Medicinal Products (BMWP), of the Committee for Medicinal Products for Human Use (CHMP), EMA, UK. J.-H.T. is chair of the Biologics Working Party (BWP), CHMP, EMA, UK. N.E., E.H., K.H., R.T. and M.W. are members or experts of the BMWP, EMA, UK. J.J.B., K.H., M.H.H., R.M.v.d.P., S.R., A.J.v.d.S., A.S.T., N.E., G.W. and M.W. are members or experts of the BWP, EMA, UK.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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1. Schellekens, H. & Moors, E. Clinical comparability and European biosimilar regulations. *Nat. Biotechnol.* **28**, 28–31 (2010).
2. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues CHMP/BWP/49348/05 (2006). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf>
3. European Medicines Agency. Refusal assessment report for Alpheon. (2007). <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000585/WC500070792.pdf>
4. European Medicines Agency. Multidisciplinary guidelines: biosimilar. (2012). <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c>
5. Schneider, C.K. & Kalinke, U. Toward biosimilar monoclonal antibodies. *Nat. Biotechnol.* **26**, 985–990 (2008).
6. European Medicines Agency. Guidance on similar medicinal products containing recombinant human soluble insulin EMEA/CHMP/BMWP/32775/2005 (2006). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf>
7. European Medicines Agency. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor EMEA/CHMP/BMWP/31329/2005 (2006). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf>
8. European Medicines Agency. Guideline on similar biological medicinal products containing interferon beta EMA/CHMP/BMWP/652000/2010 (2011). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120652.pdf>
9. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies -- non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010 (2012). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf>
10. European Medicines Agency. Guideline on similar biological medicinal products CHMP/437/04 (2005). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf>
11. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins EMEA/CHMP/BMWP/118264/2007 (2009). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf>
12. European Medicines Agency. Concept Paper on the development of a guideline on similar biological medicinal products containing monoclonal antibodies EMEA/CHMP/BMWP/632613/2009 (2009). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500014438.pdf>
13. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended. <http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf>
14. European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (revision) EMEA/CHMP/BMWP/301636/2008 corr (2010). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf>
15. European Medicines Agency. Concept paper on the revision of the guideline on similar biological medicinal product EMA/CHMP/BMWP/572643/2011 (2011). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/11/WC500117987.pdf>
16. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) EMA/CHMP/BWP/247713/2012 (2012). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127960.pdf>
17. European Medicines Agency. Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BMWP/572828/2011 (2011). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/10/WC500115611.pdf>

Huub Schellekens and Ellen H M Moors reply:

The biosimilar regulatory pathway should be based on the specific properties of biologics. We appreciate the response of Schneider *et al.* from the different EMA working parties on biosimilars and biotech as an illustration of the open and transparent way the EMA/CHMP has pioneered the biosimilar regulatory pathway[1]. Even so, they failed to show the scientific need for the comparability exercise demanded by these regulations.

In contrast with the suggestion of Schneider *et al.*[1], we have only argued that there is no scientific basis for the regulatory demand to show comparability of the quality, safety and efficacy of the biosimilar with the reference product. As stated in our Commentary, we think biosimilar manufacturers may have many good scientific and marketing reasons to compare their product with the originals[2]. We know companies have started their biosimilar development by analyzing the quality of many batches of the originator's products during several years. And based on these detailed evaluations, they have set the specifications for their products and reverse-engineered the production and downstream processes. And comparative clinical trials may obviously be important for marketing purposes.

Concerning the quality-comparability exercise, Schneider *et al.*[1] just repeat the regulatory position[3] that "it is not expected that the quality attributes in the biosimilar and reference medicinal products will be identical, provided that the identified differences are properly justified and shown to have no impact on the safety and efficacy profile, either by relevant scientific knowledge, non-clinical and/or clinical studies." But in the regulatory pathway for biosimilars clinical studies are always needed because of the complexity of biologic products and the lack of the tools for their complete characterization. And why ask for quality comparability, if the outcome is always the same?

According to Schneider *et al.*[1], the refusal and/or withdrawal of biosimilar applications of poor quality compared with the reference product highlights the importance of comparability data. However, these applications showed many other deficiencies, and neither would have been accepted if submitted as new biologics without any comparative data[4,5].

For Schneider *et al.*[1], the demand for comparability in quality is not hindering the biosimilar developers from innovating and improving their products because the originators have continuously adapted their production methods and analytical tools during the life cycle of their products. But that has obviously not happened with all products because there are products on the market that do not meet current quality standards, for instance, because of a high level of aggregation, which is one of the best

defined risk factors for immunogenicity[6,7]. Developing a biosimilar with a reduced aggregate level is relatively easy and would make the product less immunogenic and much safer. Even so, it would also lead to an increase in specific activity resulting in a different potency and dosing. According to the current regulatory position, this product would not qualify as a biosimilar and the manufacturer would be forced to apply for marketing authorization as a new biologic, which is a very expensive and time-consuming route. This may have regulatory logic, but is clearly not in the interest of innovation and ultimately of patients.

