

Summary of compliance 2008/09

Regulating the human application sector

Working together to drive up standards

Foreword

The work of the Human Tissue Authority (HTA) is determined by a combination of statutory obligations and accepted good practice; in these regards, the principles which frame our work are similar to those which frame the work of human application (HA) establishments. As a regulatory body, our approach to regulating the HA sector is determined by the Human Tissue Act 2004 (HT Act), three European Directives which have been transposed into UK law via the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations), as well as the good practice derived from key Government reports, particularly the Regulators' Compliance Code: www.berr.gov.uk/files/file45019.pdf.

This report is the second of its kind and is one of a set that the HTA has produced for each of the sectors that we license and inspect. The main aim is to give a clear summary and update about the extent of regulatory compliance in the HA sector. As well as providing a 'snapshot' of the compliance, it includes some sections dedicated to specific regulatory matters which were of prominence during the 2008/09 business year. The information and guidance in this report should be used by staff working under the authority of HA licences, particularly Designated Individuals (DIs), who may then be able to rate their establishments against others in the sector and use the information to raise their establishment's standards.

In December 2008, the Hampton Implementation Review (HIR) measured our compliance against the principles of Better Regulation: www.betterregulation.gov.uk. The HIR team found that we function in a risk-based, proportionate and transparent manner. The HIR report validates our approach in taking regulatory action only when it is needed, with an emphasis on providing advice and guidance, with the aim of preventing future non-compliance. The HTA expects DIs in the HA sector to use this report to improve standards in their sector.

Although we expect licensed establishments to comply with our standards, we would also like staff at these establishments to feel that they have the knowledge and confidence to achieve more than minimal compliance and to demonstrate good practice to us, other professionals and members of the public.



Dr Sandy Mather
Director of Regulation

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Executive summary

This report provides a summary of findings from the 44 phase 2 site-visit inspections of HA establishments, as well as the phase 1 desk-based inspections of 36 procurement organisations, that were carried out between 1 April 2008 and 31 March 2009. As a result of the phase 2 site-visit inspections, we placed 73 additional conditions on establishments' licences and offered 660 items of advice and guidance. Compared with 2007/08, there was an increase in the amount of advice and guidance we gave following phase 2 site-visit inspections (last year, we provided 472 items of advice and guidance). Encouragingly, however, there was a decrease in the number of conditions imposed. Taking into account the reduced number of inspections carried out in 2008/09, compared with 2007/08, there has been an overall increase in compliance of 10%.

When comparing the findings of last year's inspections with those conducted in 2008/09, we found that the areas of compliance and non-compliance are generally the same for both years.

As with last year, we found that the main areas identified for improvement in the HA sector continue to be related to the following issues:

- under-development of quality management systems, particularly in the area of risk assessments and internal audit
- immature systems for reporting serious adverse events and reactions (SAEARS)
- failure to implement appropriate third party agreements
- failure to meet all mandatory donor testing requirements, and
- deficits in standards for environmental monitoring during processing

Since we started licensing procurement in July 2008, we have found that procurement organisations, in particular those procuring cord blood for private use, require a significant amount of support to enable them to fully comply with regulatory requirements. We also received a high number of enquiries from both members of the public and midwives wishing to know more about the regulation of cord blood collection. For these reasons, this report includes a section on the procurement of cord blood.

Executive summary (continued)

In the last year, we refused three HA licence applications on the basis that the proposed DI was not suitably qualified. We have also found that a number of DIs are not fully aware of their statutory duties. To clarify the role of the DI, and to direct DIs to relevant resources, a dedicated section on the role of the DI is included.

The report also includes a section on SAEARs as well as a section on the annual activity data that we collect from our licensed establishments.

Compliance with regulatory requirements is increasing as knowledge and understanding of how to comply with our licensing standards improves. This encouraging trend is testament to the commitment and hard work of the establishments which continue to strive to improve their services.

Introduction

1. The findings in the report are drawn from two main sources of existing knowledge held by the HTA:
 - information and data submitted by establishments (i.e. as part of the compliance report licence application process, the annual activity data, SAEARs reports and information gathered during the phase 2 site-visit inspection process)
 - documents that we have issued to establishments (i.e. phase 2 site-visit inspection reports and licensing decisions)
2. All licensing decisions reflected in the individual inspection reports, from which the findings in this report derive, have been carefully considered with input from a legal adviser and, where appropriate, a senior member of the regulation directorate. Furthermore, all the reports have been reviewed by the DIs and agreed as being factually accurate.
3. Conditions and advice and guidance the HTA gives to an establishment are context-specific, and do not always lend themselves to be easily or appropriately transferred. We aim to make regulatory decisions that are consistent and targeted where action is needed. At the same time we exercise discretion and take specific relevant facts of the individual case into account. Therefore, decisions will vary from establishment to establishment to reflect the particular set of circumstances. This report should be read with this in mind.

Introduction (continued)

The European context

4. The HA sector is the only sector within the HTA's remit that is regulated according to explicit European standards laid down in European Council and Parliament Directive 2004/23 and European Commission (EC) Directives, 2006/17 and 2006/86. The European Union Tissue and Cells Directives (the Directives), were transposed into UK law via the Q&S Regulations in July 2007. The Directives were developed to provide a unified European framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage and distribution of human tissues and cells across the European Community.

The HTA published additional standards for the HA sector in July 2007 to comply with the Q&S Regulations. Due to the number of additional standards, only the main standards appear in this report – see the HA compliance report for a complete list: www.hta.gov.uk/_db/_documents/HTA_Human_Application_v2.pdf.

Overview of the human application sector 2008/09

- Currently there are 266 HA premises within our licensing framework – an increase of 20% over the last year (figure 1). The growth is largely attributable to the number of licences granted to procurement organisations during 2008.

Figure 1: The number of stand-alone establishments, hubs and satellites

Licensed premises	Number
Stand-alone	148
Hub	23
Satellite	95
Total	266



- There are 95 satellite sites attached to 23 different main hubs, with some hubs having multiple satellites. Further information on satellites can be found on our website: www.hta.gov.uk/licensingandinspections/satellitesites.cfm.
- During 2008/09, we carried out 44 phase 2 site-visit inspections of stand-alone or hub establishments in the HA sector, as well as a sample of linked satellite sites. Ten were second round inspections completed in accordance with the European two year inspection cycle requirements. Two of the inspections were non-routine reactive inspections, prompted by information we received about the establishments.
- Between July 2008 and 31 March 2009, we completed 36 phase 1 desk-based inspections of procurement organisations. Results from these inspections are included in a separate section in this report under the heading 'Procurement organisations'.
- During 2008/09, we held six Regulatory Action Panels (RAPs) and issued two sets of Special Directions. Two establishments made formal representations against proposed licensing decisions. Detailed explanation of RAPs, representations and other regulatory actions, can be found on our website: www.hta.gov.uk/legislationpoliciesandcodesofpractice/regulatoryenforcementpolicy.cfm.

Overview of the human application sector 2008/09 (continued)

10. We were involved in one appeal; this was related to the suitability of a DI. The initial licensing decision made at the representations' hearing was upheld by the appeal panel.
11. We refused four licence applications during 2008/09. Three of the refusals were because the DI was not suitable. We refused the fourth application because the establishment was not carrying out any activities that would require a licence at the time of application.

Additional conditions and advice and guidance relating to all 44 phase 2 site-visit inspections

Table 1: Distribution of additional conditions and advice and guidance following site-visit inspections, grouped by category of standard

	C	GQS	PFE	D	Totals
No. of main standards	3	8	5	2	18
No. of additional standards	11	70	35	5	121
No. of conditions imposed following inspection	2	59	11	1	73

Categories: C = consent; GQS = governance and quality systems; PFE = premises, facilities and equipment; D = disposal

An establishment may have a condition or advice and guidance against more than one category of standards (e.g. a condition relating to consent and a condition relating to disposal). Such establishments have been included in the figures more than once (e.g. an establishment with conditions relating to consent and disposal are included in the figures for consent and disposal).

12. Table 1 illustrates the number of additional conditions placed on HA licences and the advice and guidance offered following phase 2 site-visit inspections. These data allow a direct comparison of compliance across standards for each category, taking into consideration the number of additional and main standards.
13. Over the past year we imposed 73 conditions on licences after phase 2 site-visit inspections and offered 660 items of advice and guidance. By comparison, last year we imposed 127 conditions and offered 472 items of advice and guidance.

Overview of the human application sector 2008/09 (continued)

Findings from second round phase 2 site-visit inspections

14. Prior to the implementation of Q&S Regulations in July 2007, establishments in the HA sector were licensed to store under the HT Act for the scheduled purpose of transplantation.
15. A number of establishments that had been licensed for transplantation under the HT Act had been licensed for two years in the 2008/09 business year and, as such, required a second inspection.
16. During 2008/09, a total of 10 phase 2 site-visit inspections were carried out on establishments that had previously been licensed under the HT Act. The establishments are listed in Appendix 2, and are identified by a single asterisk. Our findings indicate that compliance with HTA standards has improved in all 10 establishments.
17. We applied fewer conditions following the second phase 2 site-visit inspections of the 10 re-inspected establishments, across all the HTA standards. A total of 19 conditions were added under the governance and quality systems (GQS) standards for the first phase 2 site-visit inspections. In the second round, we added seven.
18. During the second round inspections, compared with 2007/08, there was a three-fold increase in the amount of advice and guidance provided to establishments for all standards other than those related to consent.
19. Each of the standards imposed by the Q&S Regulations are in place to ensure that tissues and cells used in HA are of the highest quality and safety. Improved compliance with these standards will have a direct impact on improving the quality and safety of tissues and cells.

Compliance with HTA standards

Consent standards (C1–C3)

20. The EU Directives reinforce the consent requirements of the HT Act by requiring that procurement of tissue and cells for HA can only be authorised after all mandatory consent requirements in the particular Member States have been met. The Q&S Regulations put in place additional statutory obligations on establishments regarding the minimum information to be given to donors (or persons giving consent on their behalf) in accordance with European Directive 2004/23. HTA Directions 001/2006 (paragraphs 11–15) provide more detailed guidance on what must be in place in order for the consent standards for this sector to be met.
21. Consent standards are divided into three main standards: C1, C2 and C3. These are supported by a total of 11 additional standards.

Key findings

Table 2: The number of additional conditions and advice and guidance placed on licences in relation to consent standards after a phase 2 site-visit inspection

Business year	No. of establishments inspected	No. of conditions	No. of items of advice and guidance
2007/08	51	22	40
2008/09	44	2	52

22. Compliance with consent standards has improved. We placed two conditions on licences and offered 52 items of advice and guidance to establishments we inspected (table 2). By comparison, last year we imposed 22 conditions and offered 40 items of advice and guidance.
23. As with last year, we observed weaknesses relating to consent standards. They were in three main areas:
- lack of written procedures for obtaining consent
 - lack of training for staff on discussing and obtaining consent
 - lack of, or inappropriate, arrangements with third parties for obtaining consent

Consent standards (C1–C3) continued

24. A number of HA establishments are providing treatments as part of collaborations that involve other establishments both within the UK and abroad. For some of these establishments this will mean that donor consent is sought, and donors are selected by staff at another establishment that may not be licensed. In such cases, the DI of the licensed establishment will need to ensure that they have appropriate written agreements in place. If the collaborating establishment is unlicensed and based in the UK, a third party agreement will need to be in place to cover the consent and donor selection process.
25. Similarly, if the establishment is based within the European Economic Area (EEA), and is unlicensed by its Competent Authority, the HTA will expect to see a written agreement in place ensuring that the consent and donor selection process is compliant with our standards. A written agreement should always be in place with establishments based outside of the EEA.

C1: Consent is obtained in accordance with the requirements of the HT Act, the Q&S Regulations and as set out in the HTA's codes of practice

26. C1 is a generic standard frequently used to pull together several issues relating to consent. The two conditions applied to this standard addressed the lack of a satisfactory third party agreement governing consent, where it was being obtained by a third party.

