International standards and guidelines for xenotransplantation

To the Editor — As representatives of the International Xenotransplantation Association (IXA), we read with interest the Correspondence by Kwisda et al.[1] in the July issue on regulatory and intellectual property conundrums in xenotransplantation; however, we were surprised and dismayed to see not a single mention of the IXA's published regulatory guidelines. IXA is concerned that readers of the Correspondence may be tempted to draw the incorrect conclusion that there are few if any efforts being made to provide common standards and guidelines for the regulation of clinical xenotransplantation.

In particular, we strongly disagree with the authors' contention that "a patchwork of different regulatory and legal approaches means that it is unlikely that an international consensus can be found to oversee xenotransplants." In addition, we believe that the statement "A continued, systematic debate on common standards should therefore be a priority across jurisdictions" is misleading. Here, we seek to respond by providing accurate information on the status of xenotransplantation regulation so that your readers and, most importantly, those who are developing xenotransplantation products are appropriately informed of the work performed over several decades to develop a coordinated international regulatory framework for clinical xenotransplantation.

The IXA is a section of The Transplantation Society (TTS) and has worked closely for many years with TTS and the World Health Organization (WHO) in the regulatory area[2]. The WHO sponsored task force meetings in 1996, 1997 and 1999 to develop international guidance on xenotransplantation safety, equitable access, and coordination of regulation, resulting in the publication of a guidance document in 2001. A further meeting was held in 2003, at which experts from 23 countries finalized a document that was gazetted as the xenotransplantation component of Resolution WHA57.18 of the 57th World Health Assembly (WHA)[3,4]. Substantial consultation was subsequently undertaken with national jurisdictions, including the US Food and Drug Administration (FDA), the European Medicines Agency, the Australian Therapeutic Goods Administration and the (now disbanded)

UK Xenotransplantation Interim Regulatory Authority[5,6]. To help ensure an internationally coordinated approach to registration of xenotransplantation practices, a panel of experts convened by the WHO in 2005 recommended the establishment of an inventory of global clinical xenotransplantation activity (https://www.humanxenotransplant.org) that is reviewed and reported on regularly[7].

In 2008, the first WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials was held in Changsha, China. The Changsha Communiqué described 10 guiding principles and 20 recommendations for consideration by the WHO, member states, investigators and proposers of clinical trials using xenotransplantation products. This guidance was approved[8] by the WHA in 2010. A second consultation to update the communiqué was undertaken in 2011, with representation from regulatory agencies, including the FDA, the European Medicines Agency and the Chinese FDA[9]. The resulting guidance for infectious disease surveillance, prevention and response appropriate to xenotransplantation clinical trial scenarios was published shortly thereafter[10].

In 2018, IXA (in conjunction with TTS and the WHO) undertook another major update of the international guidelines, where the principles and recommendations of the preceding Changsha Communiqués were reviewed and debated in detail. More than 36 international experts representing most WHO member states participated, along with representatives of several regulatory authorities. Seventy revisions were made to the 2008 and 2011 communiqués, including a recommendation to the WHO to promote public awareness of xenotransplantation, its potential benefits, and the associated need for effective regulation by member states in an internationally consistent manner. A major focus was on donor animal "product release criteria" and "designated pathogen free" definitions, as well as quality control strategies for assuring the presence of the intended graft phenotype and any intentional genomic alterations (IGAs). Other major topics included clinical trial design and the importance of reproducible preclinical data from non-human primate models[11].

We hope that our brief review demonstrates the longstanding development and refinement of common standards and regulatory guidelines for clinical xenotransplantation. Representatives from many disciplines continue to participate in ongoing consultations to discuss progress and innovations in the field and to mirror this progress with provision of guidelines for regulatory oversight by member states.

In conjunction with the WHO and TTS, the IXA is keen to see the development and use of novel cutting-edge xenotransplantation products, including those using materials derived from animals with IGAs. These products could fill the ever-increasing gap between organ donors and transplant numbers required, thus improving public health and addressing a major societal medical need. The IXA wishes to ensure that the general medical and scientific communities understand that substantial guidance and regulatory processes are in place, along with the medical and scientific expertise necessary to undertake effective and safe clinical trials. ❐

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References

1. Kwisda, K., Cantz, T. & Hoppe, N. *Nat. Biotechnol.* **39**, 796–798 (2021).
2. Hawthorne, W. J. *Xenotransplantation* **27**, e12604 (2020).
3. World Health Organization. Ethics, access and safety in tissue and organ transplantation: issues of global concern (WHO, 2003).
4. World Health Organization. Fifty-seventh World Health Assembly. Resolutions and decisions, annexes — document WHA57/2004/REC/1 (WHO, 2004).
5. Abou-El-Enein, M. & Schneider, C. K. *Nat. Biotechnol.* **34**, 231–233 (2016).
6. U.S. Food & Drug Administration. Xenotransplantation guidances. https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/xenotransplantation-guidances (2016).
7. Hu, X. et al. *Transplantation* (in the press).
8. World Health Organization. First WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, China, 19–21 November 2008 (WHO, 2008).
9. World Health Organization. Second WHO global consultation on regulatory requirements for xenotransplantation clinical trials, October 17–19 2011, WHO, Geneva, Switzerland (WHO, 2011).
10. Fishman, J. A., Scobie, L. & Takeuchi, Y. *Xenotransplantation* **19**, 72–81 (2012).
11. Hawthorne, W. J. et al. *Xenotransplantation* **26**, e12513 (2019).

Competing interests

W.J.H., P.J.C. and L.B. declare no competing interests. E.W. is a cofounder of XTransplant GmbH.