Letter to the Editors

Response to the comments from Drs Shimazawa and Ikeda

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We are pleased that our review prompted Drs Shimazawa and Ikeda to study the submission and approval intervals across the three regions of The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with respect to personalized medicines [1]. We read this with great interest and would like to provide some observations on the interesting issues they raise, especially on harmonization of labels across different countries.

Our review is aimed at highlighting not only the clinical inadequacy and risks of prematurely including pharmacogenetic information in the labels to promote personalized medicine but also the differences in approach of different authorities when assessing the same pharmacogenetic data and how these differences translate into different labels. Apart from different perceptions of risks and benefits, labels are determined by a host of factors, not least the (subtle) differences in indications, dosing regimen approved, local medical practices, social cultures and expectations, perceptions about the veracity of the genetic data submitted and anticipated relevance of the genetic data to the domestic population. Inter-ethnic differences in drug response are all too well known [2]. We believe our review provides explanations and specifics for all these differences in labels.

The mandate of the ICH is to harmonize regulatory requirements for data by tripartite-agreed guidelines. Arising from national sovereignty, but above all accountability, harmonization is not intended to extend any deeper into domestic assessment of the data submitted, risk/benefit evaluation of medicinal products and their labelling. Pharmacogenetic data are no exception. Indeed such data may be even more susceptible to differences in social attitudes and economic pressures, even if the results of the genotype-phenotype association studies were compelling enough. Therefore, we do not share the expectation that labels should not differ significantly among different countries despite the regulatory authorities evaluating the same scientific data, see for example a study by Kosugi *et al.* [3]. At times, the inter-agency differences are even

more fundamental than just the contents of the labels. For example, 38 of the 135 applications had a negative outcome in the European Union (EU) during January 1995 to July 1999. By January 2000, the US Food and Drug Administration (FDA) had approved 13 of these 38 applications [4]. The reverse is also certainly true but this has not been studied systematically [5]. Even as recently as 2010, the two agencies could not agree on the risk/benefit of bevacizumab for the treatment of breast cancer. Even between the Member States of just one ICH region, the EU, achieving harmonization has often proved to be an onerous process, requiring legally set out referral and arbitration procedures for resolving disharmony.

A recent study by Tufts Centre for the Study of Drug Development has reported that oncology drugs are approved faster and in greater number in the US than in the EU but according to the author of the analysis, it is not clear if greater access leads to better health outcomes [6]. In the interest of brevity, we appreciate that Drs Shimazawa and Ikeda could not provide details of how they computed the delays between submission and approval in the EU but we hope that they took account of the two features of the centralized procedure that is unique to the EU. Firstly, the marketing authorization holder frequently requests a clock stop during the assessment process to respond to the issues raised by the EU Committee on Proprietary Medicinal Products for Human Use (CHMP) during primary assessment. This averaged 118 days during 2009–2011 inclusive. Secondly, when the assessment is completed, the CHMP issues only an opinion (positive or negative). This opinion requires ratification by the European Commission (EC) which, if the opinion is positive, issues a binding decision on a marketing authorization valid throughout the entire EU. This interval between the CHMP opinion and the EC decision averaged 58 days during the same 3 year period [7]. Interestingly enough, the total of these two (176 days) corresponds well with the median 6 months delay between the FDA and the EU reported by Drs Shimazawa and Ikeda. Infrequently, however, the interval may differ markedly between the two

agencies for justifiable reasons. Lapatinib, included in their list by Drs Shimazawa and Ikeda, is an excellent example. Although the applications for lapatinib were submitted to the two agencies within 1 month of each other, it was approved by the FDA in 181 days and by the EU in 614 days from submission to decision (the active review time, however, was about 320 days). This difference is related to a significant safety issue (hepatotoxicity) emerging after the FDA approval but before the EC decision process. Notwithstanding, there are clear differences between the FDA and the EU with regard to oncology products. However, overall, there are hardly any material differences between the two agencies [5].

Competing Interests

All authors have completed the Unified Competing Interest Form, available on request from the corresponding author and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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