Review of Vigilance and Surveillance Systems for Tissues and Cells

Introduction

Vigilance and Surveillance of tissues and cells used in transplantation or assisted reproduction is a recent development in most Member States of the European Union and indeed most of the world. In many cases, the development of these vigilance systems has been either due to high profile incidents involving the safety of tissues and cells or as a natural continuum from the development of haemovigilance systems in the 1990’s.

This report describes the results of a questionnaire and site visits to relevant institutes conducted between December 2006 and February 2007 as part of workpackage 4(b) of the EUSTITE project (www.eustite.org). The project is co-funded by the European Commission and aims to support Member States in the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC by providing guidance documents and training in the areas of inspection and adverse event and reaction reporting. Workpackage 4(b) focuses on vigilance and surveillance and is led by the Department of Essential Health Technologies at the World Health Organization (WHO), one of the partners in the EUSTITE project. A major objective of the workpackage is to develop and pilot tools for vigilance and surveillance of tissues and cells which will be consistent and complementary to those existing or under development globally. The work on which this report is based was carried out by an epidemiologist employed by WHO within the EUSTITE project. The report provides an overview of the state of preparation of vigilance and surveillance systems in the European Union and details of the operation of some systems with particular experience as well as an overview of developments in the field of tissue and cell vigilance in the United States and Canada.

The main objective of this document is to identify and present tools being used in vigilance systems in Member States and elsewhere which could be of interest and use to other states which are still developing their system. It also seeks to identify commonalities in approaches to vigilance and surveillance systems between Member States which would allow a better basis for a common European reporting system which would be able to link to developments outside the European Union. Therefore, whilst all EU Member States were contacted in preparing this document, the report focuses on those countries where systems are already in place. The document lists the current state of affairs with regards to transposition of the relevant EU directives as of March 2007 and then describes in detail the French vigilance system, which was the first such system to be developed, and other systems in the EU and elsewhere. The systems presented below have been selected either because they have a particular aspect which could be of use to other Member States (eg HFEA, UK and TRIP, Holland) or because they are typical of the way that Member States are
instituting their vigilance systems (e.g., IMB, Ireland). A short summary of WHO global surveillance systems, including the pharmacovigilance system and global infectious disease surveillance will provide indications of how a European system could operate.

**Methods**

A questionnaire was developed in December 2006. The questionnaire explored the history of tissue and cell vigilance in Member States, details of any established vigilance system, including structure of the system and reporting arrangements, questions regarding any available classification systems, definitions and the legal framework for the system. The questionnaire was initially distributed to EUSTITE partners and eventually forwarded to all Member States. In cases where Member States did not reply to the questionnaire, data was obtained from a survey conducted by the European Commission in December 2006/January 2007 which sought information on Member States’ level of preparedness in the implantation of the relevant directives.

The questionnaire was complemented by visits to a number of Competent Authorities for tissues and cells which have already set up vigilance and surveillance systems in order to describe in more detail the experience of these Member States. Further visits were made to the Food and Drug Administration, Washington and the Centers for Disease Control in Atlanta.
European Union overview

The three directives concerning activities related to tissue and cell vigilance were published in 2004 and 2006. The level of transposition of these directives varies in Member States. The European Commission surveyed member states in January 2007 to see the progress in transposition of the directives. By the end of January 2007, nine member states had completely transposed 2004/23 into national legislation. A further five member states had partially transposed the legislation and 13 still had to transpose the directive. The transposition of more recent directives (2006/17 and 2006/86) was even less complete: 7 member states had completely transposed 2006/17 and 5 have transposed the whole or the main parts of 2006/86.

Directive 2004/23/EC provides the following definitions for serious adverse events and reactions:

‘Serious adverse event’ means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

‘Serious adverse reaction’ means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity;

In the Commission’s survey of EU Competent Authorities, it asked whether, in transposing the Directives into national law, Member States had provided for the following types of adverse events and reactions:

**Serious adverse events**
1. The administration or the use of tissues/cells that did not fulfill the safety and quality requirements
2. A near miss: the distribution of tissues/cells that did not fulfill the safety or quality requirements at that time (but that was not administered or used)
3. The release of tissues/cells (even if not distributed) that did not fulfill the release requirements, due to a procedural problems of the release process (e.g. informatics)

**Serious adverse reactions**
1. Serious adverse reactions in the recipient which may be linked to the quality and safety of tissues and cells
2. Serious adverse reactions that cannot be attributed to the quality and safety of tissues and cells
3. Serious adverse reactions in the donor which may influence the quality and safety of tissues and cells
4. Serious adverse reactions in the donor that do not influence the quality and safety of tissues and cells

The results indicate that 10 member states have a reporting system in place, whilst the other 17 member states still have not established reporting systems, although a few are currently planning their systems and will be launching their systems shortly. There were varying responses to the types of adverse events/reactions which would be considered to be reportable in member states. This indicates that member states need further guidance both in the establishment of systems and in the interpretation of the definitions specified within the relevant directives. The full responses to the Commission’s questions relating to vigilance are shown in Appendix 1.
Detailed Review of the Selected Vigilance and Surveillance systems for Tissues and Cells in the EU

From the information gathered during the EUSTITE survey, a small number of Member States were identified where systems were established and where useful experience could be reviewed in the development of a proposed EU model. Their systems were examined in detail and are described here.

