

Authority Paper

Date	18 September 2008	Paper reference	HTA (40/08)
Agenda item	10	Author	Sandy Mather

Report of the second European Commission meeting of Competent Authorities for tissues and cells

Purpose of paper

1. This paper and the attached report briefs Members about the issues arising from the second European Commission (EC) meeting of Competent Authorities for tissues and cells which took place in May 2008. The paper has two aims.
 - to explain the benefits of the HTA participating and engaging more with the EC and other European countries in development work emanating from the European Union Tissues and Cells Directives.
 - to give the Authority more information in support of the business case for an increase in staff.

Introduction

2. This paper was discussed at the recent Regulation Members' Group meeting which fully supported the HTA engaging with the EC and other Member States to:
 - share its experiences of regulating this sector under the terms of the European Directives since April 2006; and
 - contribute to the detail of implementation.
3. The strategic objective of this engagement is to ensure that by investing resources now, the HTA and the UK will save money in the future. This is consistent with the value for money principles of economy, efficiency and effectiveness as set out in the Human Tissue Act (2004) and the UK government's policy of keeping the burden of regulation to a minimum.

Key messages

4. There are four key messages in this paper.

The EC are increasing their expectations about the degree to which standards set out in the Directives are met

- At the time of the meeting the EC had commenced formal enforcement action on 16 occasions – involving at least 9 Member States which had not transposed one or more of the three Directives.

The EC has invested in projects to produce guidance about how to implement aspects of the Directives and will expect a return on their investments.

- a single European Coding System
- European Registry for Organs, Tissues and Cells (EUROCET project)
- European Union Standards and Training for the Inspection of Tissue Establishments (EUSTITE)
- vigilance and Surveillance Reporting system for serious adverse events and reactions (linked to EUSTITE project)
- quality system guidance;

and two new projects –

- analysis and comparison of tests and testing laboratories
- import and export to third countries

Staffing pressures in the HTA have limited our involvement in these projects to minimal or zero.

- HTA has been not been able to release resources to contribute to the European Coding Work or the EUROCET project.
- HTA has been minimally and intermittently involved in the EUSTITE project, the Vigilance and Surveillance project and the Quality System guidance project.
- HTA currently has insufficient staff to contribute to the two new projects.

The HTA needs to invest more resource into engaging with the EC and supporting the development work they have sponsored.

- HTA will benefit by learning more about the evolving EC systems so that we can prepare more effectively for any changes. This will improve communication between the HTA's staff and licensed establishments.
- HTA could contribute more to the development of new EC systems which in turn could help to ensure alignment with existing HTA systems and reduce unnecessary additional financial investment in the future.
- HTA has been at the vanguard of implementing this European legislation and can share knowledge and experience to help other Member States.
- HTA is in a position of strength at present and has an opportunity to influence strategy and decision making.
- HTA should participate actively in groups that are helping to formulate the EC policy and inform high level debates and decisions.

Conclusion

5. Members are asked to note this report for information.

Report of the second European Commission meeting of Competent Authorities for tissues and cells

Purpose

1. This paper summarises the key issues discussed during the second meeting of Competent Authorities for tissues and cells which was held on 29 and 30 May 2008 at the European Commission (EC). The paper also discusses the implications of these issues for the HTA.

Background

2. This was the second meeting of Competent Authorities for tissue and cells. The first was in February 2007. At the first meeting, very few countries had implemented any part of the three Directives. Indeed, there were only a handful of Member States who had formally identified a Competent Authority at that time. The UK was one of the first to establish a Competent Authority and one of the first to license tissue establishments according to the terms of the Directive. The HTA started licensing tissue establishments under the HT Act in April 2006. The full requirements of the three Directives were transposed into UK law via the Human Tissue (Quality and Safety for Human Application) Regulations in July 2007.

Infraction proceedings

3. The EC introduced the meeting by giving an overview of how each Member State had transposed the Directives and how they were being implemented in practice. The EC advised that it had initiated infraction proceedings against those Member States who had not transposed any or all of the three Tissues and Cells Directives into domestic legislation (see table 1 below).

Table 1

Directive	Infringement procedures
2004/23	Reasoned opinions ie formal enforcement letters sent to 5 Member States and another 2 letters currently being drafted.
2006/17	Reasoned opinions letters sent to 8 Member States and another 2 to be sent.
2006/86	Reasoned opinions letters to be sent to 9 Member States by beginning of June.

