Comments on DEG Enterprise Consultation on a Proposal for a Harmonised Regulatory Framework for Tissue Engineering,
Comments by Glyn Stacey PhD, Head of Division of Cell Biology and Imaging and Director of the UK Stem Cell Bank, 30 April 2004.

The title of tissue engineering is probably now fixed buyt may lead some to falsely believe that products they are developing are not subject to this initiative. Tissue engiuneering implies a certain group of prodcts wher more rtraditional en gineering components such as scaffolds are involved wjhereas this proposal seems to cover a wider range of products. The long discussed solution in the UK was to describe the products rae as Human-derived Tissue Products which seems to accurately fit the current scope of this document.

General words of caution:

1) Some countries have started out on development of guidelines and codes of practice. Please utilise these efforts and assess the individual strengths and weaknesses of each drawing out the best elements. Emphasis should be placed on those documents which have drawn on a wide range of in puts through consultation and were written by groups with wide ranging expertise from commercial, regulatory, medical, scientific and technical backgrounds.
2) Existing regulations and guidelines for tissue transplantation and cell derived products such as vaccines and recombinant therapeutics may be useful reference points but deal with very different products and applications. They should therefore be used with care i.e. do not simply transfer sections of regulatory text from one product area to another such as for virus testing
3) Cell therapy is still at an early stage and there are likely to be very many pitfalls and completely unexpected results. I sincerely hope that each product will be evaluated for risk on a case by case basis using a core risk assessment procedure based on:
    a. Donor medical history
    b. Donor screening (NB evaluation of reliability and sensitivity of test data – this will involve laboratory evaluation, use of reference materials as in tissue banking and possibly involvement of laboratories in European/national QA networks which issue samples for diagnostic tests
    c. Virological risk, based on patterns of infection in the populations
    d. Medical and scientific knowledge of the tissue of origin
    e. Knowledge of the diverse and unexpected responses of cells in vitro
    f. Knowledge of fundamental quality safety And standardisation issues for in vitro cell culture including adventitious agents, cell stability and plasticity, scale-up issues etc.
    g. Knowledge of the response of any artificial component of the product in animals, human tissue or cell culture

Specific Comments on Text

P6 section c) Borderline products: prescriptive or highly accurate descriptions are only setting themselves up to be challenged and are prone to rapidly becoming obsolete in rapidly developing areas such as cell therapy and tissue engineering. It would seem sensible at this early stage of development for this area to develop

definitions that encompass an area of work and that will stand up for a reasonable period of time – over-prescriptive definitions may not remain relevant even at the date of publication of the EU regulation!

Page 8 bullet on Directive93/42/EEC: I anticipate numerous products incorporating elements of biological but nonhuman origin that will be evaluated by groups neither designed nor qualified to assess medical products. The potential for inconsistent and unsafe assessments is a serious concern to me.

Page 8 second bullet: Surely something must will cover storage and distribution

Page 10 part c) first bullet paragraph 2: Standardisation of testing g and QC procedures will; be a major issue and there needs to be some mention of obligation to use appropriate reference materials or engage in QA programmes whereby labs analyse standardised samples blind.

P11 table: agree with all centralised procedures
P12 Table: Agree with all main elements and strongly agree with section beginning "The application should contain …". However, there should be some mechanism involving training and networking that provides some mechanism for harmonising national scientific assessments

P13-14 no disagreements

P15 Post market surveillance: Long term traceability is mentioned but there should be more on "lookback" and sample tracking procedures and these should also address traceability to informed consent for use of tissue. Informed consent is a difficult area varying both between and within nations.

P15 Under storage and distribution: What about stability studies for materials

P16 no comment

P17 To quality safety and efficacy I suggest add standardisation (reference materials, training, QA networks etc.)