France

Summary

The French vigilance and surveillance systems for tissues and cells are co-ordinated by two agencies: the Agence Française De Sécurité Sanitaire Des Produits De Santé (AFSSaPS) for tissues, cells and ancillary products and the Agence de Biomédecine (ABM) for gametes and reproductive cells. Information flows from local centres dealing with tissues and cells, through local co-ordinators of Biovigilance to the national agencies. There are no regional centres and information is collected and analysed centrally. Investigations are co-ordinated locally and results of investigations reported centrally. The two national agencies collaborate in investigations which deal with cross-cutting issues.

Background

Biovigilance was established in France by a decree in 2003. Following this decree, AFSSaPS started operating a vigilance and surveillance system for tissues and cells in the beginning of 2004. In 2006, ABM started work on a vigilance and surveillance system for gametes and reproductive cells, which was due to start operating in 2007.

Agencies involved in Biovigilance

ABM is responsible for vigilance and surveillance of gametes and reproductive cells. Surveillance started in January 2007 and involves around 350 centres. ABM is also responsible for the co-ordination of transplant services and maintains waiting lists for the different types of transplants (organs, cornea, hematopoietic stem cells). ABM has a network of local staff involved in the vigilance of reproductive cells called AMP-vigilants.

AFSSaPS is responsible for vigilance and surveillance of all other health products including for example tissues, organs, cells, ancillary products, blood, medical devices, cosmetics and medicines. AFSSaPS runs a network of local correspondents of biovigilance (LCB). The AFSSaPS vigilance and surveillance activities encompass the whole chain of the transplant process, from the procurement of organs, tissues and cells through to recipient follow-up following transplantation.
Other groups

National Commission on Biovigilance

This advisory commission is made up of representatives from the four organisations (Direction de l’Hospitalisation et de l’Organisation des Soins responsible for health activities and establishments, Direction Générale de la Santé which is in fact the health ministry, AFSSAPS and ABM) and 23 other stakeholders in Biovigilance. It is seated within AFSSaPS.

Its roles are to:
- Examine and provide its opinion on the main information collected by the AFSSaPS biovigilance system
- To propose the establishment of studies and investigations which it deems relevant
- To provide recommendations based on these studies and investigations to improve the quality, safety and efficacy of products in the field of biovigilance
- To deliver an opinion to the Director of AFSSaPS on measure taken or to be taken in order to prevent the recurrence of adverse effects/reactions.
- To review and validate the annual report of the Biovigilance cell of AFSSaPS.

The Health Minister can approach the commission on any topic related to Biovigilance and ask its advice on such topics.

A similar commission will be created for ABM in 2007 and will deal solely with issues related to ART.

Vigilance and Surveillance System

Definitions

AFSSaPS defines adverse events and reactions as follows:

Adverse Reaction (“Effet Indesirable”):
A harmful and unexpected response in a patient, living donor or recipient, which can be attributed to a product or activity within the field of biovigilance.
An adverse reaction may be serious if:
- It may result in death
- It could be life-threatening for the patient
- It could be of risk to the security of one or more living donors or recipients.

Adverse Event (“Incident”):
Failure or alteration of an isolated element, a process or a system related to activities in the field of biovigilance and which could result in an adverse reaction in the donor or the recipient.

An adverse event may be serious if:

- There is the possibility that the adverse event could happen again and could compromise the safety of one or more living donors or recipients
- The adverse event could result in a serious adverse reaction

These definitions are compatible with the EU directive, though not identical. In particular, these definitions allow for the reporting of adverse events or reactions which are not serious and would therefore be excluded through the EU definitions. This is considered necessary to allow AFSSaPS to monitor the quality of health products. Furthermore, because of new therapeutic approaches with tissues and cells and lack of experience in these approaches, there is a need for detailed information to assess the safety of these approaches. In the future, AFSSaPS might limit its vigilance and surveillance to serious events/reactions.

The Agence de Biomedecine has different definitions for adverse events and reactions:

Adverse Reaction (“Effet indésirable”):
A harmful and unexpected response, in a patient or gamete donor, which is linked, or possibly linked, to the biological or clinical activities of medically assisted conception.

Adverse Event (“Incident”):
An incident linked with the clinical or biological activities of medically assisted conception (related to the collection of gametes, in vitro fertilisation, transfer of embryos and artificial insemination, freezing, conservation, transport or the attribution of gametes and embryos), due to an accident or an error, which could result in an adverse effect in the patient or the donor of gametes.

There is a classification system which defines how serious an event or reaction is deemed to be. This is described below.