Schneider *et al.*[1] state that "pharmacokinetics is normally a very sensitive parameter for establishing biosimilarity." This is a very surprising position, as pharmacokinetics of biologics is considered difficult to evaluate, highly variable between individuals and often not relevant for clinical activity[8,9].

Most biologics have extreme biological activity, are dosed at microgram levels, and only circulate in very low concentrations, demanding the utmost of the analytical methods. Most often, immunoassays are used based on the identification of epitopes that may not reflect the biological activity and whose sensitivity is low compared with the sensitivity of the tools used to quantify classic drugs. Biological activity may be determined by bioassays, which are cumbersome to perform, need to use living cells and sometimes living animals, and have even more sensitivity and specificity issues than immunoassays, especially if the biological activity of a biological in serum needs to be determined. Relating serum levels with clinical efficacy is often impossible because of the nonlinear dose-response, degradation at the injection site or direct entry in the lymph system. Feedback mechanisms may exist that influence pharmacokinetics, or an endogenous homolog may alter the pharmacokinetic behavior of the exogenously administered biologic. But the most important difference between biologics and classic drugs is their immunogenicity, which may influence the pharmacokinetics of the biologics.

The difficulties of comparative pharmacokinetics of biologics is otherwise well recognized by the CHMP/EMA. In the European Public Assessment Report (EPAR) issued by the CHMP of Avonex (interferon beta 1a; IFN beta 1a), one of the marketed interferon beta products, it was stated that limited pharmacokinetic data were available with respect to tissue distribution, plasma protein binding and metabolism due to the difficulties in measuring intact interferon beta-1a (ref. 10). The pharmacokinetics was considered highly variable due to the large intersubject variability and the poor assay sensitivity, making pharmacokinetic comparisons impossible. This was confirmed in a study of the pharmacokinetics of two highly similar interferon beta-1a products that showed a greater than 200% difference in pharmacokinetic parameters[11].

Schneider *et al.*[1] agree that most of the comparative clinical studies with the current biosimilars did not meet the guidelines. Whatever the reason, it confirms that comparative clinical data are not essential for the evaluation of the safety and efficacy of a biosimilar.

The biosimilar regulatory pathway in Europe is derived from the legislation on generics. It therefore leans too much on the classic generics paradigm in which pharmaceutical equivalence and bioequivalence are used as surrogates for clinical data. Even so, clinical data are an essential part of the biosimilar pathway and rightly so. But because of these clinical data, there is no need for the surrogates.

Future amendments of the European regulatory guidelines on biosimilars should be based on the specific issues of biologics, such as immunogenicity and their lack of intrinsic toxicity. Adverse effects of biologics are either the result of an exaggerated biologic effect or of the induction of antibodies. Innovation, validation and standardization of potency assays and predictive tools for immunogenicity are therefore the best way forward to ensure the introduction of safe, effective and affordable biosimilars.

1. Schneider, C. *et al. Nat. Biotechnol.* **30**, 744–746 (2012).
2. Schellekens, H. & Moors, E. *Nat. Biotechnol.* **28**, 28–31 (2010).
3. European Medicine Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMEA/CHMP/BWP/49348/2005 (2006). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf>
4. European Medicine Agency. Withdrawal assessment report Marvel insulin (2010). <http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067086.pdf>
5. European Medicines Agency. European public assessment report (EPAR) for Alpheon (2007). <http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/000585/WC500017451.pdf>
6. Hermeling, S., Jiskoot, W., Crommelin, D., Bornaes, C. & Schellekens, H. *Pharm. Res.* **22**, 847–851 (2005).
7. Prümmer, O. *Biotherapy* **10**, 15–24 (1997).
8. Baumann, A.. *Curr. Drug Metab.* **7**, 15–21 (2006).
9. Mahmood, I. & Green, M.D. *Clin. Pharmacokinet.* **44**, 331–347 (2005).
10. European Medicine Agency. European public assessment report Avonex (2006). <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000102/WC500029420.pdf>
11. Alam, J. *et al. Pharm. Res.* **14**, 546–549 (1997).

Silos hamstring Chinese plant biotech sector

To the Editor:

Although multinational companies dominate research and development (R&D) on genetically modified (GM) crops elsewhere in the world, GM crop R&D in China is mainly conducted by the public sector[1,2]. Since 2008, Chinese R&D on GM crops and animals has been spurred by $3.8 billion of new funding from the National GM Variety Development Special Program (GMSP), which supplements existing public funding mechanisms for this type of research. We set out to assess the innovativeness and focus of China's public R&D program on crop biotech by surveying 147 colleges in universities and public research institutes that engaged in the recent GMSP. Our results suggest that the widespread siloing of expertise in different aspects of GM crop R&D may be thwarting the efficient coordination of research efforts nationally. Overcoming these silos may therefore represent an important goal for the Chinese public agbiotech sector.

Our survey was conducted in 2010 by mail and followed up by telephone calls. Survey forms were sent to the research management division in 147 colleges at universities or national and provincial institutes. At each institution, the division head assigned a task force to ensure these forms were distributed to all research teams that participated in GMSP. Each research team leader was then asked to fill in questionnaires in the survey forms. Research teams were defined as a group of scientists within any college or