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Authors' reply

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We are grateful for the comments of Sumimasa Nagai and colleagues on our review of oncology biosimilars.¹ Although Japan is the second-largest pharmaceutical market worldwide, the first oncology biosimilar only received regulatory approval in Japan in 2011 (filgrastim). The English-language literature published before our Review's cutoff point of Oct 30, 2014, for our review identified epoetin as the only biosimilar that had received regulatory approval from Japan's Pharmaceuticals and Medical Device Agency (PDMA); however, as noted by Nagai and colleagues, epoetin was not approved for indications related to chemotherapy.^{2,3} English-language descriptions of subsequently approved oncology biosimilars in Japan (all filgrastims) were published after our literature cutoff.⁴ Somatotropin received PDMA approval in 2009; however, it is not an oncology biosimilar. We welcome the planned increase in the availability of English-language translations of Japanese regulatory information, which will remove the need to rely solely on English-language information for biosimilars that have received PDMA approval.⁵

We also welcome the clarifications of regulatory requirements in Japan. As noted by Yamaguchi and colleagues,³ and in the country-by-country descriptions of regulatory requirements included in table 1 of our Review,¹ Japan's PDMA requires that sponsors show similarity between a biosimilar candidate and the reference product through clinical and non-clinical studies, and structural and functional analyses. However, in some instances, formal comparative efficacy studies might not be required.³ Also, pre-approval clinical studies can be done in other countries, if extrapolation of foreign clinical trial data to the Japanese population is justified (although, as noted by Nagai and colleagues, these studies should preferably be done in Japan).² We appreciate the clarification of our statements regarding Japanese regulations on biosimilar pharmacovigilance and substitution, for both of which we cited English-language publications.^{5,6} The clarifications are that the proposed design of risk management plans must be approved by the PDMA before regulatory approval, and that automatic substitution is not allowed in Japan even after postmarketing

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surveillance has ended.³ Internationally, regulatory processes for biosimilar drugs are in a constant state of flux, and these processes will need to be updated, especially after therapeutic oncology biosimilars for rituximab, bevacizumab, and trastuzumab are introduced.

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