**Classification systems**

**AFSSaPS**
AFSSaPS has prepared a document for the local correspondents of Biovigilance. This document is intended as a guide for the setting up of a local biovigilance system. It also lists common adverse events and reactions and describes deadlines on when events or reactions should be reported. Serious adverse events or reactions need to be notified immediately whilst less serious ones could be reported only in the annual activity report.
Events are grouped according to where in the chain of transplantation the event occurs. Within each group, some examples are given. For each example, the document sets a deadline by which the event/reaction should be reported. These deadlines can be either “immediate”, “within 15 days” or “only in the annual activity report”. The categories are listed below:

A: Incidents occurring at the time of tissue donation or to the donor
B: Incidents occurring between donation and use of the tissues
C: Incidents occurring at the point of use of the tissue or to the recipient

**ABM**

ABM has a similar document listing adverse events or reactions which are reportable. The classification system is different in that it focuses on who the incident affects. The following are the categories in this classification system:

A: Incidents which affect members of the couple
B: Incidents which affect the gametes, embryo, or reproductive tissues
C: Incidents affecting the foetus or the child
D: Incidents related to the establishment
E: Incidents affecting staff
F: Others

All adverse events/reactions are to be reported as soon as possible. Furthermore, ABM has set up a system to assess the level of importance of an adverse event/reaction. This system assesses the seriousness of an adverse event/reaction and the number of times an event/reaction occurred within the same establishment and categorizes the importance of the event/reaction. The system has three levels ranging from C1, when no action is necessary, through C2, when a risk assessment is necessary, to C3, when the situation is unacceptable and measures to decrease the risk need to be taken immediately. This document is available as Appendix 2.

**Data collection**

Data is reported to the National agencies by two separate networks of local biovigilance staff. The director of every healthcare facility involved in the field of biovigilance and every tissue establishment is legally obliged to nominate a focal person (FP) for biovigilance. In the AFSSaPS system, they are called Local Correspondents for Biovigilance whereas in the ABM system they are called AMP-vigilants. These local focal persons are generally medical staff, pharmacists, biologists or scientists and may have multiple roles related to biovigilance, depending on which activities are carried out at their centre. They are also occasionally shared between different health establishments in the same area. FP’s are not funded by AFSSaPS or ABM.
FPs are responsible for performing local investigations and reporting to the national centres. The networks of FPs are co-ordinated by the two national agencies and lists of contacts are updated and shared every three months.

**Reporting**

Once a potential adverse event or reaction is identified, the medical practitioner or person who identifies the event/reaction should contact the FP of his establishment. It is then the responsibility of the FP to co-ordinate an investigation and report to the national agency. Reporting is done through fax or email. A separate parallel pathway exits which allows a medical practitioner to notify directly the national agency in emergencies or whenever the local correspondent is not available (such as during weekends).

Since there is no regional level in the French vigilance and surveillance systems, FPs report directly to the national centres, ABM for reproductive cells and AFSSaPS for organs, tissues, human cells and ancillary products.

**Data collected**

AFSSaPS and ABM use two different reporting forms. The form used by AFSSaPS is available in Appendix 3. For each incident, AFSSaPS allocates a case-number and records information about the event/reaction. Detailed information about each case is recorded and includes information about how the event/reaction was identified, which step in the transplant process the event occurred, details of the local investigation and of any steps taken locally or by AFSSaPS in response to the notification and/or investigation. Similar information is collected by ABM.

The systems also collect information which allows the agencies to assess the quality and efficiency of the services provided by tissue establishments. Both AFSSaPS and ABM collect activity data from reporting centres. Near misses are not specifically recorded or defined, but could be reported as adverse events.

**Response to reports**

**Investigations**

Investigations are co-ordinated locally by the FP who initially reports the adverse event/reaction. Results of investigations are communicated to AFSSaPS once they are finished, except in serious cases, when the agency is informed immediately and involved in the investigations.

ABM has similar arrangements; the FP is expected to inform ABM about the incident immediately and send part A of the reporting form. Part B should be sent once the investigation is finalised.
If multiple health establishments might be affected by a particular adverse event/reaction, it is the role of the FP investigating the initial event/reaction to inform FP’s of other establishments who might be affected.

As mentioned above, ABM will be using a matrix to determine action necessary following a report. This matrix relates the severity, level of acceptability of particular events or reactions and frequency. This system will be updated after the experience of the first few years.

AFSSaPS and ABM have not yet established guidelines for performing investigations. Such guidelines might be considered in the future based on the experience of the first few years of surveillance. In case of multiple reports, AFSSaPS can decide to create specific working groups to determine necessary action.

If a serious event/reaction is reported or an event/reaction occurs with abnormally high frequency, inspectors from AFSSaPS can visit tissue banks as part of their investigation. If the event or reaction occurs in a health establishment, AFSSaPS inspectors would need to perform a joint visit with Health ministry inspectors.