Consent standards (C1–C3) continued

27. In the case that a third party procures tissues and / or cells on behalf of a licensed establishment, the third party agreement must ensure that consent is obtained in accordance with the requirements of the HT Act 2004, the Q&S Regulations and the HTA's codes of practice. The following is an example of a condition placed against this standard.

Example condition – By 6 March 2009 the DI shall ensure that the third party agreements that are in place with third party procurers require all such third parties to obtain appropriate consent in accordance with the requirements of the HT Act, the Q&S Regulations and the HTA's code of practice on consent.

Reason for the condition – The establishment has incomplete third party agreement arrangements with third party procurers, and is therefore not compliant with the requirements of HTA Directions 002/2007.

28. We gave significant amounts of advice and guidance to establishments to help them with put in place appropriate third party agreements. Establishments should regularly review current third party agreements to ensure that they comply with all regulatory requirements. Further information on third party agreements can be found on our website: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/thirdpartyagreementfaqs.cfm.

C2: Information about the consent process is provided and in a variety of formats

29. This standard is concerned with ensuring that donors are provided with sufficient information to make an informed decision. Before any donation, clear and unambiguous information should be provided. For further information see HTA Directions 001/2006 (paragraphs 11–15), which give detailed guidance on what minimum information must be provided to donors or those giving consent on their behalf.
30. No conditions were applied and only 10 items of advice and guidance were offered, indicating that, overall, establishments are compliant with this standard.

Consent standards (C1–C3) continued

C3: Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent

31. We did not apply any conditions to licences regarding this standard. Advice and guidance was provided on 18 occasions. Last year's report also identified this as an area of weakness for a number of establishments. Box 1 lists some actions that will help achieve compliance with this standard.

Box 1: Actions for improving compliance with standard C3

DIs should:

- put in place tailored training sessions that supplement the generic consent training
- ensure that staff consent training is recorded in the relevant staff records
- put in place procedures for identifying staff trained to take consent

Governance and quality systems standards (GQS1–GQS8)

32. Effective governance and robust quality systems are essential foundations to ensuring compliance with regulatory requirements. HTA Directions 002/2007 set out what must be in place to satisfy the standards relating to GQS.
33. GQS standards are divided into eight main categories of standards and are supported by a total of 70 additional standards.
34. The findings from 2008/09 relating to GQS standards are similar to those for 2007/08. We have therefore not duplicated text and advise you to refer to last year's report if you require further detail: www.hta.gov.uk/_db/_documents/HTA_human_application_summary_inspection_report_final.pdf.

Key findings

35. Governance and quality standards remain the area with the least compliance in this sector. We placed 59 conditions on licences relating to non-compliance with these standards. We also provided 424 items of advice and guidance. By comparison, last year we placed 90 conditions on licences against the GQS standards and provided 317 items of advice and guidance (table 3).

Table 3: The number of additional conditions and advice and guidance placed on licences in relation to governance and quality systems standards after phase 2 site-visit inspections

Business year	No. of establishments inspected	No. of conditions	No. of items of advice and guidance
2007/08	51	90	317
2008/09	44	59	424

36. There has been a net reduction of 20% in the number of conditions imposed during the last year (taking into account the number of inspections carried out). This indicates that more establishments in this year's cohort have good quality management systems (QMS).

Governance and quality systems standards (GQS1–GQS8) *continued*

37. Although there was a higher level of compliance with the GQS standards, we found that, where there were non-compliances, they mirrored those found in 2007/08. As with last year, we found that establishments:

- did not have all the required documented policies and procedures in place
- had deficits relating to the documented quality system
- were not carrying out risk assessments for all practices and procedures, and in particular there was a often a failure to assess the premises for risk
- were not carrying out a full schedule of audits

GQS1: All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process

38. We imposed 22 conditions on licences and offered 108 items of advice and guidance to establishments. Generally, we found that compliance with this standard could still be improved.

39. Many establishments needed to improve the way in which documents were controlled in order to ensure that only current, authorised documents were in use. Documents should be reviewed, approved, dated and documented by an authorised member of staff.

Governance and quality systems standards (GQS1–GQS8) *continued*

40. We found that there were still a number of establishments that did not have documented procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells were transferred to another licensed establishment or establishments. In particular, we found that small commercial establishments sometimes found it difficult to meet this requirement. Box 2 lists actions to help compliance with GQS1.

Box 2: Actions for improving compliance with standard GQS1

DIs should ensure:

- there are procedures for all licensable activities and that these are reviewed and audited on a periodic basis
- they have in place a documented procedure to ensure tissues are not released from quarantine until their suitability for issue has been verified and recorded
- they have in place a procedure to document the critical materials and reagents used and ensure they meet the required standards
- they have in place a documented procedure to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications
- they have in place a documented procedure for the management of non-conforming consignments to ensure that there is no risk of cross-contamination
- they have in place a documented procedure for handling returned products
- they have in place a documented procedure for transferring tissues and cells to another licensed establishment in the event of termination of activities
- they refer to HTA Directions 001/2006 and 002/2007 for further information on the documented procedures that are expected to be in place to order to comply with the Q&S Regulations

Governance and quality systems standards (GQS1–GQS8) continued

GQS2: There is a documented system of quality management and audit

41. We imposed nine conditions on licences and offered 62 items of advice and guidance for this standard. Last year we imposed 27 conditions and offered 47 items of advice and guidance.
42. Directions 001/2006 (paragraphs 20–24) require establishments to put in place and maintain a documented QMS. For further details on the minimum requirements for a QMS please refer to the above Directions.
43. Last year we reported that DIs frequently cited a lack of available resources as the reason for failing to comply with this standard. We found this still to be the case during 2008/09.
44. In last year's report, we identified some key actions that establishments could usefully consider to assist them in developing the QMS. As they remain applicable, they are summarised in box 3.

Box 3: Key actions for developing a Quality Management System

DIs should consider:

- drawing upon the quality management expertise of other local departments
- training a member of staff within the team to develop and maintain a QMS
- visiting and learning from another licensed establishment that has an established QMS in place
- ensuring that the appointed quality manager has protected time to carry out the quality management function

Governance and quality systems standards (GQS1–GQS8) *continued*

45. A number of establishments still did not have a schedule of internal audits, which could lead to an ad hoc and incomplete approach to undertaking them. The following are examples of the types of audit we would expect to see in an audit schedule:

- record audit – to ensure records are legible and complete
- process audit – auditing specific procedures to ensure staff are working to documented standard operating procedures (SOPs)
- traceability audit – to ensure that the establishment can trace material from the donor (or point of receipt if supplied by a third party) to the recipient or disposal of the material
- premises audit – to ensure that premises remain fit for purpose

46. DIs should use the HTA's HA compliance report as a tool for carrying out internal audits. It is a requirement of paragraph 47i of Directions 002/2007 that establishments complete a self-assessment of compliance against HTA standards every 6–12 months. We will request a completed copy of this report either before or during a phase 2 site-visit inspection.

47. We found that establishments had not yet put in place provision for an independent audit of systems and processes. An independent audit could be carried out by:

- other departments within the licensed establishment (e.g. clinical audit department)
- an external organisation (e.g. DIs in similar establishments but who have no conflict of interest in the establishment's practices)
- professional auditors

Governance and quality systems standards (GQS1–GQS8) continued

GQS3: Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills

48. We imposed five conditions on licences and offered 65 items of advice and guidance. Last year we imposed ten conditions and offered 46 items of advice and guidance. The non-compliances identified this year are largely comparable with last year's.
49. Similar to last year, we found that a number of establishments were understaffed. Due to the lack of objective professional guidance on, for example the number of processes a technician can carry out while maintaining the quality and safety of tissues and cells, we have advised DIs to carry out a risk assessment of staffing levels. This will establish whether staffing levels are sufficient to ensure that suitable practices can be maintained and regulatory requirements complied with. The risk assessment can then be used as evidence for the need for the provision of additional resources if necessary. Box 4 details some actions to help compliance with this standard.

Box 4: Key actions for complying with standard GQS3

DIs should ensure:

- staff are suitably qualified
- there is a documented induction process in place
- staff have access to continuing professional development provisions
- staff have adequate knowledge of the scientific and ethical principles relevant to their work and the regulatory context within which they work
- staff have access to the HTA's DI e-learning course and HTA e-newsletters
- staff understand the structure of their organisation and the QMS used within their establishment

Governance and quality systems standards (GQS1–GQS8) continued

GQS4: There is a systematic and planned approach to the management of records

50. We placed seven conditions on licences and gave 94 items of advice and guidance. Last year we placed 30 conditions on licences and offered 87 items of advice and guidance. Generally, establishments appeared to have recognised the importance of effective record management and had begun implementing effective systems and processes to support it. However, there were still areas for improvement; some establishments did not ensure that all relevant data were documented, recorded and stored on validated systems (box 5).

Box 5: Key actions for complying with standard GQS4

DIs should ensure:

- records are retained (30 years for traceability data and 10 years for raw data)
- they have a contingency arrangement for the retention of records in the event of the establishment ceasing activities
- they have in place a documented agreement with end users to record and store the data required by paragraph 71 of Directions 002/2007
- they have in place a documented agreement with end users to report any serious adverse events or reactions that may be linked to the quality and safety of the tissues or cells
- they are familiar with the requirements of paragraphs 33–36 of HTA Directions 001/2006 and paragraphs 45–46 and 70–73 of HTA Directions 002/2007

Governance and quality systems standards (GQS1–GQS8) continued

GQS5: There are documented procedures for donor selection and exclusion, including donor criteria

51. We imposed five conditions on licences and offered seven items of advice and guidance. Last year we added 13 conditions and offered five items of advice and guidance. As this set of standards is aimed at reducing the risk of disease transmission from donor to recipient, it is particularly encouraging to have found that a greater number of establishments are meeting the standards this year.
52. The majority of conditions placed on licences related to the testing of donors in accordance with the requirements of Annexes A and B of Directions 001/2006.
53. Last year's report noted that the HTA was seeking clarification from the European Commission (EC) and Member States on the set of tests that needed to be carried out on autologous donors and their samples.
54. It is now clear that autologous donors must comply with the full testing requirements. In future, we will expect to see that establishments procuring tissues or cells for autologous use comply with the full testing requirements. For further details on autologous testing, refer to Directions 001/2006, in particular Annex A (paragraph 2.1.1) and Annex B.
55. When material is removed from an adult or child who lacks capacity, the removal must be in the patient's 'best interests' and is covered by common law and the Children Act 1989 and / or the Mental Capacity Act 2005 (for persons 16 and over).
56. The Human Tissue Act (Persons who lack Capacity to Consent and Transplants) Regulations 2006 provide for circumstances in which consent can be deemed to be in place in the case of an adult who lacks capacity to consent to storage or use of material: www.opsi.gov.uk/si/si2006/20061659.htm. For example, consent for storage of skull flaps or skin procured from adults lacking capacity is 'deemed' to have been given if the person storing the material is acting in what they reasonably believe is in the patient's 'best interests'.

Governance and quality systems standards (GQS1–GQS8) *continued*

57. The same principles apply to testing an incompetent adult: if it is considered in their best interests to remove and store material, then it will also be in their best interests to test them to ensure they are provided with the same level of protection as a competent patient.
58. Under the HT Act, a child is defined as being under 18 years old. Children may consent to a proposed medical procedure or to the storage of and use of their tissue if they are competent to do so. A child will be considered competent to give valid consent if he or she has sufficient intelligence and understanding to enable them to fully understand what is involved. If the child is not competent, consent could be provided by someone with legal parental responsibility for the child.
59. Some DIs have assumed that if they asked a patient to consent to testing for autologous purposes then that consent would not be given. Contrary to this, we have found that the vast majority of patients who have been provided with sufficient and appropriate information will consent to testing (see box 6: Case study). Furthermore, it is the patient's right to be provided with the opportunity to do so and a decision to not test should never be taken on a competent person's behalf. Box 7 lists actions for improving compliance with the standard.

