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# Editorial

# Who will regulate the regulators?

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The clinical use of haematopoietic stem cell transplantation has made tremendous progress in the last 30 years. Although the procedure is still associated with appreciable risks of morbidity and mortality, tens of thousands of patients in more than 40 countries worldwide owe their lives to the successful application of this relatively new technique. It was developed first using syngeneic and HLA-identical sibling donors, but more recently the use of alternative donors has made the therapy possible for many more patients. Panels or registries containing identifying information and detailed HLA typing for more than nine million volunteers are now established in 38 countries and about 5000 matched unrelated donor transplants have been carried out in each of the last 5 years. It is unquestionably desirable that the centres responsible for recruiting and typing the donors and maintaining the registries adhere to the strictest ethical and technical standards. Regulatory agencies in the various countries have an obligation to ensure that these standards are reached and maintained. Nevertheless, it appears now that the continued operation of these donor centres at the international level may be under threat.

A prime requirement for a successful transplant is to use a donor who is closely HLA matched with the patient. For this purpose, a HLA-identical sibling is currently the best choice, but only available for a minority of patients. For patients lacking matched siblings, the tissue typing in recent years of relatively large numbers of volunteers as mentioned above has enabled clinicians to identify suitable unrelated donors. The HLA system is complex. There are more than 1800 recognised alleles at the six major HLA loci on the short of arm of chromosome six. This means the diversity of HLA types is enormous and the chance of finding a matched unrelated donor would be negligible were it not for the phenomenon of linkage disequilibrium – the term that describes the propensity of specific alleles to be inherited together. Even so, the chance of finding a perfect match for a patient of caucasian ethnic origin is less than 50%. The chance of finding a donor for patients in other ethnic groups is lower, mainly because the panels of volunteers of non-caucasian ethnic background are still much smaller. Thus, for all patients, but especially for those who are members of an ethnic group that constitutes a 'minority' in the country where they reside, the chance of finding a good match is greatest if the search can be 'internationalised', that is, extended to all donor panels worldwide.

To facilitate such international searches, two highly important but closely related initiatives were taken in the 1990s. First, Jon van Rood in Leiden started collecting data on registered donors, each with his or her unique HLA phenotype, from all collaborating donor centres and organised this information into a book christened 'Bone Marrow Donors Worldwide'. The book enlarged annually and soon became unwieldy – to be replaced first by a floppy disk that could be mailed to transplant centres and now by a comprehensive internet site (www.bmdw.org). In whatever format, BMDW serves the important function of allowing rapid identification of potential donors across national borders. Second, members of the international transplant community came together to found the World Marrow Donor Association, an organisation committed to facilitating transfer across national boundaries of haematopoietic stem cells collected at a donor centre in one country for the benefit of a patient undergoing a transplant in another country.[1] In the last 10 years, the WMDA has addressed a multitude of specific issues, including donor recruitment, standardisation of the techniques for stem cell collection, labelling and transportation, documentation, donor confidentiality, liability, insurance, donor centre accreditation, costs of harvesting and, by no means least, ethics. WMDA convenes regular scientific and administrative meetings, has wide international representation and is highly regarded in the haematopoietic stem cell transplant community. So far, so good.

In the last 2 years, government agencies in many countries have sought to specify and eventually to enforce a series of standards governing the production of defined pharmacological and biological products intended for administration to human subjects. This is a worthy exercise, but it becomes complicated when the product is prepared or manufactured in one country for administration in another. It becomes especially complicated when the only suitable product is one collected from a human donor quite specifically for an individual patient residing in another country, because no other donor will match. Unless a rational approach is adopted by the regulators, every hospital in the world that supplies a product, in this case haematopoietic stem cells for transfusion to a specific patient, would have to be registered, inspected, accredited and licensed as a manufacturing centre by regulators in any other country to which they may possibly send donations. Since the requirements are not harmonised, each hospital would have to comply at different times with several different sets of requirements, covering such items as product labelling, and the choice of infectious disease marker tests and the laboratory where the tests are to be performed, to name just two areas where each regulator may have different requirements.

National regulators must surely have realised that for all of them to inspect and accredit every centre worldwide that might be asked to provide stem cells for use in their own country is almost certainly an impossible task. Another option would be to prevent the use of stem cell products from all foreign centres not accredited in a particular country, a proposal that in the worst case scenario would abruptly bring international transplants to a halt and even in the best case scenario would undoubtedly deny some patients a life-saving therapy. There is a third – and far superior – alternative. Officials responsible for regulating the importation of blood stem cells should take note of the World Health Assembly resolution (WHA 57.18) which advocated cooperation '….in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells……..'.[2] A good starting point would be to examine the progress made by the WMDA in creating global standards and starting the process of accreditation.[3] The WMDA standards have proved effective in safeguarding the quality of haematopoietic stem cell products for more than a decade. An attempt to pursue any other course would be clinically disastrous.

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## References

1 Goldman JM, for the WMDA Executive Committee. A special report – bone marrow transplants using volunteer donors – recommendations and requirements for a standardized practice throughout the world. *Blood* 1994; **84**: 2833–2839.
2 World Health Assembly. Human organ and tissue transplantation. *Transplantation* 2004; **78**: 493.
3 Gahrton G, van Rood JJ, Oudshoorn M. The World Marrow Donor Association (WMDA): its goals and activities. *Bone Marrow Transplant* 2003; **32**: 121–124.