**Information flow**

The chart below shows the basic information flow for the AFSSAPS system. The whole system is centred round the local correspondent for Biovigilance. There are however links with other systems and professionals throughout.
A similar structure is envisaged for the vigilance system for reproductive cells.

**Emerging Diseases**

**Risk assessment**
Both ABM and AFSSaPS perform risk assessments for emerging diseases on a case by case basis. AFSSaPS can be asked to perform such investigations by the National Biovigilance Commission or of its own initiative. These risk assessments generally involve a number of agencies, typically AFSSaPS, ABM, the Institut de Veille Sanitaire and others as necessary. A recent example of such a risk assessment was the determining of the risk of Chikungunya to services, when a group was set up between ABM, AFSSaPS and the Institut de Veille Sanitaire. Once a risk assessment has been performed this is communicated directly to all FP’s.

**Feedback**

**Type, frequency of reports**
ABM will be producing an annual report with information on the biovigilance system. This report will be sent to participating centres. There are no plans for routine feedback to participating centres except when investigations indicate the need to alert other sites.
AFSSaPS currently produces a short report which is included as part of the AFSSaPS organisational Annual Report. A newsletter, which is available on the AFSSaPS website, is published every two months and provides information on activities and case-reports from all the vigilance systems operated by AFSSaPS.

In the near future, LCB’s in tissue establishments will be sending an annual activity report to AFSSaPS. Furthermore, AFSSaPS is also planning to produce an annual report on biovigilance activities which would be submitted to the National Commission on Biovigilance for approval and sent to the European commission.

In 2007, AFSSaPS is planning a series of meetings to improve participation in the system. The meetings will start in February 2007 in some regions and aim to inform LCB’s and local stakeholders of the reasons for the vigilance system and to encourage them to report adverse events/reactions.

**Current experience**

Over the two years that the AFSSaPS system has been set up, a total of 171 adverse event reports and 74 adverse reaction reports have been submitted. The total number of reports each year has fluctuated slightly during the three years of surveillance (2004: 82, 2005: 69, 2006: 94). In 2006, almost 80% of reports were of adverse events. During the last two years, around 60% of reports each year have been from health establishments, with the rest being from tissue establishments, manufacturers and the Agence de Biomedecine.
The Netherlands

Background
TRIP (Transfusion Reactions in Patients) receives and analyses reports of transfusion reactions and promotes hemovigilance in the widest sense, in order to contribute to improved transfusion safety in the Netherlands. TRIP has done this since 2003. Because of similarities with this system, the Dutch Ministry of Health Care, Welfare and Sport asked TRIP to develop a ‘tissue vigilance’ system (as referred to in Article 11, Directive 2004/23/EC). The European Directive has not been implemented in Dutch legislation yet (and therefore input is still voluntary), but this process is almost finished. Thus the Health Care Inspectorate of the Dutch Ministry of Health Care, Welfare and Sport is the ‘Competent authority’ and responds to the reports in its supervisory capacity. TRIP analyses and compiles the data and will provide the annual overview.

From September 2005 until August 2006 TRIP investigated the tissue and cell ‘chains’ and made contact with professional groups and tissue establishments. A reporting procedure was proposed and a reporting form was developed. The documentation has been published on the TRIP website (www.tripnet.nl).

In August 2006, TRIP sent an official letter to all registered tissue establishments and hospitals in the Netherlands with information on the European Directive and the (voluntary) pilot.

No special events which could have speeded up the vigilance process occurred in the Netherlands

System Description
The system developed by TRIP is a national system. All relevant establishments were informed and consulted in the development of this vigilance system. In addition to this activity, several branches of tissue activity already had internal tissue-specific reporting systems. TRIP started in 2002 with a haemovigilance system and is now working on this tissue vigilance system. TRIP haemovigilance reporting covers all adverse reactions and incidents but the tissue vigilance reporting only covers the product-related events as required by the Directive. The two systems are separate in principle, although there are similarities.

Because the EU legislation so far specifically excludes organ transplantations, these are not included in the tissue vigilance system which is under development.

The definitions of events/reactions are the same as used in the European Directive.

Reactions are classified in terms of clinical outcome (complete recovery, minor sequelae, serious sequelae, death). There is additionally a classification system in terms of imputability (rating the likelihood that the undesired event was due to the transplantation of the product).

Only serious adverse events and reactions related to the quality of the product should be reported, i.e. those specified in the Directive and these are reported centrally (nationally). The system collects the total number of products supplied for patient application.
**Operation**

Every tissue establishment has a ‘Responsible person’ (referred to in Article 17, Directive 2004/23/EC). This person reports adverse events and reactions to the Authority and TRIP. In addition, the hospitals have been informed of the availability of the reporting system and have been encouraged to appoint a tissue vigilance officer to oversee the protocols and compliance within the tissue chains. Hospitals report to the tissue establishments and to TRIP in parallel (in future online reporting will facilitate this). Both the Authority and TRIP have procedures in place to link the duplicate reports. There is no specific time-limit for reporting events and reactions, however they should be reported as soon as possible. Reporting is currently by sending a form by mail or fax (forms are available on the website) but as is the case for hemovigilance, TRIP is working on a web-based reporting system which will ease the procedure.