Box 6: Case study

A competent adult patient presents with severe burns that will require treatment by applying autologous skin grafts; some of the skin will be stored in case a second graft is required. The DI must ensure that the patient is provided with sufficient information on the purpose and nature of the treatment. Also, the patient must be provided with information on the requirement to carry out virology testing and the rationale for doing so, in order to obtain their consent for this procedure. The information provided could include the following information about testing:

- it reduces the risk of cross-contamination during processing and storage of the sample
- it reduces the risk of adverse effects of any mix up in applying the wrong tissue to a patient
- it is a legal requirement

Governance and quality systems standards (GQS1–GQS8) *continued*

60. As with the previous year, some establishments were continuing to test only for Hepatitis B surface antigen (HBsAg) and were omitting to test for the Hepatitis B core antibody (anti HBc). It is important that both tests are carried out. HBsAg is one of the first markers to become positive in Hepatitis B infection. Anti HBc persists for a very long time although it may decrease slightly over time. The two tests together will maximise the chance of identifying Hepatitis B infection that occurred in the recent or more distant past. When anti HBc is positive and HBsAg is negative, a risk assessment should be performed to determine eligibility for clinical use. This will usually involve additional testing so expert virological advice would be required to determine if donated tissues and cells could be used.

Box 7: Key actions for complying with GQS5

The DI should ensure:

- microbiological tests are carried out on the donor's serum or plasma (unless an exemption applies – see paragraph 2.2 of Annex B of HTA Directions 001/2006)
- the donor selection criteria identifies where additional tests might be necessary (e.g. CMV, malaria)
- where autologous material is to be stored the donor has been tested in accordance with Annex B of HTA Directions 001/2006
- repeat testing is carried out in accordance with Annex B of HTA Directions 001/2006
- they maintain a record of the results of any tests carried out
- imported material has been tested to equivalent standards
- test kits are CE marked or appropriately validated for use
- donations received from donors with plasma dilution of more than 50% are used only if the testing procedures are validated for such plasma or if a pre-transfusion sample is available

61. The testing requirements currently required by the HTA reflect the minimum set of tests required by the European Directives 2004/23 and 2006/17. Some Member States have set more stringent requirements. The HTA will keep the current testing requirements under review and may provide further guidance in the future following any recommendations issued by the EC or the Advisory Committee on the Safety of Blood, Tissues and Organs.

Governance and quality systems standards (GQS1–GQS8) continued

GQS6: A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail

62. We placed three conditions on licences and offered advice and guidance on seven occasions. Last year we imposed nine conditions and offered advice and guidance on 18 occasions.
63. It is a requirement to ensure that all tissues and cells used in HA can be traced from the donor to the recipient and vice versa.
64. Similarly, it is a requirement to ensure that all products and materials coming into contact with tissues and cells are traceable. On the rare occasions when donated material, or products associated with the donated material, are found to pose a risk or potential risk to patients, it is essential that the donated material or product can be recalled, and the source of the risk identified.
65. Some establishments found it difficult to meet the requirement to maintain an audit trail, which includes details of when and where the tissues or cells were acquired, the uses to which the tissues or cells were put, when the tissues or cells were transferred and to whom.

Example condition – By 1 May 2009, the DI will validate the computer program used to generate a unique identifier for each batch of tissues or cells. Alternatively, the DI may consider replacing the current computer program with a system validated to provide a unique identifier every time one is requested.

Reason for the condition – Evidence collected on inspection showed that the computer system used to generate a unique identifier for each batch of cells collected had, in one known instance, allocated the same identifier to two procurements. This condition will ensure that the current computer system receives appropriate validation or is replaced by an appropriately validated system to make certain this error does not happen again. If an error of this type was not identified, there is a significant risk that incorrect cells could be allocated to a patient which would pose a serious threat to patient safety.

Governance and quality systems standards (GQS1–GQS8) *continued*

66. Establishments are reminded that where an activity is carried out under a third party agreement, the coding and traceability provisions apply to the activity undertaken by the third party. DIs should ensure that any third party agreement they have in place has incorporated this requirement. See paragraphs 117–122 of HTA Directions 002/2007.
67. In 2006, the EC commissioned a project in to implement a single European coding system. The final report was presented at a meeting with representatives from the Competent Authorities in 2008. The European Standardisation Committee developed a proposal that there should be a high level code which includes the country identification and tissue establishment number so that material could be traced from country to country. However, the EC has not yet decided what sort of system there should be for allocating codes, who should run it and what role Competent Authorities would have (if any) in allocating codes to tissue establishments.
68. The EC has advised that the project has been delayed pending completion of a comprehensive Regulatory Impact Assessment on the implementation of a single European coding system. There will be a full public consultation on the assessment and the outcome will be published during 2010. We will issue further guidance and / or Directions when the detailed requirements of the system are agreed and finalised.
69. Meanwhile, establishments should continue to ensure a coding and records system facilitates traceability in accordance with paragraphs 40 and 54–55 of HTA Directions 001/2006 and paragraphs 79–87 of Directions 002/2007.

Governance and quality systems standards (GQS1–GQS8) continued

GQS7: There are systems to ensure that all adverse events, reactions and / or incidents are investigated promptly

70. Establishments must have procedures in place for identifying, reporting, recording and investigating adverse events and reactions. This includes reporting actual and suspected serious adverse events (SAEs) and serious adverse reactions (SARs), known collectively as SAEARs to the HTA via the online reporting system. For more information on SAEARs, see the HTA website: www.hta.gov.uk/licensingandinspections/faqsonseriousadverseeventsandadversereactions.cfm.
71. During 2008/09 we placed two conditions on licences and offered advice and guidance on 50 occasions. Last year we placed 22 conditions on licences and offered advice and guidance on 57 occasions.

Box 8: Key actions for complying with GQS7

The DI should ensure:

- there are documented procedures in place to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards
- there is a recall procedure in place
- there is an agreement with end users and / or third parties to report SAEARS to the DI
- staff working under the licence are aware of the reporting requirements
- a member of staff is nominated to report SAEARS to the HTA in the DI's absence
- the responsibilities of personnel investigating events and reactions are clearly defined

72. Staff working under the authority of a licence are often unaware of the need to report SAEARs to the HTA. Furthermore, the roles and responsibilities of staff in relation to reporting and investigating events / reactions and initiating recalls are frequently not adequately documented. DIs are strongly advised to refer to HTA Directions 001/2006 to ensure that they are meeting all the requirements relating to SAEARs (see box 8). More detailed information about SAEARs, including some case studies, is provided in the SAEARS section of this report.

Governance and quality systems standards (GQS1–GQS8) continued

GQS8: Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately

73. We placed six conditions on licences and offered 31 items of advice and guidance following phase 2 site-visit inspections. Last year we imposed 21 conditions and offered 32 items of advice and guidance. We found that although most establishments carried out health and safety risk assessments, they did not have documented risk assessments for all practices and processes that might present a risk to the quality and safety of tissues and cells. The following is an example of the type of condition placed on licences against this standard.

Example condition – By 1 March 2009, the DI shall ensure that documented risk assessments are conducted for all licensable activities. Risks that may affect the quality and safety of the cells shall be addressed. Updated and new procedures shall be risk-assessed to ensure that they adequately address any identified risks. The DI shall put in place a schedule to ensure that as a minimum the risk assessments are reviewed annually, or when any changes are made that may affect the quality and safety of tissues and cells.

Reason for the condition – Not all practices and processes have been assessed for risk. Risk assessments are currently not reviewed regularly or when any changes are made that may affect the quality and safety of tissues and cells. Procedures have changed and associated risk assessments have not been updated. Several areas of concern have been noted with the environmental monitoring of the establishment. These should have been highlighted and addressed by risk assessments.

Governance and quality systems standards (GQS1–GQS8) continued

Box 9: Key actions for complying with GQS8

The DI should ensure:

- risk assessments are reviewed regularly and, at a minimum, annually
- staff working under the licence are aware of the outcomes of any risk assessments
- there is a schedule of risk assessments for all licensable activities and that it is adhered to
- material stored before the introduction of a new process, donor selection or testing criteria is risk-assessed and that the risk assessment is approved by the DI

74. Where tissues and cells were procured before the implementation of the current donor selection and testing requirements, we have advised that a thorough risk assessment should be carried out and documented (see box 9). This is a pragmatic response which ensures that a robust and defensible decision can be made regarding the continued use (or otherwise) of valuable tissues or cells. On rare occasions, and where a risk assessment supports the decision, tissues and cells procured from donors usually excluded from donating may be used (e.g. where a donor had a history of disease of unknown aetiology). For further guidance, see Directions 001/2006, Annex A.

Premises, facilities and equipment standards (PFE1–PFE5)

Table 4: The number of additional conditions and advice and guidance placed on licences in relation to premises facilities and equipment standards after phase 2 site-visit inspections

Business year	No. of establishments inspected	No. of conditions	No. of items of advice and guidance
2007/08	51	22	111
2008/09	44	11	162

Key findings

75. We placed 11 conditions on licences and offered 162 items of advice and guidance (see table 4). Last year we placed 22 conditions on licences and offered 111 items of advice and guidance. In general, we found that licensable activities were being conducted on premises that were suitable and were adequately equipped. However, like last year, we identified some areas for improvement, particularly in relation to environmental monitoring.

PFE1: The premises are fit for purpose

76. We placed two conditions on licences and offered 13 items of advice and guidance. Last year we imposed nine conditions and gave 11 items of advice and guidance. Areas of non-compliance with this standard often related to establishments not carrying out risk assessments of premises, which meant that there was no validation that the premises were suitable.

77. During a phase 2 site-visit inspection, the HTA carries out a visual inspection of the premises in order to assess suitability. We imposed only one condition and offered one item of advice and guidance relating to security procedures. Compliance in this area is highly encouraging and indicates that there is controlled access in areas where tissues and cells are stored, or where patient records are held.

Premises, facilities and equipment standards (PFE1–PFE5) continued

78. DIs and LHs have a duty to ensure that relevant third party premises (RTPPs) are suitable. During the 2008/09 business year we did not inspect any RTPPs. However, a trial of inspecting RTPPs will start in the 2009/10 business year. These inspections will enable the HTA to learn more about how licensed establishments are assessing the suitability of RTPPs and the level of risk associated with them.

PFE2: Environmental controls are in place to avoid potential contamination

79. We placed four conditions on licences, issued one set of Special Directions and offered 30 items of advice and guidance. Last year we imposed 15 conditions and offered 18 items of advice and guidance. There were still a number of establishments that were failing to implement effective cleaning and decontamination procedures and to undertake appropriate environmental monitoring. The four conditions that we imposed all related to the securing of appropriate environmental monitoring, including putting in place procedures for particle and microbiological monitoring.

Example condition – By 1 December 2008, the DI should ensure that effective cleaning procedures are introduced and a full root cause analysis and corrective or preventive actions are put in place for the failure to achieve appropriate environmental conditions for processing. Consideration should be given to the use of hot air hand dryers in the vicinity of the cleanroom, validating contact times for sanitisation with ethanol and assessment of the rotational use of biocidal cleaning agents. The establishment should also consider the need to have an open drain in the ante-room to the cleanroom area. Procedures for changing into protective clothing and transfer into the cleanroom should also be reviewed.

Premises, facilities and equipment standards (PFE1–PFE5) continued

Example Special Direction – The DI must immediately cease the processing of high-risk samples within the laminar flow cabinet situated in the main laboratory. Processing within the cabinet in the main laboratory must not resume until the laboratory has been validated to be at least equivalent to Good Manufacturing Practice (GMP) Grade D in terms of particle and microbial counts as required by Directions 002/2007, and the laminar flow cabinet has been validated. Alternatively, procedures for processing high-risk samples within the cleanroom that includes a cleaning process that does not pose a health and safety risk to staff may be developed and implemented.