4. 39% of Member States have experienced difficulties in transposition for a number of reasons, including:
 - time constraints;
 - lack of resources, capacity and knowledge;
 - need for organisational change;
 - political debate and ethical issues; and
 - competing priorities for the legislative process.
5. The EC explained that these Directives had been slightly more difficult to implement than previous ones related to health (blood, tobacco and communicable diseases). This was for two reasons: firstly, the Directives were of a technical and detailed nature; and secondly, there was less pre-existing regulation in place than for the other health Directives.

Duties of the European Commission with respect to the Directives

6. The EC explained that they had specific legal obligations to provide additional guidance to Member States on a range of issues including the following.
 - Coding
 - Quality management systems
 - Serious adverse event and reaction reporting
 - Annual report of tissue establishment activities
7. Consequently, the EC had funded a range of projects to help develop this advice. Some of these projects were mid-way through completion and others were either being commissioned this year or were reporting their findings this year. The timing is not helpful, neither for the Competent Authorities nor the tissue establishments.
8. The EC acknowledged that they would have preferred to provide guidance on these areas before the Directives were implemented. It would be reassuring to think that they will learn from this and plan differently for the upcoming organ directive.

European Coding system

9. This project has been ongoing for the last two years and there appears to be significantly more work involved in it. As background, article 25 of Directive 2004/23/EC and article 10 of Commission Directive 2006/86/EC set out a requirement for a single European coding system to ensure proper identification, description and traceability of any donated material in the EU. The EC

requested CEN (the European Standardisation Committee) to develop the technical recommendation for such a European coding system. CEN set up an expert team, chaired by Ruth Warwick from the UK, to lead this piece of work. The team has spent considerable time and energy speaking to Competent Authorities about this work to seek their engagement about how best to develop and implement a system. The second stage started in April 2007 and the final workshop meeting was held in February 2008. The work included over 70 participants from tissue, blood and eye banks, Member States, healthcare, transplant organisations, universities and coding organisations mainly from Europe. There were also a few representatives from tissues banks in Canada, Australia, USA and Japan.

10. The report from the working group was presented at this meeting where there was general support for a high level key code. This code would include the country ID and tissue establishment number so that material could be traced from country to country. There was also discussion about implementing a fuller key code to include the following.

Table 2

Country ID + Tissue establishment	Unique donation number	Product code
-----------------------------------	------------------------	--------------

11. Two main issues were discussed. The first was about the cost of implementing new systems for coding to ISBT 128 requirements and the second was related to procurement organisations. Taking each issue in turn:

Coding to ISBT 128 requirements

12. The expert group proposed that the coding system be the same as that for blood and haematopoietic stem cells i.e. the ISBT 128 system. The ISBT 128 Technical Advisory Group already advises on the ongoing development of the ISBT 128 standard to support new developments and new nomenclature/definitions. Ruth Warwick's expert group recommend that the use of ISBT 128 be a partnership between the EC and the International Council for Commonality in Blood Banking Automation (ICCBBA) with linkages to WHO to ensure a global perspective (particularly relating to nomenclature).

Procurement organisations

13. In the proposed system the key code includes reference to a tissue establishment (see table 2 above). However, in the UK and other Member States, procurement organisations may also be responsible for allocating these codes. This means the key code could be expanded to give the option of

identifying either tissue establishments or procurement organisations, or where appropriate, both.

14. ICCBBA provides the product codes and the prefix for a donation number. The donation number itself could then be sequentially applied at the tissue establishment (or on behalf of it if a sector, regionally or nationally managed system is used). No donor, processing or destination details of individual units are supplied to ICCBBA. Member States would decide if the approved Facility Identifier Numbers (eg the unique licensing number the HTA allocates to tissue establishments and procurement organisations) should be allocated at Competent Authority or tissue establishment level; and ICCBBA would work with the Member States to deliver according to whatever Member States' rules require.
15. Two options were put forward by the project group. The first was that each Competent Authority could apply for an ISBT licence and issue codes to tissue establishments and procurement organisations. Alternatively, each tissue establishment or procurement organisation could apply for its own ISBT licence so that they could allocate codes directly. The first option may be more costly in the long run and would also place operational management responsibility on the regulatory authority, which would be inappropriate. The consensus was that each tissue establishment and procurement organisation should apply for their individual ISBT licences.
16. This is a complex piece of work which has considerable resource implications for the HTA as well as licence holders. The report summarises many recommendations for further work: some needs to be taken forward by the EC, some by Member States and/or the Competent Authorities.
17. The report recommends that Member States and Competent Authorities consider the following:
 - a) hardware, software and training requirements
 - b) how tissue establishments codes and donation numbers are allocated, controlled and issued
 - c) translation tables for the transition period
 - d) policies for a possible period of dual labelling, labelling of imported and exported materials and retrospective labelling of inventory.
18. The report recommends that the EC needs to consider the following:
 - a) The EC Health & Consumer Protection Directorate-General (DG SANCO) to establish a Committee to:

- ensure minimum agreed specifications are met
- provide documents to support code implementation
- provide training material

b) DG SANCO should establish forums to oversee EU definitions and be points of reference and advice to Member States and tissue establishments for:

- key codes
- nomenclature
- EU's relationship with ICCBBA

The HTA has not had significant input to this project yet because of insufficient staff.

EUROCET (European Registry for Organs, Tissues and Cells) project

19. This is another project sponsored by the EC which was initiated to contribute toward implementation of article 10 of Directive 2004/23. This states that:

tissue establishments shall keep a record of their activities, including the types and quantities of tissues and/or cells procured, tested, preserved, processed, stored and distributed, or otherwise disposed of, and on the origin and destination of the tissues and cells intended for human applications, in accordance with the requirements referred to in Article 28(f). They shall submit to the competent authority or authorities an annual report on these activities. This report shall be publicly accessible.

20. The same article also requires that the Competent Authorities establish and maintain a publicly accessible register of tissue establishments that specifies the activities for which they have been accredited, designated, authorised or licensed. The HTA currently provides a list of all licensable establishments on the website, which is updated on a monthly basis.

21. The aim of EUROCET is to maintain a central web-based register so that every citizen in Europe can see which establishments and organisations are licensed or authorised by a Competent Authority. The website can also store data about revocations, suspensions, licensable activities and tissue stored within each tissue establishment in each Member State. The website is multi-lingual and can be accessed at www.eurocet.org.

22. The EC has fully endorsed the project and asked all Competent Authorities to input and maintain valid data on it. We have not input into it to date because of insufficient staff.

Reporting systems for serious adverse reactions/events (SAR/SAE)

23. The EC funded a large three year project called EUSTITE (European Union Standards and Training for the Inspection of Tissue Establishments). Part of the project's remit was to develop an EC-wide reporting system for serious adverse events and reactions. The HTA contributed to this project in its early stages and we have shared our experience of developing and implementing an online reporting system.
24. EUSTITE have now developed what they describe as a Vigilance and Surveillance Scheme which includes tools and guidance for both tissue establishments and Competent Authorities to grade adverse events and reactions and also to assess imputability. Both tools are interesting but also quite complex to understand and implement. EUSTITE have invited Competent Authorities to participate in a pilot of the scheme between July 2008 and June 2009.
25. Article 7 of Directive 2006/86/EC requires that Member States submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events received by the Competent Authorities. 2008 will be the first reporting year and will include the reporting period 1 September 2007 to 31 December 2007. The EC are developing a pilot system for Competent Authorities to submit the report and have asked for volunteers to participate in it. The EC advised that although the first report is due on 30 June they will be piloting in June and the formal report template will be issued to Competent Authorities in July.
26. The HTA has volunteered to participate in both of these pilot projects, but both have resource implications.

Inspection systems

27. The EUSTITE project also includes a significant piece of work about developing tools and guidance for inspectors. Tools include an inspection report template and interview audit tool etc. The HTA has contributed to early development work on this and has now been invited to participate in the pilot training course for inspectors which also includes an e-learning package. We have nominated two staff to participate in this, and again there are resource implications.
28. The EC will also be running a training day for inspectors in October 2008 (date to be confirmed). It is not clear how this links with the EUSTITE project.