**Investigation and Feedback**

Tissue establishments and hospitals are required to perform investigations. Tissue establishments then determine whether any action is necessary following a report and TRIP will advise if requested. There are currently no established guidelines on the actions which need to be taken following particular events/reactions. Following a report, the Authority then determines whether supervisory action is required.

**Assessing Risk due to Emerging Diseases**

TRIP does not operate a system which assesses risk of emerging diseases to tissue and cells. However in the area of infectious disease the National Institute for Public Health and Environmental Health (RIVM) monitors worldwide infectious hazards and there is close consultation between this centre and (among others) the blood supplier. Links between hemovigilance and tissue vigilance activity are being enhanced and this will contribute to a speedy response when necessary.
Ireland – Irish Medicines Board

Background
Ireland did not have a vigilance and surveillance system for tissues and cells prior to the EU directives. The Irish Medicines Board (IMB) has therefore implemented a National vigilance and surveillance system for tissues and cells based on the requirements of the relevant EU directives.

System Description
Tissue establishments are required to have a responsible person as specified in the directives. They are required to report only serious adverse events and reactions. The system is a centralised one and reports are sent directly from Tissue Establishments to IMB. An Access-based database is currently used to record incidents. Reporting is through fax/email forms, although in the future, if there are a significant number of reports, a web-based reporting system could be developed.

The Irish system uses the same definitions for adverse events and reactions as defined in the EU directives and no classification systems are currently in use. The IMB, however, would consider using a classification system based on a system which is recognised internationally, such as MedDRA.¹

Operation
Procurement Organisations and organisations responsible for application of tissues and cells are requested to report to the tissue establishment who should then report to IMB. They may also report directly to IMB, however this is not encouraged. There is, at present, no specified time frame for reporting of adverse events/reactions, however the IMB Guide to reporting serious adverse reactions and serious adverse events associated with human tissues and cells requests that reports should be submitted as soon possible following detection of the event/ reaction. The IMB requires a follow-up report from tissue establishments once a full investigation of the incident has been performed.

Investigation and Feedback
Once an initial report is received, the IMB pharmacovigilance section assesses the report and then determines whether any further action is necessary. The IMB may require the reporting establishment to provide further information and may provide recommendations following review.

¹ MedDRA or Medical Dictionary for Regulatory Activities is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA is used in the US, European Union, and Japan. Its use is currently mandated in Europe and Japan for safety reporting. (http://www.meddrasmsso.com/MSSOWeb/index.htm)
The report is also assessed by the wider Human Medicines and/or Compliance Departments which may produce further recommendations as necessary. The IMB has access to clinical and preclinical experts where such input is warranted. The Pharmacovigilance Section liaises closely with the Compliance Department who will review any requested follow up action during subsequent triggered or routine inspections. There are currently no guidelines on responding to particular adverse events or reactions.

**Assessing Risk due to Emerging Diseases**

The IMB does not have a system for the routine assessment of risk due to emerging diseases. Such assessments are made on a case by case basis.
United Kingdom – Human Fertilization and Embryology Authority

Background

The HFEA was the first statutory body of its type in the world and its creation reflected public and professional interest in the potential future of human embryo research and assisted reproduction treatment. The recommendation for such a regulatory body had come from the 1984 report of the Committee of Inquiry into Human Fertilisation and Embryology (the Warnock Report). The HFEA was established in August 1991 following the passing of the Human Fertilisation and Embryology Act 1990 (HFE Act). The vigilance and surveillance system run by the HFEA has been operating since 2001 and is currently being adapted to meet requirements of the European directives.

System Description

HFEA operates a system which can take information from a wide variety of sources. There are specific forms for reporting; however reports are accepted even if they are not in this specific format. The system can take in information from tissue establishments, other competent authorities, manufacturers of products used in processes, professional bodies and the general public. There are memoranda of understanding with other competent authorities which allow sharing of information on events and reactions which can impact multiple fields.

Data on reports are entered into a custom database which allows the tracking of each incident and recording of any actions taken. HFEA requires tissue establishments to perform their own investigations and will provide support when requested. In cases where there is lack of cooperation, HFEA can decide to start its own investigations.

The current definitions are somewhat different to those defined in the EU directives; these definitions are however being updated in order to comply.

General definition of an incident:

- An incident can be defined as any occurrence that is inconsistent with the routine care of the patient or the routine operation of the organisation.

Definition of a near miss:

- A near miss can be defined as any occurrence, which but for luck, skill or judgement would in all probability have become an incident.

Definition of a clinical incident:

- A clinical incident is something that results in patients unintentionally suffering injury as a result of clinical error or malfunction of medical equipment in the course of treatment or diagnosis.