80. If tissues or cells are exposed to the environment during processing, an air quality – with particle counts and microbial colony counts – equivalent to GMP Grade A is required; with a background environment appropriate for the processing of the tissue or cell concerned, but at least equivalent to GMP Grade D. A subsequent microbial inactivation process obviates the above requirement. GMP air quality standards are defined in Eudralex Volume 4: Good Manufacturing Practice (GMP) Guidelines, Annex 1 – Manufacture of Sterile Medicinal Products (the EU GMP Guidelines Annex 1) and EU Directive 2003/94/EC.
81. The EU GMP Guidelines Annex 1 has been updated and came into operation on 1 March 2009. Establishments are advised to review this updated version to ensure that their practices and procedures are in compliance with the information it contains. It should be noted that there has been a change to the maximum permitted airborne particle concentration for each grade. Table 5 lists the requirements.

Premises, facilities and equipment standards (PFE1–PFE5) continued

Table 5: The maximum permitted airborne particle concentration by size for each environment grade (table reference: the EU GMP Guidelines Annex 1).

Grade	Maximum permitted number of particles per m ³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5 µm	5.0 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

82. To meet ‘in operation’ conditions, these areas should be designed to reach certain specified air-cleanliness levels in the ‘at rest’ occupancy state. The ‘at rest’ state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The ‘in operation’ state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.
83. ‘In operation’ classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. The international standard EN ISO 14644-2 (cleanrooms and associated controlled environments) provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

Premises, facilities and equipment standards (PFE1–PFE5) continued

84. Establishments undertaking processing should have a programme of routine environmental monitoring, which includes not only particle counts but also microbiological monitoring. The establishment should set appropriate alert and action limits for the results, and perform trend analysis on the data, to ensure that the equipment is performing to the expected standard (box 10). SOPs should define the limits and the actions to be taken if these are exceeded.

Box 10: Key actions for complying with PFE2

DIs should ensure they:

- are familiar with the updated Annex 1 'Manufacture of Sterile Medicinal Products'
- have a documented procedure for cleaning and decontamination of all storage facilities, detailing how often this will take place
- have a procedure in place for quarantining non-conforming tissues / cells

PFE3: There are appropriate facilities for the storage of tissues and / or cells, consumables and records

85. A total of three additional conditions were placed on licences and 38 items of advice and guidance were given. Last year, we imposed nine conditions and offered 25 items of advice and guidance. Generally, establishments had storage facilities which were secure and, where necessary, appropriately monitored. Box 11 lists some actions for good compliance.

Box 11: Key actions for complying with PFE3

DI should ensure:

- the acceptable temperature ranges for the stored material is acquired from the suppliers and that temperature monitoring procedures reflect these ranges
- all staff are trained in the use of the temperature monitoring system and are aware of how to report and act upon temperature rises past the acceptable level
- a system is implemented for temperature monitoring and recording in areas where consumables with a specified temperature storage range are being stored e.g. dimethyl sulfoxide (DMSO)
- the maximum storage period for tissues / cells is documented

Premises, facilities and equipment standards (PFE1–PFE5) continued

PFE4: Systems are in place to protect the quality and integrity of tissues and / or cells during transport and delivery to its destination

86. Establishments must ensure that when tissues and cells are distributed they are appropriately labelled to ensure traceability. Furthermore, they must be packaged and transported in a manner that maintains their integrity, and minimises the risk of contamination (box 12). On the whole, compliance was good. However, we offered 36 items of advice and guidance during 2008/09, compared with 31 last year; indicating that some establishments still required support in order to fully comply.
87. We placed only one condition against this standard.

Condition – The DI shall ensure that whenever material is distributed by the establishment, packaging requirements conform with the requirements laid out in HTA Directions 001/2006 and 002/2007. The packaging requirements should be set out in the form of an SOP to ensure implementation.

Reason for the condition – The establishment distributes material from the licensed premises but does not currently fully adhere to the requirements set out in the Directions 001/2006 and in particular paragraphs 54 and 55 of the Directions 002/2007.

88. Establishments are reminded that they are required to put in place third party agreements with courier companies as couriers provide a service that may affect the quality or safety of the tissues and cells.

Box 12: Key actions for complying with PFE4

The DI should ensure:

- the packaging used for the transport of cells between the laboratory and the clinic is validated to ensure that cells are maintained within the specified temperature range
- the primary packaging containing tissues and / or cells is labelled with all the information required by HTA Directions
- there are third party agreements in place with couriers
- records of transportation and delivery are kept

Premises, facilities and equipment standards (PFE1–PFE5) continued

PFE5: Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored

89. As with last year, we found that establishments generally complied with this standard. We placed only one condition on a licence. However, we offered 46 items of advice and guidance which mainly related to the cleaning and validation of critical equipment and contingency plans for equipment failure. Advice and guidance as opposed to a condition may be appropriate where, for example, the temperature of fridges are monitored but they are not incorporated into a system of preventive maintenance. In this case, risk to the quality and safety of the tissues and cells exists, but it is minimal. In Box 13 there are some actions for aiding compliance with the standard.

Box 13: Key actions for complying with PFE5

The DI should ensure:

- critical equipment and technical devices are validated and maintained, and that records are kept of validation and maintenance
- new or repaired equipment is validated before use and the validation is documented
- there is a documented contingency plan in the event of critical equipment failure
- there are documented agreements with maintenance companies
- cleaning of critical equipment is recorded

Disposal standards (D1–D2)

90. The disposal standards are drawn from the HTA's code of practice on disposal and the traceability requirements of HTA Directions 001/2006 and 002/2007.
91. Disposal standards are divided into two main categories of standards D1 and D2.

Key findings

92. Overall, establishments demonstrated a high level of compliance with the disposal standards. We imposed only one condition and offered 22 items of advice and guidance. Last year we imposed two conditions and gave ten items of advice and guidance.

D1: There is a clear and sensitive policy for disposing of tissues and / or cells

93. We identified only one non-compliance leading to a condition for this standard. A further nine items of advice and guidance were provided aimed mainly at ensuring the policies for disposal were up-to-date and in line with the HTA codes of practice.

D2: The reasons for disposal and the methods used are carefully documented

94. No conditions were imposed for this standard, indicating that establishments are aware of the need for recording the disposal of tissue. Thirteen items of advice and guidance were offered to DIs. Most of the advice was aimed at ensuring that disposal logs contained all relevant details including the date, reason and method of disposal.

Procurement organisations

Background

95. The Directives set out to establish a harmonised approach to the regulation of tissues and cells for HA (patient treatment) across Europe. The Directives require that systems are put in place to ensure that all tissue and cells used in HA are traceable from donor to recipient.
96. The full transposition of the Directives into UK law via the Q&S Regulations in July 2007 extended the HTA's remit to include organisations that procure, test, process, distribute or import / export tissues and cells for HA.
97. The activity of procurement is defined (see Annex C HTA Directions 001/2006) as '...the process by which tissues and cells are made available'; this process includes the physical act of removing tissue and cells and also the process of donor selection and evaluation.
98. The Q&S Regulations have raised complex issues, particularly in relation to the activity of procurement. This led to the HTA's moratorium on enforcing the full requirements of the Q&S Regulations with respect to procurement, until clarity about the issues had been reached. Only following dialogue with the EC, the Department of Health and other Member States, were we in a position to take forward and enforce the full licensing requirements for procurement.
99. To support the process of licensing procurement organisations the HTA held two workshops. The first was in December 2007 and brought together key stakeholders from the umbilical cord blood sector. The second, in January 2008, brought together representatives of various commercial and non-commercial establishments involved in licensable activities, as well as representatives from relevant professional bodies. Summaries of the workshops can be found on our website, along with 'frequently asked questions' (FAQs), relating to the licensing of procurement generally and FAQs targeted specifically at cord blood collection: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/cordbloodprocurementfaqs.cfm.

Procurement organisations (continued)

100. All procurement organisations were required to apply for a licence by 5 July 2008. We received a total of 36 applications and all establishments were subjected to a phase 1 desk-based inspection during the third quarter of the 2008/09 business year.

101. Since bringing procurement organisations into the licensing framework, we have become aware that some individuals procuring cord blood for private use are still not clear about the regulatory requirements that apply to them.

Key findings from phase 1 desk-based inspections of procurement organisations

102. We applied a total of 18 conditions during the phase 1 desk-based inspections over the four categories of standards (see table 6).

Table 6: The average number of additional conditions placed on procurement organisations' licences following phase 1 desk-based inspections

HTA standards	No. of conditions
C	2
GQS	14
PFE	0
D	2

Categories: C = consent; GQS = governance and quality systems; PFE = premises, facilities and equipment; D = disposal

103. Phase 1 desk-based inspections indicated that, overall, compliance was good. The majority of the conditions imposed were against the governance and quality systems standards, particularly management of records and risk assessments of practices and processes.

104. Advice and guidance is not documented at the phase 1 desk-based inspection stage. However, in addition to the workshops, we provided significant one-to-one advice and guidance to support DIs throughout the application process and initial licensing phase.

Information on umbilical cord blood collection (procurement)

105. In July 2008, we started licensing establishments that were involved in the procurement of cord blood. Although currently one of the smallest sub-sectors within the HA sector, it has generated a relatively high level of regulatory activity.
106. A number of cord blood banks are directly responsible for providing information to potential donors, ensuring that appropriate consent is taken, distributing the cord blood collection kits and ensuring that the appropriate screening tests are carried out. These activities fall under the umbrella of procurement.
107. Procurement is defined as ‘...a process by which tissues or cells are made available’. It is clear that the activities undertaken by cord blood companies fall within a process of making tissues and cells available.
108. The collection of the cord blood usually takes place in a hospital setting. The collection must take place either on licensed premises or on relevant third party premises (see box 14).
109. Many maternity units are not licensed to carry out the procurement of cord blood; however procurement can still take place on unlicensed premises as long as there is an appropriate third party agreement in place between the licensed establishment and the third party procuring on the establishment’s behalf.

Box 14: Important information

The HTA is aware of isolated occasions of cord blood being collected on unlicensed premises and in the absence of a third party agreement. This is an illegal activity which has resulted in us issuing formal warnings to the people and establishments concerned. If further illegal activity occurs, the HTA will take significant regulatory action.

110. The intention underpinning the Directives is to ensure “a high level of health protection in the Community” in relation to “each one of the steps in the human tissues and cells application process”. While collection of cord blood continues to take places outside the authority of a licence or third party agreement, that assurance cannot be provided.

Information on umbilical cord blood collection (procurement) (continued)

111. A third party that procures under a third party agreement on behalf of a licensed establishment must be assessed by the DI as being suitable to do so on the basis of their qualifications, training and experience (see box 15). This assessment will ensure:

- the third party is qualified to assess the suitability of the environment in which the cord blood is collected
- steps are taken to minimise that risk of contamination
- they are appropriately trained in cord blood collection
- they are bound by the agreement to notify the DI about any adverse event during the collection that could affect the safety or quality of the cord blood.

Box 15: Key actions for DIs of cord blood banks

The DI should ensure:

- they have robust and appropriate third party agreements in place with individuals or organisations that collect cord blood on behalf of the licensed establishment
- the third party agreement is issued and signed before the collection takes place
- they have systems in place for auditing the third party arrangements to ensure that they are being complied with
- they have documented procedures in place for ensuring that third parties are suitably qualified
- third parties are aware of the requirement to report adverse events or reactions to them
- they have third party agreements in place with couriers
- the donor selection and consent requirements are adhered to
- any sample which is received following an unlawful collection (i.e. on unlicensed premises and not under a third party agreement) is reported to the HTA as a serious adverse event and investigated by the DI
- robust systems are in place to identify the validity of the procurer upon receipt of the cord blood and before its acceptance for processing and storage
- the third party agreement references the procedure by which the procurement should take place

Information on umbilical cord blood collection (procurement) (continued)

112. We have received a large number of enquiries from midwives and members of the public concerning the collection of cord blood and when it can legally take place. In view of this clear need for information, we have developed some advice addressing some of the most frequently asked questions. These can be found on the HTA's website:

Cord blood procurement for professionals:

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/cordbloodprocurementfaqs.cfm

Cord blood collection for parents:

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/cordbloodprocurementfaqsforparents.cfm.