Quality system Guide

29. The EC have funded a project to develop guidance for tissue establishments about how to implement quality systems. The final project is due to report at the end of 2008. The company taking forward the work is called Alcimed. Some of the Competent Authorities advised the EC that there was too much other ongoing implementation work to participate in and so had decided not to engage in this project. However, the HTA has already met with Alcimed to feed into the early stages of this project.
30. The EC explained that the guidance is for tissue establishments. However, it is reasonable to assume that if we issue it in the UK, our regulatory staff should be familiar with it as they will be asked to clarify aspects of it as people try to use it.

New projects to be commissioned

31. The EC advised that they are currently advertising for another project (80,000 euros for a 12 month contract) to look at two issues:
- analysis and comparison of tests and testing laboratories
 - import and export to third countries

General issues raised during the meeting

32. The EC is interested in how each Member State is using third party agreements. They found that 76% of Member States are using third party agreements (most frequently entrusting one stage of cell processing to third parties) and the EC would like to know more about this and more detail about how they are being used. Member States are likely to be asked to provide information about this.
33. Almost all Member States are applying the requirements for testing as set out in the Directives. Approximately a fifth of them are applying higher standards including NAT testing for HIV1, HVB and HCV.
34. In the UK, we have found that some medical staff removing skin and bone for autologous use, do not meet the testing Directive's requirements for testing. This is primarily where the patient is unconscious eg head or burns injuries. Only Denmark said that they were experiencing similar problems. France explained that they have fully implemented these requirements. They overrule the consent requirements of the legislation and allow the testing to be completed without consent as the patient is being treated in an emergency. Patients across Europe must be receiving autologous transplants of bone and skin, but it may be

that other Member States did not report it as a problem because they are not at that level of implementation.

35. One Member State asked whether other Competent Authorities categorised amniotic membrane, which is routinely used in ocular surgery as an advanced therapy and regulated under the Advance Therapy Medicine Products (ATMP) regulations. They had looked into the issue and found some advice from the Food and Drug Administration who advised that if the membrane performs the same function in the recipient as in the donor, then it is not an ATMP and should be regulated under the EUTCD. The scientific advice was that amniotic membrane acts as a barrier in the eye in the same way as it would in utero, so is performing the same function – therefore is not an ATMP. The European Medicines Agency (EMA) advised that this may be the advice from scientists, but that lawyers may have a different view. The EMA advised that their expert committee will be in place from December 2008 onwards and will deal with queries such as this.
36. DG Enterprise will be starting a public consultation on how the Medical Devices Directive can be improved. This will have an impact for the HTA as it refers to devices containing non viable human cells. The HTA should input to this consultation.

Implications for the HTA of the increasing work emanating from the EC

37. The HTA has contributed to some of the projects (inspection training and adverse event reporting) as far as resources have permitted. However, the capacity to contribute to others is hampered by current staffing levels.
38. It would be advantageous to the HTA to contribute to all of these projects for a variety of reasons in order to:
- influence developments
 - learn about the systems
 - contribute to their development which in turn could help to ensure alignment with existing HTA systems and reduce financial investment in future systems; and
 - share knowledge that has been accrued during UK inspections to date.
39. It is clear that the degree of regulation and associated work needed to implement the Directives fully in each Member State has been under-estimated. This is work both for the regulator, which provides advice and guidance to new and inexperienced tissue establishments, and procurement organisations as well as for the licence holders themselves. The more the HTA learns about the requirements of the Directives, the more it is apparent that we don't know

enough. As the Directives are understood in practice more fully, the implications of their detailed requirements are becoming clearer.

Conclusions

40. The EC is now exerting more pressure on Member States to comply with the provisions of the Directives.
41. The EC has committed significant funding to a range of projects to support the full implementation of the Directives across all Member States. Some of the outputs of the projects funded by the EC will go through the comitology process (the system of EC committees through which some EU business passes) and be amended where necessary before being formally adopted by the Commission; other outputs will not. Most of the outputs from the projects are likely to be issued as guidance that the Commission expect Competent Authorities to follow.
42. It is clear that the EC will expect a return on their investment in guidance to implement the Directives and it appears that their expectation is likely to be full compliance sooner rather than later.
43. There are significant resource implications for the HTA, both in terms of meeting the full requirements of the Directives and also contributing to the development of systems and processes as part of the EC funded projects. There are significant benefits to be gained from increasing resources to allow appropriate contribution to this work.
44. This report supports the HTA's business case for increased staffing levels – particularly at regulation manager level.