HFEA definition of an adverse incident (HFEA Code of Practice):
• Adverse incidents are defined as any event, circumstance, activity or action which has caused, or has been identified as potentially causing harm, loss or damage to patients, their embryos and/or gametes, or to staff or a licensed centre.

All breaches of the HFE Act and/or failure to follow the HFEA Code of Practice must be reported as adverse incidents to the HFEA. The HFEA will also investigate patient complaints that relate to adverse incidents.

**Operation**

The reporting system within HFEA is similar to that in other organizations, with fax/email reports. There is currently no web-based reporting system. HFEA has however developed two interesting systems: a Risk Matrix system which is used to evaluate the risk due to incidents, and an alert system through which information on incidents can be shared between tissue establishments.

**Matrix system**

HFEA uses a risk matrix through which an assessment can be made of the importance of the incident and the type of follow-up necessary. The matrix assesses the severity of an incident and the likelihood of recurrence. The matrix gives a score to each combination of likelihood of recurrence and severity and this is used to determine the follow-up action necessary. Appendix 4 includes more details about the Risk Matrix used by HFEA (taken from the *Standard Operating Procedures Incidents and Near Misses V1.0* available at [http://www.hfea.gov.uk/docs/Incidents_and_Near_Misses_18.08.06.pdf](http://www.hfea.gov.uk/docs/Incidents_and_Near_Misses_18.08.06.pdf)).

**Alert system**

HFEA has instituted an alert system which allows sharing of information on incidents in order for centres to learn from the experience of others and to develop protocols to avoid similar situations from occurring. These alerts are generally produced when a series of events or reactions of the same type are noticed or when particularly severe incidents are reported. These alerts are initially discussed internally, with professional bodies and external experts as necessary through a peer-review process. Further details of the alert system are available in Appendix 5 (taken from the *Standard Operating Procedure Incidents and Near Misses V1.0* available at [http://www.hfea.gov.uk/docs/Incidents_and_Near_Misses_18.08.06.pdf](http://www.hfea.gov.uk/docs/Incidents_and_Near_Misses_18.08.06.pdf)).

**Investigation and Feedback**

HFEA describes the steps following the submission of a report in its Standard Operating Procedures (Appendix 4). In summary, once a report is received, HFEA enters the information about the incident into a database. HFEA then completes a risk assessment to determine the appropriate level of action. Some of the reports do not require any action and are recorded for ‘information only’. Details are retained for ongoing trend analysis and report pattern detection.
Where the risk assessment process confirms that an investigation is appropriate, the department will either investigate itself through an HFEA inspector. This is usually done for serious incidents and the investigation may involve a visit to the site of the incident and collaboration with other agencies, for example, The Medicines and Healthcare Products Regulatory Authority (MHRA), the Healthcare Commission and the Health & Safety Executive (HSE). These investigations can lead the HFEA to issue an Alert (described above).

Standard Investigations will usually follow incidents where there is a minor harm (and that had a low potential for more serious harm).

Other reports may concern incidents that do not fall within the remit of HFEA. These incidents are usually discussed with the relevant organization.

When the investigation has been completed, HFEA communicates with the tissue establishment and provides an opportunity for the establishment to comment on the conclusions reached. If further information becomes available after this point HFEA may decide to re-open the investigation. All incident information, including investigation results and conclusions drawn, are archived and the data used for trend analysis.
Review of Experience in the United States

**CDC and TTSN**

A number of different organizations are involved in regulatory oversight and vigilance of organs and tissues in the United States. HRSA has oversight for organs whilst FDA has regulatory authority for tissues and blood. CDC does not have a role in oversight but is involved in risk assessment and investigation of incidents.

Following a workshop of key stakeholders in 2005, a number of priorities were identified and this resulted in the development of the Transplantation Transmission Sentinel Network (TTSN). TTSN is a collaborative effort between the United Network for Organ Sharing, CDC, government oversight agencies, accrediting and trade organizations and clinicians organizations. The primary tasks for TTSN are to develop an electronic communications forum that will serve all groups involved in allograft transplantation, to improve dissemination of information to clinicians, health professionals and patients and to develop a notification algorithm for trace-back and trace-forward allograft tracking.

TTSN will provide a system to perform allograft tracking electronically rather than through a paper-based system. This will allow banks and end-users to generate reports on graft utilization. Through this system, there will also be a mechanism for the reporting of adverse reactions and for the communication of potential or confirmed reactions to organ procurement organizations and Tissue banks.

The application is being designed in stages and will be completed by March 2008.

**FDA**

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration is responsible for regulating human cell, tissue and cellular and tissue-based products (HCT/P) under 21 CFR Parts 1270 and 1271. CBER also operates a vigilance system for Tissues and cells through the MedWatch Reporting system. MedWatch is a standardized adverse event reporting system which is also used for adverse event reporting of drugs and other biologics.