Information on serious adverse events and reactions (SAEARs)

113. Under the Directives, the HTA is required to set up a system for tissue establishments to report serious adverse events (SAEs) and reactions (SARs). The system has been in place since 1 April 2007. In last year's summary of inspections, we reported that during the 2007/08 business year, we received a total of 27 initial reports; although only 18 of them were serious adverse events or reactions as defined by the Directives.
114. During the 2008/09 business year we received a further 57 initial reports; 39 SAEs and 18 SARs, of which 42 were considered to be reportable (table 7).

Table 7: The initial number of suspected SAEARs reported during 2008/09 with the actual number following HTA evaluation

Type of event	Initial number of reported SAEARs	Actual number of reported SAEARs after HTA categorisation
SAEs	39	34
SARs	18	8

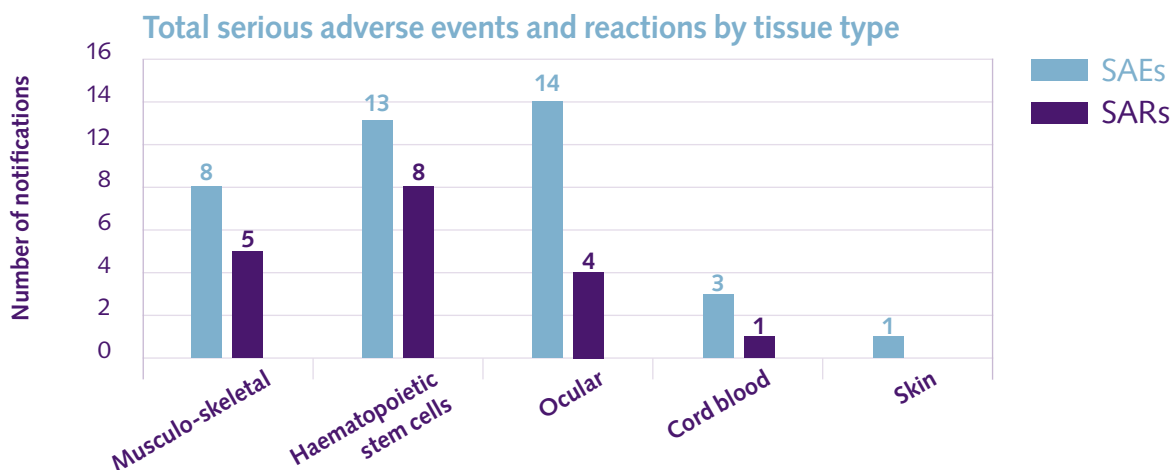
115. Once in receipt of notification of a SAE or SAR, we follow an internal process for reviewing the reports. Where we identify that the establishment needs advice, or where the establishment proactively seeks advice, we work with the DI to ensure that they take appropriate corrective and preventive action. We have advised DIs to, for example, review and update all associated procedures and then undertake a risk assessment of the likelihood of a similar event occurring again.

Information on serious adverse events and reactions (SAEARs) (continued)

116. Where it is not clear whether an event or a reaction should be reported to the HTA, we would encourage reporting as we will then decide whether or not it falls within the definition of a SAE or SAR. This will ensure that all actual SAEs and SARs are reported. Establishments may find it useful to assess whether or not an event or reaction is reportable, by using the 'vigilance and surveillance' tools that are being developed in a project led by the EC. Further information on the project and the tools can be found on the European Standards and Training in the Inspection of Tissue Establishments website: www.eustite.org.
117. Where an SAE or SAR has affected one or more HTA-licensed establishments, we have issued a regulatory alert. We have also monitored SAE and SAR reports for trends.
118. Any suspected SAE or SAR must be submitted to the HTA without delay. In practice, we have found that establishments have taken, on average, 41 days following the occurrence of a SAE before submitting a notification report. They have then taken a further 73 days, on average, to submit the follow-up report which details what internal investigations were undertaken and what measures were put in place in order to minimise the risk of a similar event occurring again.
119. Although there has been a delay in reporting in the majority of cases, we have been encouraged that establishments have initiated internal investigations immediately following the SAE or SAR. Further, they have then implemented control and preventive actions (CAPAs) to minimise the risk of similar occurrences. Nevertheless, in response to our findings that there is a delay in reporting to the HTA, we will be issuing guidance to establishments to ensure that, in the future, notification reports are submitted in a timely manner.

Information on serious adverse events and reactions (SAEARs) (continued)

Figure 2: Number of serious adverse events and reactions reported to the HTA during 2008/09, by tissue type



120. The largest number of reports were for SAEs related to ocular tissue (figure 2) The smallest number of reports were for SAEs and SARs associated with cord blood and skin. A more detailed analysis is provided below.

Serious Adverse Events (SAEs)

121. We received a total of 39 SAEs during the period 1 April 2008 to 31 March 2009. The largest number of events (14 or 36%), were reported from establishments working with ocular tissue. The relatively high number of reports from the ocular tissue banking community appears to reflect the level of vigilance within the community, as well as the volume of activity. The second largest number of events (13 or 33%), were reported by establishments working with haematopoietic stem cells (HSCs). This is also likely to be due to the increased vigilance, as the events were isolated.

122. In April 2008 we issued a regulatory alert in response to a number of reports we received relating to defective seals on the outer packaging of pots used for the storage of fresh frozen femoral heads. Sterility tests carried out by the manufacturer indicated that the outer surface of the inner packaging was not sterile in some of the affected units. The defects had implications for the sterility of the material and were traced to a manufacturing fault in several batches of pots. A recall was initiated and all users were instructed to discard material stored in affected pots. A number of SAEs relating to femoral heads were reported following the alert which may account for the relatively high number of reports relating to musculo-skeletal tissue.

Information on serious adverse events and reactions (SAEARs) (continued)

Boxes 16, 17 and 18 contain case studies of real serious adverse events:

Box 16: Case study 1

Corneal tissue had been issued for transplant but was returned to the eye bank by the end user

A consultant ophthalmologist received a cornea in a transport bottle that had been checked and released for issue by eye bank staff. At the time of release, the microbiology test was negative and there were no signs of contamination.

On receipt of the corneal tissue, the consultant ophthalmologist noticed that the metal cap of the transport bottle was at an angle and that the medium in the bottle looked paler than usual. He was concerned that the change in colour of the medium may indicate bacterial contamination of the tissue, which would present a risk to the patient if the cornea was transplanted.

The consultant ophthalmologist contacted the DI of the eye bank who advised that the tissue medium received from the supplier had recently changed appearance and the new medium was paler than that previously supplied.

The cornea was returned to the eye bank where the tissue and medium were tested for bacterial contamination, both of which were negative.

Corrective and preventive actions

Relevant staff were retrained in the procedure for sealing transport bottles.

The HTA suggested that an information leaflet should be included with all corneas that were supplied in the new, paler tissue media. This would alert end users to the change in appearance of the tissue medium and prevent further concerns with the quality of the tissue media.

Wider learning for the sector

Any obvious changes to packaging, media or processing of tissues and cells should be accompanied by an information leaflet that provides sufficient information to the end user detailing any changes to accepted procedure. This will allow end users to be fully informed of changes and prevent any unnecessary concerns.

Information on serious adverse events and reactions (SAEARs) (continued)

Box 17: Case study 2

Cartilage biopsy placed in media that was out-of-date

Cartilage tissue was procured for an autologous chondrocyte implantation procedure. This involved sending the tissue to a European tissue establishment for processing before its return to the UK for end use in the donating patient. In this instance, the European tissue establishment supplied all reagents required in the procedure and was responsible for the transportation of the tissue to and from the processing laboratories.

The biopsy was placed in out-of-date tissue media and had to be disposed of, resulting in the loss of autologous tissue.

Root cause analysis

The procurement organisation carried out a root cause analysis and identified the following as factors contributing to the serious adverse event:

- the European tissue establishment responsible for processing did not have robust procedures to ensure that commercial kits sent to healthcare providers were checked and tracked for expiry dates
- staff at the UK procurement organisation incorrectly assumed that media was checked by representatives of the tissue establishment responsible for processing
- the UK procurement organisation failed to identify that the stock delivered to it was out-of-date and this resulted in it being placed in the operating theatre

Corrective and preventive actions

- the European tissue establishment has implemented a new system whereby all biopsy transport media will be supplied from one manufacturing facility and tracked electronically for destination and expiry date
- the UK procurement organisation has implemented secondary checks of the expiry dates of media. Designated theatre staff now check media at point of delivery and secondary checks are carried out one week before a scheduled procedure
- stock checks are now carried out at the procurement organisation and any expired media removed
- the European tissue establishment has now re-trained all relevant staff in the new procedures and training records are kept

Information on serious adverse events and reactions (SAEARs) (continued)

Box 17: Case study 2 (continued)

Wider learning for the sector

This is an example of where more than one establishment is responsible for tissues during the course of a procedure.

In this case, an adverse event highlighted that both establishments were not fully clear on what was their responsibility and when. This situation may arise when an establishment is carrying out activities on behalf of another establishment under a third party agreement, or when a licensed establishment is carrying out activities for another establishment under a service level agreement. In both cases, relevant agreements should clearly specify which establishment is responsible for what activity in order to avoid potential adverse events.

Box 18: Case study 3

Unlawful procurement of umbilical cord blood

A woman's umbilical cord blood was procured in the car park of hospital premises which were neither licensed by the HTA nor operating under a third party agreement with a licensed establishment.

The cord blood bank (the HTA-licensed establishment) was made aware of the nature of the procurement after it had accepted the sample and sent it for bacterial sterility testing. The sample had been contaminated and was subsequently disposed of.

What led to the serious adverse event?

The midwife at the unlicensed premises correctly advised the father that procurement could not take place on hospital premises as this would constitute unlawful activity as the hospital did not have a licence or a third party agreement with a licensed establishment. A friend of the couple went ahead with the procedure in the car park despite this advice.

The cord blood bank accepted the cord blood for storage without checking that it had been procured lawfully.

Information on serious adverse events and reactions (SAEARs) (continued)

Box 18: Case study 3 (continued)

Wider learning for the sector

It is the responsibility of establishments storing umbilical cord blood to ensure that all procurement is carried out on HTA-licensed premises, or under a third party agreement.

Procurement must only ever be carried out by trained professionals. It is the responsibility of the DI to ensure they are trained and that where applicable, they assess the suitability of (RTTPs).

Serious adverse reactions (SARs)

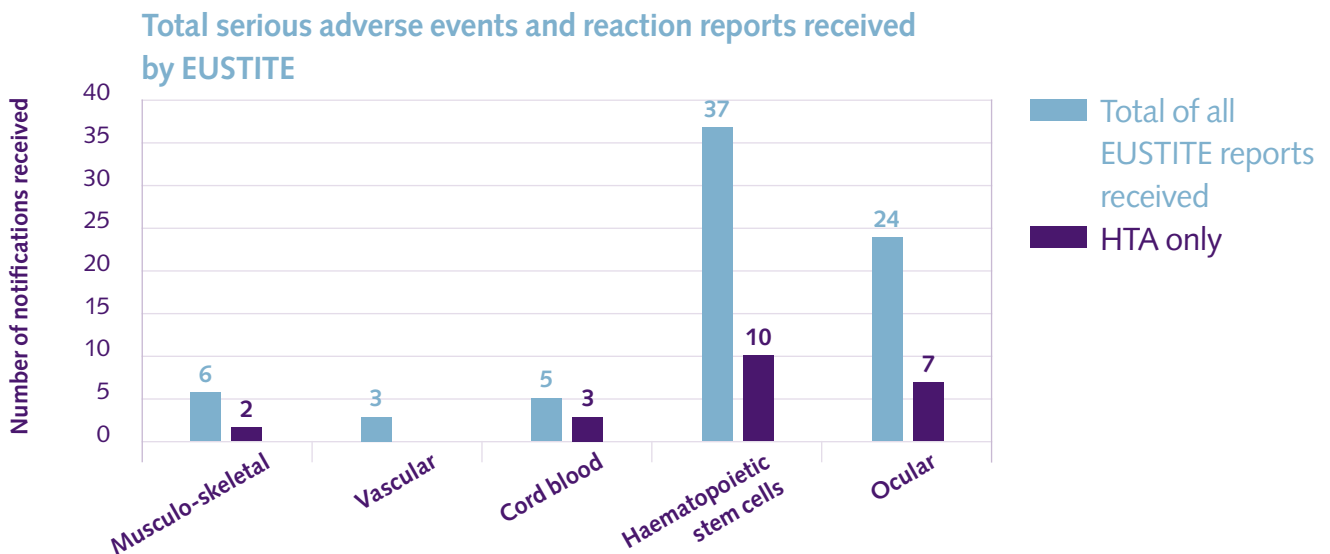
123. We received a total of 18 SARs during the period 1 April 2008 to 31 March 2009. Although the highest number of SAEs related to ocular tissue, there have been a relatively small number of SARs associated with this tissue type. This comparatively low figure could again be due to the high level of vigilance within the ocular community for reporting and managing SAEs; effective management of an event generally prevents the occurrence of a reaction.
124. As well as there being a relatively high number of SAEs linked to HSCs, the highest number of reactions (eight or 44%) related to this tissue type. This is likely to be due to patients receiving treatment using HSCs having weakened immune systems and they are therefore at greater risk of contracting infections that lead to SARs.
125. It is noteworthy that for many of the reactions reported, no clear link with the quality and safety of the tissue could be established. It was often the case that, instead, reactions were associated with a procedure common to the treatment administered.

