INTERNATIONAL XENOTRANSPLANTATION ASSOCIATION

a section of The Transplantation Society

October 14, 2008

Subject: European Commission Public Consultation on "DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS"

Dear Sir or Madam,

I am writing on behalf of the current Council and former Presidents of the International Xenotransplantation Association (IXA). IXA is a section of the international Transplantation Society (TTS), and its membership is comprised of the leading investigators, ethicists, and key opinion leaders in the field of cross-species or "xeno-" transplantation.

We have read the "DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS " [2 July 2008 version]. The revised guidelines support two important societal goals, to protect public health while supporting application of new candidate treatments to alleviate human suffering and disease. The guidelines and a companion document (describing an "amendment to the clinical trial application as regards advanced medicinal products") include reference to use of cell, tissue, or organ xenografts as "advanced therapy investigational medicinal products (ADIMPs)". In aggregate, these documents anticipate that such proposals will be actively considered for approval. In response, the opinions below reflect the consensus opinion of the IXA Council, with the concurrence of TTS leadership.

While IXA strongly supports efforts to improve human health through the use of xenografts, we are equally enthusiastic in our insistence that any such trial be securely founded upon peered-reviewed preclinical data suggesting that efficacy is likely (i.e., that therapeutic benefit for the recipient may be expected). Although significant progress is being made, we are not aware of any evidence to support initiation of a clinical xenograft trial at this time.

It is the consensus opinion of the xenotransplantation community that cross-species transfer of living cells and tissues involves potential risks not only to xenograft recipients, but also to their close contacts, and others. These risks must be specifically managed to prevent unlikely but potentially serious and avoidable harms. For this reason, it is essential that any trial be subject to objective, unbiased oversight by national regulatory authorities. Specifically, such a trial should not be delegated to a commercial or academic sponsor without thorough, ongoing supervision. Such oversight is an important public health imperative, and a clear duty of good government. The language of the Good Clinical Practice document should clearly articulate such a vision, and establish national oversight that is compliant with internationally agreed standards as a condition for xenograft trial conduct.

The Draft contains commendable recommendations for "traceability" of any ATIMP. For the special case of xenotransplantation, as detailed above, sample archiving and longterm follow up is essential to detect spread of a "xenozoonotic" infection if it should occur, and effectively quarantine that infection. Thus, any xenograft application must provide a detailed plan to ensure mandatory longterm clinical follow up and archiving of samples. Although consensus recommendations have not yet been established, a minimum interval of ten years following transplant has been proposed to retain donor and recipient materials that will be potentially informative to investigate a documented or suspected xenozoonotic infection (reference Section 2.10). Reporting requirement language should be strengthened for the case where the ATIMP contains animal cells (reference Section 2.4.1). In this context, what provision will be made in case a commercial sponsor goes bankrupt, or an academic sponsor loses funding, retires without a successor, or chooses to leave the field? In our estimation the approving regulatory body must be willing, and able, to commit sufficient resources to resolve such problems if they occur. Such a public commitment is only sensible if the probable public benefit justifies the risks.

We wish to emphasize that, in addition to surveillance of the xenograft recipient, the xenograft recipient's close contacts will also likely require consent and surveillance. At a minimum, we feel it is very important that the final EC Good Clinical Practice document should clearly acknowledge that oversight and regulation of xenograft trials will likely be different than for autologous or allogeneic cells, tissues, and organs. We also feel very strongly that oversight by a national health authority with a specific framework for xenotransplantation be implemented as a precondition for approval of any trial involving xenografts.

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Of note, the IXA is working with international experts to develop consensus recommendations to define the circumstances when xenotransplant trials should go forward. These consensus guidance documents will be available for islet transplantation by the end of 2008, and for other organs by the end of 2009. (Interim guidance for islets can be found at http://www.transplantation-soc.org/sections.php?s=01.) In addition, we are strongly supporting a WHO initiative to internationally coordinate the regulation of xenotransplantation by national health authorities, through a WHO-sponsored meeting scheduled for November 18-21 in Changsha, China. We recommend that the EC GCP document should contain clear reference to WHO, EU, IXA, and (where available) national guidelines regarding conditions for approval of cell, tissue, or organ xenograft trials.

Ethical issues in xenotransplantation may exceed available expertise in many locales, including evaluation of consent and monitoring procedures. Local Institutional Ethics Committees and national regulatory authorities should be encouraged to access expertise appropriate to fully evaluate all relevant aspects of the trial in question.

The possibility of "xenotourism", like other transplant "tourism", poses moral, scientific, and public health hazards that will complicate actions restricted to the EU or EC (reference WHA 57.18). Language to discourage or prohibit allo- and xenotransplant tourism should be strongly considered for inclusion in your Good Clinical Practice guidance.

We hope that these comments will be constructive, and will help further improve this important document. Please let me know if IXA can be of any further assistance, now or in the future.

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