Investigation of adverse reactions is co-ordinated by the Tissue Safety Team (TST). TST consists of CBER representatives from the Office of Biostatistics and Epidemiology (OBE), Office of Cellular, Tissue and Gene Therapies (OCTGT), Office of Compliance and Biologics Quality (OCBQ), Office of Communication, Training and Manufacturers Assistance (OCTMA), and the Office of the Director (OD). The key purpose of the TST is to coordinate responses to reports of HCT/P adverse reactions and to develop procedures and policies to facilitate rapid and comprehensive responses by FDA. Other functions include outreach and education.
Reporting is mandatory for HCT/P establishments and voluntary for Health Care professionals, patients and consumers. HCT/P establishments are required to:

- Investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution and
- Report to FDA and serious adverse reactions involving a communicable disease if it is:
  a) Fatal
  b) Life threatening
  c) Results in permanent impairment of a body function or permanent damage to body structure or
  d) Necessitates medical or surgical intervention including hospitalization.

The Office of Biostatistics and Epidemiology is the official contact for MedWatch reporting involving HCT/Ps and is responsible for processing and epidemiologic review of the reports. OBE is also responsible for forwarding those reports to the appropriate contacts within CBER for further action and follow-up.

Upon receipt of a MedWatch form or a report forwarded from the Center for Devices and Radiologic Health reporting an adverse reaction associated with an HCT/P, the OBE notifies the Office of Cellular, Tissue and Gene Therapies (OCTGT) and the Office of Compliance and Biologics Quality (OCBQ).

If the MedWatch report indicates an infectious disease transmission or possible transmission that may be associated with a HCT/P, the OBE point of contact will immediately inform the other Tissue Safety Team members to determine next steps. Further information is requested as necessary from the user or from the manufacturer and a decision is made on the need to notify other agency components (including senior management), and those outside the Agency. OCTGT obtains scientific information about the microorganism involved, in order to determine its significance. OCTGT then shares this information with other members of the TST. The OBE is also responsible for entering data on events into the Adverse Events and Reporting Systems Database (AERS).

The OBE organizes quarterly meetings with OCTGT and OCBQ to review the results of the evaluation of incoming reports and determine if trends indicate a need for changes in procedures, advisories to the medical community, or other CBER action.

If the TST recommends further investigation, OCBQ, issues an assignment to the Office of Regulatory Affairs (ORA) to perform a field investigation and serve as the primary contact with ORA. OCBQ also maintains a database of all HCT/P adverse reaction reports they receive, including all MedWatch reports. The database is linked to summaries of the follow-up information provided by OCTGT and is available to staff in OBE and OCTGT.
When the case is considered "closed", OCTGT will summarize all information and send to everyone who has been previously contacted.

If at any time, the TST determines the report to be a significant event, a decision is made after discussion by the TST to follow-up with the appropriate contacts outside CBER and then, if appropriate, to alert CBER senior management. Any additional information is communicated to all who have been previously contacted, so that everyone involved is up-to-date.
Overview of WHO-led Surveillance systems

Pharmacovigilance

The WHO defines pharmacovigilance as ‘The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

The aims of pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines, especially with regard to the prevention of unintended harm from the use of drugs; to improve public health and safety in relation to the use of medicines by the provision of reliable, balanced information resulting in more rational use of drugs; and to contribute to the assessment of the risk-benefit profile of medicines, thus encouraging safer and more effective use of medicines and a resolution of the sometimes apparently conflicting interests of public health and individual patient welfare.

Working with the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC), WHO promotes pharmacovigilance at the country level. Activities of the UMC include:

- co-ordinating the WHO Programme for International Drug Monitoring
- collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs
- collaborating with member countries in the development and practice of pharmacovigilance alerting regulatory authorities of member countries about potential drug safety problems via the WHO signal process.

The publication ‘Safety of Medicines – a guide to detecting and reporting adverse drug reactions’ is directed at clinical users and aims to raise awareness of the magnitude of the drug safety problem and the importance of reporting events and reactions. The publication includes some definitions which may be applicable or adaptable to the field of tissues and cells:

An adverse drug reaction (ADR) is ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’.

In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

An unexpected adverse reaction is ‘an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug’.
A *side effect* is ‘any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug’. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose.

An *adverse event* or *experience* is defined as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’. The basic point here is the coincidence in time without any suspicion of a causal relationship.

A *serious adverse event* is any event that:
- Is fatal
- Is life-threatening
- Is permanently/significantly disabling
- Requires or prolongs hospitalization
- Causes a congenital anomaly
- Requires intervention to prevent permanent impairment or damage

A *signal* refers to ‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously’. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

The UMC uses complex data mining and other statistical tools in order to identify drug combinations which result in adverse reactions or specific combinations of medications and adverse reactions. These signals are then further analysed and discussed and where necessary alerts are issued.