Information on serious adverse events and reactions (SAEARs) (continued)

Serious adverse events and reactions in the European Union

126. The HTA has a statutory duty to report annually to the EC on notifications of SAEs and SARs received; we submitted the first report in July 2008. We are currently working with the EC to monitor trends in reporting to facilitate the implementation of Europe-wide control measures.
127. We are also working with EUSTITE and other Competent Authorities on the development of tools to harmonise the grading of SAEs and SARs within Europe. Therefore, as well as submitting an annual report to the EC, we have also submitted quarterly reports relating to SAEs and SARs to EUSTITE.

Figure 3: Number of serious adverse events and reactions reported to EUSTITE during the 2008/09 business year, by tissue type



128. We submitted a large number of SAEs and SARs to EUSTITE compared with our European counterparts (figure 3). This is due to the comparatively large number of establishments we regulate and perhaps because our reporting system is more established than others. However, the overall distribution of SAEs and SARs per type of tissue is very similar throughout the EU.

Information on the role of the Designated Individual (DI)

129. This part of the report is intended to provide an overview of the role of the DI, which is central to the licensing framework. It is a pre-requisite to granting a licence that the HTA is satisfied that the proposed DI is suitable to supervise the activity or activities authorised by the licence.
130. The Q&S Regulations set out the following criteria for assessing whether or not a DI is suitable. A DI must:
- a) have a diploma, certificate or other evidence of formal qualification in the fields of medical or biological sciences awarded on completion of a university course of study, or other course of study recognised in the United Kingdom as equivalent or
 - b) be otherwise considered by the HTA to be suitably qualified on the basis of academic qualifications and practical experience and
 - c) have at least two years' practical experience which is directly relevant to the activity to be authorised by the licence
131. Note that (b) and (c) are essential and not optional requirements.
132. In more than 90% of cases, DIs (other than those working with acellular material) have been assessed as suitable on the basis that they have a medical or scientific qualification and have two years practical and relevant experience. A different picture emerges for DIs working with acellular material; 70% of them considered themselves suitable as they have academic qualifications and practical experience and two years of relevant practical experience. The remaining 30% applied on the basis of their scientific qualifications and practical experience. The difference in the background and experience of DIs working with acellular material is largely due to storage (as opposed to procurement or processing) being the primary licensable activity they oversee. The material they store is usually imported from another country, or from an HTA-licensed establishment.

Information on the role of the Designated Individual (DI) (continued)

133. During the process of transposing the Directives into UK law, the HTA worked closely with the Department of Health in drafting the Q&S Regulations to ensure that, where possible, proportionality could be built into the legal requirements. In particular we were keen to ensure that we could exercise a measure of discretion in assessing the suitability of a DI. A clause was inserted into the Q&S Regulations that allows us to consider a DI to be suitably qualified on the basis of academic qualifications other than medical or biological.
134. The HTA recognised that a DI without medical or biological qualifications would need to be supported in their role. For that reason, HTA Directions 002/2007 contain the following paragraph:
- Where the DI does not have a medical or biological qualification, then the DI must have access to a nominated registered medical practitioner and / or a scientific adviser, as the HTA considers appropriate, to assist the DI and provide advice and guidance in relation to clinical and scientific activities.
135. DIs who do not possess medical or biological qualifications must have an appropriate scientific or medical advisor. As we have seen for DIs of establishments working with acellular material, this is of particular significance.
136. We have been asked for advice about suitable alternative qualifications in the absence of a medical or biological qualification. Generally, the HTA would require an alternative qualification that has direct relevance to the activity being undertaken. For example, a number of the DIs whose activities relate to acellular material have qualifications in quality management and / or business management, as well as a minimum of two years' practical experience that is directly relevant to the licensable activity.
137. In the case of DIs overseeing procurement, the HTA would expect to see other qualifications appropriate to the nature of the procurement taking place e.g. a senior nursing or midwifery qualification could in certain contexts be suitable. It is essential that procurement activities are robustly supervised as the steps involved in procurement i.e. donor selection, consent and collection of the tissues or cells are critical to ensuring that tissues and cells procured meet the required standards of quality and safety.

Information on the role of the Designated Individual (DI) (continued)

138. We recognise that education and support by the HTA is necessary for DIs to be successful in ensuring compliance with the regulations. A standard condition on all licences is that DIs complete training within a year of taking on the role. We have invested significant resources in providing such training and support and since April 2006, we have run a total of nine DI training events and one HA conference. In addition an online DI e-learning programme was launched in 2007.
139. We are aware that a number of DIs have not yet completed training. We will be monitoring all DIs to ensure that they do so within a year of being deemed suitable and we will take regulatory action where we find this not to be the case.
140. During our inspections we have noted that DIs frequently comment that they do not have protected or sufficient time to carry out their DI duties. It is essential that DIs have 'ring-fenced' time for carrying out their statutory duties as this will improve their ability to ensure that suitable practices are taking place under the licence. We have offered advice and guidance on this on a number of occasions following a phase 2 site-visit inspection. An example of the type of advice and guidance provided to establishments regarding this is given below:
- DIs are advised to ensure they have protected time to carry out their duties statutory duties. Their role as DI should be incorporated into their job descriptions so that it is acknowledged as a significant work objective.
141. Since we started to license the human application sector, 21 establishments have changed their DI. On a few occasions the HTA has been notified of the change to a DI after the event. We have also become aware, on rare occasions, of DIs either leaving or being absent from the licensed establishment for an extended period. It is essential that we are notified at least one month in advance of a proposed change of DI so that we can make an assessment of the suitability of the replacement DI as it is unlawful to continue licensable activities without a DI. Further information on the role of the DI can be found on our website: www.hta.gov.uk/licensingandinspections/peopleatlicensedestablishments/disandlicenceholdersundertheq&sregulations.cfm. A change of DI proforma is available on our website: www.hta.gov.uk/licensingandinspections/peopleatlicensedestablishments/howtomakechangestoyourlicence.cfm.

Information on establishments working with acellular material

142. Following transposition of the Directives into UK law via the Q&S Regulations, the HTA focused on directing its resources to ensuring that those activities that posed the greatest risk in terms of the quality and safety of tissues and cells used in HA were brought within the regulatory framework.
143. This risk-based approach included the consideration that the use of acellular material (such as demineralised bone) in HA, posed a significantly lower risk in terms of quality and safety than the use of cellular material.
144. In October 2008, the EC issued a rapid alert to Competent Authorities advising them to implement a recall notice regarding certain acellular products. This was due to a concern that the products in question may have originated from donors who had not been selected according to the full donor selection criteria requirements of Directive 2006/17/EC.
145. At the time of the rapid alert being issued the HTA was not licensing activities involving acellular material. Despite this, we were able to work positively with the organisations concerned to ensure that there was no risk to patient safety.
146. The event led to the HTA reconsidering its position on regulating acellular products. In February 2009, we published a revised position statement on our website stating our intention to license importers and distributors of acellular material: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/positionstatementonregulatinghumanembryonicstemcelllinesforhumanapplication.cfm. At the same time, the HTA communicated with all organisations identified as carrying out relevant activities in the UK, requesting that they apply for a licence by 6 April 2009. We have received 11 licence applications from organisations that import and distribute acellular material within the UK.
147. Some DIs questioned whether acellular material fell within the definition of tissues and cells. Under the Q&S Regulations, the term 'tissue' is defined as 'all constituent parts of the human body formed by cells'. Following dialogue with the EC, other Member States and our own internal legal advisers, the HTA is clear that products rendered acellular fall within the scope of the definition.

Information on establishments working with acellular material (continued)

148. To support new DIs working with acellular material with their licence application, the HTA invited them to participate in a training event held in March 2009. We envisaged that participation in the event would help to strengthen and foster stakeholder engagement, and provide practical information on the licensing and inspection process.
149. In addition to this training, we have invested significant time in speaking with DIs on an individual basis, providing advice and guidance to facilitate and expedite the licensing process.
150. A number of DIs have expressed uncertainty regarding the arrangements that should be in place with the end users of the products that they distribute to. Establishments that distribute must ensure that they have the following arrangements in place with end users:
- documented agreements with end users to ensure they record and store the data required by Directions 002/2007
 - that they provide information to end users on how to report a serious adverse event or reaction and have agreements with them specifying that they will report these events or reactions
151. The majority of acellular distributors import material from the US. These establishments should refer to HTA Directions 004/2007, as they specifically address the requirements for establishments involved in the import/export of material from non European Economic Area (EEA) countries. Further information on import / export and distribution can be found in HTA Directions 002/2007, in particular paragraph 108.
152. As a general principle, tissues or cells that are imported from outside of Europe are expected to meet equivalent standards of safety and quality as those laid down by the Directives.

Information on establishments working with acellular material (continued)

153. Box 19 lists some key actions that DIs of establishments working with acellular material are advised to consider. They are not intended to be a definitive list of requirements and DIs are encouraged to ensure that they are fully aware of all the regulatory requirements relevant to the activities they undertake.

Box 19: Key actions for DIs of establishments working with acellular material

DIs should ensure:

- they have an agreement in place with the organisation undertaking procurement and consent to ensure that the consent is obtained in accordance with the requirements of HTA Directions 004/2007
- they have an agreement with the procurement and processing organisations ensuring that there are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the standards laid down by the Directives on medical devices and *in vitro* diagnostic medical devices
- they have put in place a system to ensure that imports from non EEA states meet the standards of quality and safety set out in Directions 001/2006, 002/2007 and 004/2007
- donor documentation specified by Directions 001/2006 is collected and maintained records are retained (30 years for traceability data and ten years for raw data)
- donors are selected and tested in accordance with the requirements of Directions 001/2006 and that the donor selection information and testing results are recorded. The donor selection is to be carried out by authorised personnel and reviewed by a qualified health professional
- they have an agreement in place with establishments undertaking processing, ensuring that processing is carried out in an appropriate, monitored environment as required by Directions 002/2007, and that the tissues and / or cells are not distributed unless they meet the standards laid down by Directions 001/2006 and 002/2007
- they have an agreement in place with the organisation procuring and processing tissues and / or cells ensuring that the organisation identifies, validates, regularly inspects and maintain records for their critical equipment and technical devices
- they have documented agreements with end users
- they have in place third party agreements in place with transport companies

Information on establishments working with acellular material (continued)

154. It is also important to ensure that the specific labelling, packaging and transport requirements are adhered to. Further detail on the expected standards can be found in HTA Directions 002/2007, and in particular paragraphs 53–55 of those Directions.
155. DIs might also find it useful to refer to our FAQs on third party agreements: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/thirdpartyagreementfaqs.cfm. They may also like to refer to our FAQs on import/export and distribution: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/distributionandimportexportfaqs.cfm.
156. The HTA is aware that it will take some time for DIs in this sector to become fully conversant with all the regulatory requirements. We would encourage DIs to approach the HTA for advice and guidance if they are uncertain about any issues relating to their licence.

