well-established use’ (WEU) in the EU. The controversial aspect of the paper by Ito et al., however, is not the legal background or discussion...
of the variety of application types in different regulatory bodies but rather the methodology. The aim of the authors was to evaluate the validity of the decisions made by the PMDA based on ‘Public domain applications’ through an independent, critical academic review [5]. The data used for the analysis were the public PMDA review reports, the articles cited in the review reports and interview surveys with applying companies. The drugs involved were carboplatin, dacarbazine, cytarabine, fludarabine, and, well-established combination regimens BEP, VeIP and MVAC. Based on these three data sources, the evidence was re-evaluated by two medical oncologists [5]. In this respect, it can be argued whether a re-evaluation by two oncologists only can be considered an optimal method to approach the problem, at least in case of assessment reports of conventional marketing authorisation applications. Further, the authors mention that ‘if opinions of the two oncologists differed, a consensus opinion was reached by discussion’ [5]. Given that the regulatory decisions are based not only on an extensive work of clinical, preclinical and pharmaceutical assessors, but also on a thorough review carried out by expert scientific committees and scientific advisory groups, this indeed seems to be more of an opinion than a formal scientific assessment. In the EU, for instance, all new innovative medicinal products in the field of oncology are evaluated by the centralised marketing authorisation procedure in which two independent assessment teams will carry out the initial evaluation followed by a review by experts in the national regulatory agencies. Thus, the robustness of the regulatory assessment needs to be kept in mind when public assessment reports are evaluated by individuals from the scientific and clinical communities.

Consequently, the obvious question that follows is, how to then retrospectively analyse the validity of regulatory decisions in an objective, scientific manner? It is easier to ask than to answer. In this particular case, perhaps a more extensive review of literature—instead of evaluation of studies mentioned in the public review reports only—might have been helpful to place the results into a broader perspective, considering that the drugs and regimens studied were well-established ones for which a large amount of evidence can be found. Another approach could also be to compare the regulatory processes and the level of evidence that have led to the approval of different agents for the same indication. Third, the guidance, scientific advice and protocol assistance given by the regulatory agencies have increased and become more detailed over the years. Notably, an updated version of the EMA ‘Guideline on the evaluation of anticancer medicinal products in man’ has been recently published [6]. Given the more and more detailed guidelines, the comparative point of view might be of interest in this respect, i.e. to study, how well the conduct of clinical trials, data provided by the companies and regulatory assessment reports reflect or follow the current guidance or vice versa.

Another issue that the paper by Ito et al. [5] raises is related to the quality and structure of the public assessment reports that are produced by the regulatory agencies, i.e. what would an ideal assessment report be like to enable a comprehensive analysis and what kind of data should be made publicly available? Notably, in only 7 cases of the 14 approvals made via the Japanese ‘Public domain application’ route, a review report was publicly available [5]. The question above, however, cannot be discussed without first asking the question ‘ideal to whom’—the clinician, the scientific community, the pharmaceutical industry or perhaps the patient? As pointed out by Tafuri et al. [7], the regulators have the legal task to evaluate ‘all the available data’ and come to an informed decision about the benefit-risk of the product under review within the legal/regulatory framework. Consequently, the review process and assessment report is neither only for the authorities nor the scientific community, and ultimately, it should serve the public health. For a clinician, the data provided should be a concise review of the data to describe the benefits and risks of the product in comparison to the best available treatment option(s). The scientific community, on the other hand, would value a vast amount of data, analysed by different methodologies and involving aspects beyond quality, efficacy and safety, as well as extensive discussion of the data provided. It should be stressed that a regulatory assessment report differs from an ordinary scientific article in many aspects, although it may not be less scientific in nature. While an original scientific contribution aims at reporting the results in a concise format and to put them into a context via discussion, the aim of the assessment report is rather to justify and reason the opinion based on the huge data package consisting of hundreds of volumes. Furthermore, evaluation of a marketing authorisation application is always a dynamic and interactive process, and thus, even in the best-case scenario, a public assessment report can only be a simple reflection of the procedure. In order to fully assess the regulatory assessment reports, one would need to have a multidisciplinary team looking at the original study reports. However, this approach raises the question of confidentiality of the data. It is obvious that the pharmaceutical industry will be reluctant to release as much data as the most eager referees of the public assessment reports would like to get. In terms of public assessment reports, the pharmaceutical industry would probably rather appreciate a thorough analysis of the regulatory decision making and reasoning, while retaining a high level of confidentiality of their data at the same time. Obviously, the regulatory authorities will have difficulties to striking a fair and legally viable balance between the two different interests.

As clear and straightforward as the principle of a ‘positive benefit–risk ratio’ for drug approval may be, the reality is often not. The regulatory framework may sometimes operate too much according to ‘one size fits all’ principle, while the products and the context of their use may vary enormously. There are recent very complicated examples, such as the marketing authorisation evaluation of Glybera (alipogene tiparvovec), the first gene therapy product approved in the EU [8]. As transparency and harmonisation in regulatory decision making are increasingly called for by the industry, by the clinicians and patients, independent scientific analysis and discussion of regulatory procedures are more than welcome [9, 10]. In fact, it could be one of the driving...
forces to increase the transparency and credibility of regulatory decision making.

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disclosure

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references