Information on Advanced Therapy Medicinal Product regulation (including stem cell therapies)

157. Since 30 December 2008, a new regulatory framework applies to Advanced Therapy Medicinal Products (ATMPs). Where ATMPs make use of human tissues or cells as part of their starting material, the HTA regulates the donation, procurement and testing of the tissues and cells. The Medicines and Healthcare products Regulatory Agency (MHRA), as the Competent Authority for medicinal products and medical devices, discharges the UK's national responsibilities for ATMPs (e.g. for manufacturing, distribution, clinical trials and pharmacovigilance), and therefore regulates all subsequent activities where tissues and cells are manufactured into ATMPs.
158. In March 2008, the HTA and MHRA issued a joint policy statement on the relationship between the Advanced Therapy Medicinal Products (ATMP) Regulation and the Q&S Regulations: www.hta.gov.uk/_db/_documents/Joint_Policy_Statement_on_Advanced_Therapy_Medicina_Products_v0_7.pdf.
159. ATMPs are defined in the ATMP Regulation 2007 as '...innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells'. An ATMP is further defined as one of the following:
- a) a gene therapy 'medicinal product': this category includes genetically modified cells, provided the therapeutic effect is directly conferred by the genetic manipulation
 - b) a somatic cell therapy 'medicinal product': such a product may contain autologous or allogeneic human cells which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means
 - c) a tissue engineered product: contains or consists of cells or tissues that have either been subject to 'substantial manipulation' or that are not intended to be used for the same essential function(s) in the recipient as in the donor
 - d) a combined ATMP, which contains a medical device in combination with tissues or cells

Information on Advanced Therapy Medicinal Product Regulation (including stem cell therapies)

(continued)

160. There is some debate as to what constitutes 'substantial manipulation'. The ATMP Regulation 2007 provides detail of what is not substantial manipulation but not of what is. In light of this there is frequently uncertainty as to whether or not a given product will be deemed to have been substantially manipulated and therefore an ATMP. HTA inspectors have been given training to help them identify a potential ATMP; however, establishments should seek classification from the MHRA if they are in any doubt.
161. Stem-cell (gamete-derived) based products that involve the disaggregation of a human embryo in their formulation are initially licensed by the HFEA. At the point where the embryo no longer exists and cells are harvested, these human cells would fall under the remit of the HTA. The development of a product using these cells is under the remit of the HTA until such time as the MHRA classifies the product as an Investigational Medicinal Product (IMP) or the product is classified as an ATMP. Once this classification has been confirmed, the manufacture, clinical trial approval and marketing approval (for IMPs) are under the remit of the MHRA and not the HTA.
162. We have asked the Committee for Advanced Therapies (CAT) for a decision on whether the starting material for Human Embryonic Stem Cells (HESCs) derived products should be considered to be the gametes or the cell line. Until we receive a definitive answer the above regulatory framework remains applicable.
163. We have participated in the development of the first version of an interim UK regulatory route map for stem cell research and manufacture. It is anticipated that this route map will be a useful reference tool for all researchers working in translational stem cell research to understand the regulatory requirements associated with such research. The route map can be accessed on the Department of Health website: www.dh.gov.uk/ab/GTAC/index.htm.

Information on Advanced Therapy Medicinal Product Regulation (including stem cell therapies)

(continued)

164. We have identified approximately 12 of our licensed establishments which have products that can be defined as ATMPs. Over the next 12 months the HTA will be trialling joint inspections of two of these establishments with the MHRA. We are aware of concern within this sector that, because establishments are subject to at least two regulators, there may be difficulties in making the transition from one set of regulatory requirements to another. We have been working closely with the MHRA to ensure this does not happen. It is anticipated that by trialling joint inspections the HTA and MHRA will be in a position to agree a joined-up approach to inspecting such establishments. This in turn should result in the provision of consistent advice, and certainty of regulatory requirements – supporting a smooth transition from one regulator to another.
165. This is a complex area of regulation and the HTA is keen to work with its stakeholders to identify and work through some of the complexities as they arise.
166. There is further information on our website, including ATMP FAQs: www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/advancedtherapymedicinalproductsfaqs.cfm.

Information on annual activity data collected in 2008/09

167. Licensed establishments must submit annual data to the HTA (see paragraph 58 of Directions 001/2006). The reporting period for this data is January to December as prescribed by the EC.
168. To support this process, establishments are expected to maintain a record of the types and quantities of tissues and / or cells imported and / or exported and on the origin and destination of such imported and / or exported tissues and / or cells intended for HA.
169. It is also a requirement that establishments carrying out licensable activities on behalf of a licensed establishment under a third party agreement, maintain a similar record (see paragraph 90 of Directions 002/2007).
170. We carried out our first round of annual activity data collection in 2007, for the period July to December 2007. The second round of data collection was for January to December 2008 and establishments were requested to submit the data during January and February 2009.
171. To assist us with ensuring continual improvement in how we collect this data, we asked establishments to provide feedback on how they had found using the HTA template. Overall the feedback was that the template was easy to use and a huge improvement on the previous year's approach. There remain areas that need to be improved upon, e.g. greater clarity about what constitutes one donation. We were also asked whether we could tie in the reporting cycle with other data reports (e.g. European group for Blood and Marrow Transplantation reports in April). Unfortunately, the reporting date is specified in European legislation so can not be changed unless the EC makes an amendment to the reporting dates.

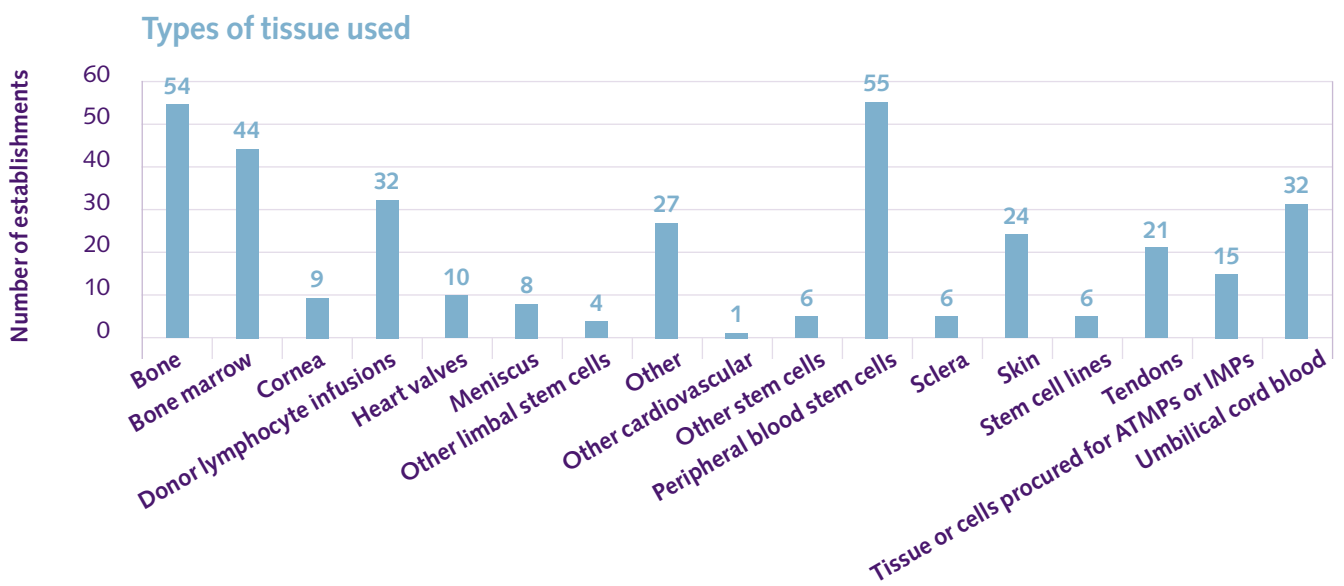
Information on annual activity data collected in 2008/09 (continued)

172. It is also a requirement that the HTA makes the data collected publicly available. We will fulfil this requirement by making the data available via the Eurocet website in an anonymised format: www.eurocet.org. In addition to this, we will occasionally make some of the high level data available at relevant events (e.g. DI training events), and in certain publications such as this report.

173. For the 2008/09 reporting period we collected data from 163 establishments. Some of the data received are displayed graphically in the figures below.

174. The figure below shows the number of UK establishments working with particular types of tissue and / or cells during the last reporting period (figure 4). Some establishments work with more than one tissue / cell type.

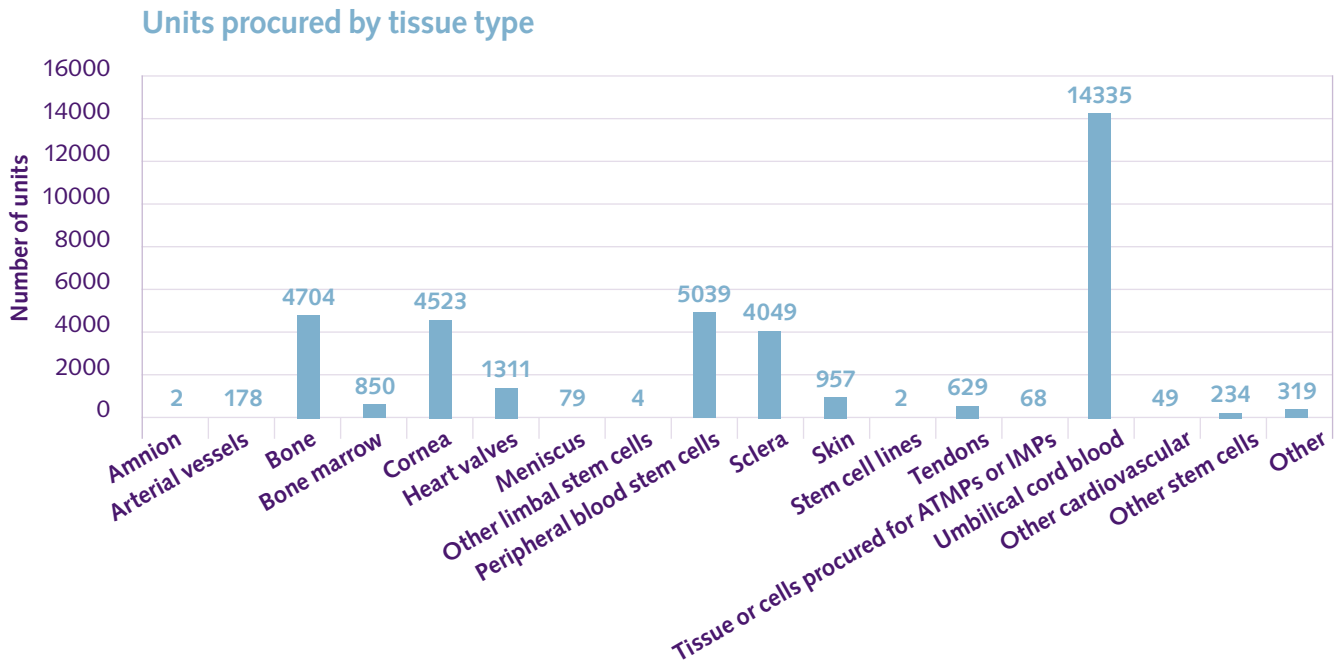
Figure 4. The number of establishments working with particular types of tissue and / or cells during 2008/09



Information on annual activity data collected in 2008/09 (continued)

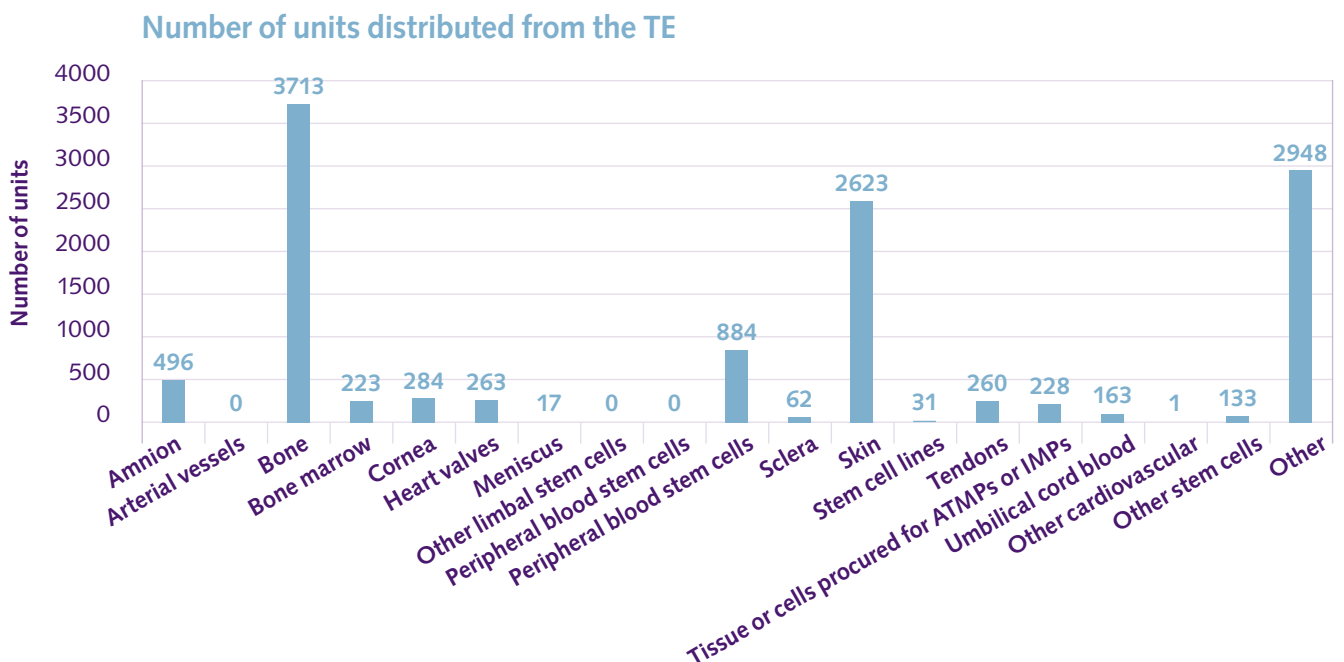
175. Figure 5 shows the numbers of tissues and cells procured during the reporting period per type of tissue.

Figure 5. The number of units of tissues and cells procured during 2008/09



176. Figures 6, 7 and 8 show the numbers of tissues and cells distributed (moved within the EEA), numbers accepted into tissue establishments (TEs) and numbers imported or exported during the last reporting period by tissue type.

Figure 6. The number of units of tissues and cells distributed from the TEs during 2008/09

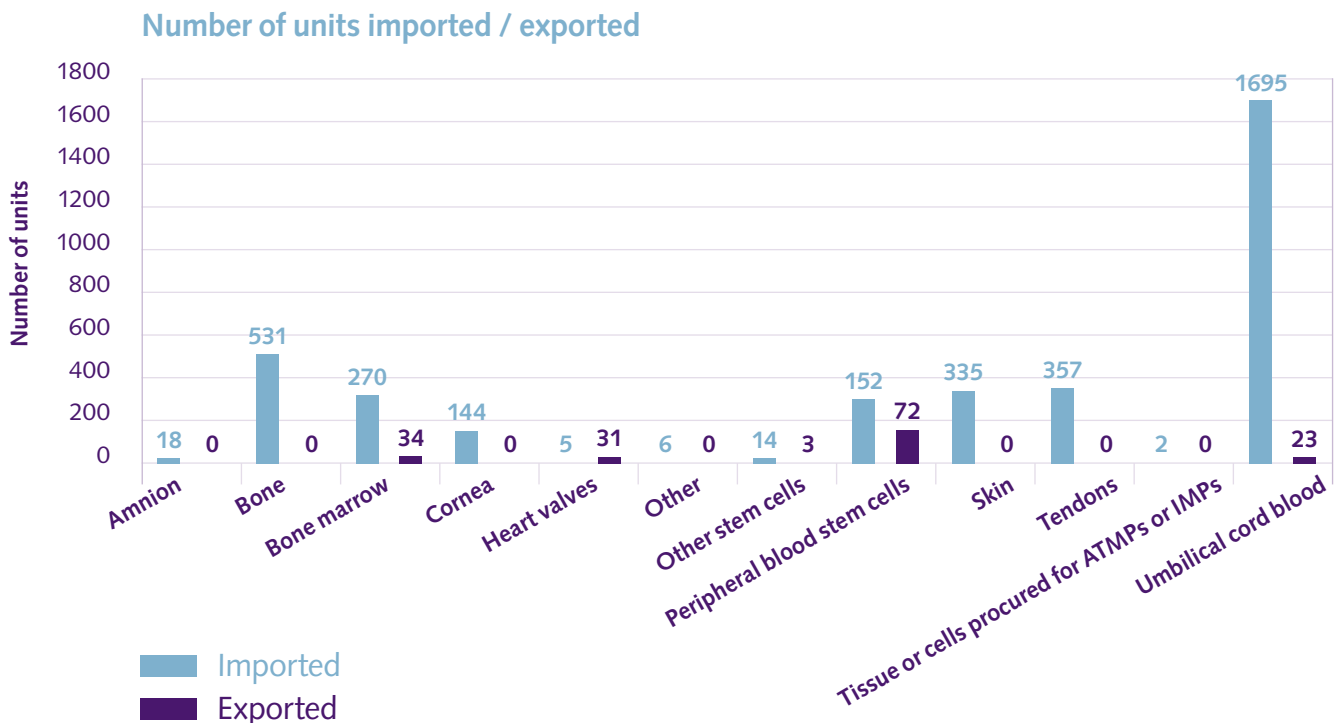


Information on annual activity data collected in 2008/09 (continued)

Figure 7. The number of units of tissues and cells accepted into the TEs during 2008/09



Figure 8. The number of units of tissues and cells imported or exported by the TEs during 2008/09



Information on annual activity data collected in 2008/09 (continued)

177. Although the HTA is statutorily bound to collect this data, we are also considering how we can make best use of it. In future, the data will be used as a tool for updating our licensing management system and inspectors will make reference to the data before an inspection. We will also consider how it may be used as part of the risk assessment process.

Appendix 1:

FAQs and information on the HTA website

Acellular material

www.hta.gov.uk/legislationpoliciesandcodesofpractice/regulationofacellularmaterial.cfm

ATMPs

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/advancedtherapymedicinalproductsfaqs.cfm

Change of DI proforma

www.hta.gov.uk/licensingandinspections/peopleatlicensedestablishments/howtomakechangestoyourlicence.cfm

Codes of practice that give professionals practical guidance on human tissue legislation

<http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/codesofpractice.cfm>

Cord blood FAQs for parents

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/cordbloodprocurementfaqsforparents.cfm

European Standards and Training in the Inspection of Tissue Establishments

www.eustite.org

Human application compliance report

www.hta.gov.uk/_db/_documents/HTA_Human_Application_v2.pdf

Hampton Implementation Review

www.betterregulation.gov.uk

Human Tissue Act (Persons who lack Capacity to Consent and Transplants) Regulations 2006

www.opsi.gov.uk/si/si2006/20061659.htm

Import, export and distribution

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/distributionandimportexportfaqs.cfm

Appendix 1:

FAQs and information on the HTA website (continued)

Joint policy statement on the relationship between the Advanced Therapy Medicinal Products (ATMP) Regulation and the Q&S Regulations

www.hta.gov.uk/_db/_documents/Joint_Policy_Statement_on_Advanced_Therapy_Medicina_Products_v0_7.pdf

Licensed human application establishments

www.hta.gov.uk/_db/_documents/Licensed_Establishments_in_Human_Application_Sector_July_09.pdf

Midwives and maternity units: the legal requirements for cord blood (procurement) collection

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/cordbloodprocurementfaqs.cfm

Procurement

www.hta.gov.uk/licensingandinspections/licensingunderthequalityandsafetyregulations/licensingofprocurementorganisations.cfm

Q&S Regulations FAQs

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/qualityandsafetyregulationsfaqs.cfm

RAPs, representations and other regulatory actions

www.hta.gov.uk/legislationpoliciesandcodesofpractice/regulatoryenforcementpolicy.cfm

Regulators' Compliance Code

www.berr.gov.uk/files/file45019.pdf

Role of the DI

www.hta.gov.uk/licensingandinspections/peopleatlicensedestablishments/disandlicenceholdersundertheq&sregulations.cfm

Satellites

www.hta.gov.uk/licensingandinspections/satellitesites.cfm

Serious Adverse Events and Serious Adverse Reactions

www.hta.gov.uk/licensingandinspections/faqsonseriousadverseeventsandadversereactions.cfm

Appendix 1:

FAQs and information on the HTA website (continued)

Stem cell lines

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/regulationofstemcelllinesfaqs.cfm

Stem cell route map

www.advisorybodies.doh.gov.uk/genetics/gtac/index.htm

Third party agreements

www.hta.gov.uk/licensingandinspections/sectorspecificinformation/humanapplication/thirdpartyagreementfaqs.cfm

Appendix 2:

List of establishments that received an HTA phase 2 site-visit inspection during business year 2008/09

- Aberdeen and North East Scotland Blood Transfusion Centre (11101)
- Addenbrooke's Hospital (11072)
- Angel Biotechnology Holdings (11127)
- Belfast Cord Blood Bank (11077)
- BioHorizonsUK (11008)
- Bone Bank Morrison Hospital (11043)*
- Castle Hill Hospital (12174)
- Chapel Allerton Hospital – Leeds Teaching Hospitals NHS Trust (22505)
- Chelsea & Westminster Hospitals NHS Foundation Trust Burns Unit (11146)*
- Cryo-store (11136)*
- Cumberland Royal Infirmary (11126)
- Derby Bone Bank (11029)
- Derriford Hospital, Plymouth (11093)*
- Exeter Bone Bank (11012)
- Freeman Hospital (11121)
- Guy's and St Thomas' Stem Cell Laboratory (11037)
- Institute of Ophthalmology (11059)*
- Intercytex (11002)
- King's College Hospital (11006)*
- Leicester Bone Bank (11011)
- Leicester Islet Isolation Laboratory (11085)
- Mayday Healthcare Trust (11124)
- Morrison Hospital (11060)*
- Musgrave Park Hospital Trust (11032)
- National Health Service Blood and Transplant- Tissue Services (11018)
- Paul O'Gorman Laboratory of Cellular Therapeutics (11016)
- Queen's Medical Centre (11035)**
- Oxford Heart Valve Bank Oxford Radcliffe Hospitals NHS Trust (11106)**
- Rayne Cell Therapy Suite Department of Haematological Medicine, King's College London (11023)
- ReNeuron (22501)
- Royal Bournemouth (11129)

Appendix 2:

List of establishments that received an HTA phase 2 site-visit inspection during business year 2008/09

- Royal Orthopaedic Hospital (12379)
- Royal Brompton Heart Valve Bank (11048)*
- Royal Marsden (11001)
- Royal Victoria Infirmary (11122)
- SCI Southampton (11053)
- South Devon Healthcare NHS Trust (11088)
- South East Tissue Services,
Scottish National Blood Transfusion Service (11010)
- Stem Cell Laboratory (11031)
- Stem Cell Transplant Laboratory,
University of Nottingham/Nottingham City Hospital (11073)
- University Hospital of Wales (11094)
- Whiston Hospital (11109)*
- York District Hospital (12480)
- Ysbyty Gwynedd Stem Cell Bank (11125)

* Establishments that were subjected to a second phase 2 site-visit inspection

** Establishment was inspected late in March 2009 so results are not included in this report

Details of all licensed establishments are listed on the HTA website at:

www.hta.gov.uk/licensing/licensed_establishments.cfm

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