**Global Infectious Disease Surveillance**

The World Health Organisation performs surveillance of infectious diseases and particularly outbreaks on a global basis. These activities are organized through a number of different initiatives. WHO global alert and response systematically gathers official reports and rumours of suspected outbreaks from a wide range of formal and informal sources. Formal reports of suspected outbreaks are received from ministries of health, national institutes of public health, WHO Regional and Country offices, WHO collaborating centres, civilian and military laboratories, academic institutes, and nongovernmental organizations (NGOs).

In order to ensure a comprehensive picture of the epidemic threat to global health security, WHO also gathers epidemic intelligence from all informal sources. With the advent of modern
communication technologies, many initial outbreak reports now originate in the electronic media and electronic discussion groups.

The Global Public Health Intelligence Network (GPHIN), developed by Health Canada in collaboration with WHO, is a secure Internet-based multilingual early-warning tool that continuously searches global media sources such as news wires and web sites to identify information about disease outbreaks and other events of potential international public health concern. GPHIN is one of the most important sources of informal information related to outbreaks. More than 60% of the initial outbreak reports come from unofficial informal sources, including sources other than the electronic media, which require verification. As part of Alert and Response Operations, global epidemic intelligence is primarily focussed on communicable diseases (e.g. haemorrhagic fevers, cholera, meningitis, salmonellosis and encephalitis).

The International Health Regulations (2005) are a further tool which is currently being implemented in global infectious disease surveillance. The regulations, which are binding on Member States, ask WHO Member States to report outbreaks of disease of international significance. IHR(2005) therefore provides a further tool for WHO to identify outbreaks which might have particular importance.

Outbreaks identified through these systems are then entered on an event-management database and verified. WHO then provides Member States with support where necessary in the response to these events. These responses draw technical resources from within the WHO system and from the Global Outbreak Alert and Response Network (GOARN) which is a collaboration of 110 technical institutions, nongovernmental organizations (NGOs) and networks; it represents a pooled resource for alert and response operations.
Tools for vigilance and surveillance

**Risk Matrix**

The use of a risk matrix is fairly common in risk assessment in industry and in healthcare incident reporting systems. In Europe, both the HFEA and ABM have established similar systems which allow the assessment of risk for each reported incident and the management of incidents through pre-determined algorithms. The two risk matrices are available in Appendices 2 and 4. Such systems could easily be adapted for use in most European countries and could provide a standard way of responding to incidents. An adapted matrix could also be used for a European vigilance system to determine the response needed to reports from Member States.

**Imputability**

The field of haemovigilance has long used imputability levels in order to determine the likelihood that a serious adverse reaction in a recipient can be attributed to the blood or blood component transfused or that a serious adverse reaction in a donor can be attributed to the blood donation process. Such systems can be used in tissue and cell vigilance in classifying the likelihood that a reaction was indeed related to the transplantation process, and this could be used to determine the level of response needed by a national competent authority. The following scheme is taken from the French Haemovigilance system:

- **Level 4:** certain = conclusive evidence for attributing the adverse reaction to the blood transfusion
- **Level 3:** likely = evidence in favour of attributing the adverse reaction to the blood transfusion without any other obvious causes
- **Level 2:** possible = evidence is indeterminate for attributing the adverse reaction either to the blood transfusion or to alternative causes
- **Level 1:** doubtful = other possible causes but no evidence for excluding the role of the blood transfusion in the occurrence of the adverse effect
- **Level 0:** excluded = conclusive evidence for attributing the adverse reaction to causes other than the blood transfusion

**Severity**

All biovigilance systems use some method for the assessment of the severity of harm associated with a given adverse reaction, with a scale generally ranging from ‘minor inconvenience’ to ‘death’. Again, the field of haemovigilance, in particular the International Society for Blood Transfusion, has developed a scoring system that could be adapted for use in the field of tissues and cells. A modified version which was presented to the EUSTITE VSMAC is included below:

- Grade 1: non-serious
Mild clinical consequences which do not necessitate hospitalisation and/or result in long term disability or consequences for the recipient.

- Grade 2: severe
  Recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or the adverse reaction resulted in persistent or significant disability or incapacity; or the adverse reaction necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.

- Grade 3: life-threatening
  The recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death

- Grade 4: death
  Grade 4 should be used only if death is possibly, probably or definitely related to tissue/cell transplantation.

**Algorithms**

The WHO International Health Regulations (2005) include a decision instrument (algorithm) for Member States to determine whether an event is reportable under these regulations or not. Annexes to the document furthermore list a few examples of how the key items in the algorithm need to be applied. Algorithms may be used by EU Member States in determining what is reportable to the National competent authority, what is reportable to a European vigilance system and the types of responses necessary at each level. The IHR decision instrument is shown below and the whole IHR document is available at http://www.who.int/csr/ihr/en/. 
Triggers

The CDC is developing a simple algorithm for clinicians which would facilitate the identification of events which should be reported and considered as possible adverse reactions. The triggers being considered are currently mainly applicable to infectious diseases but could be extended to other sentinel events. The following events should trigger a report:
• Removal of tissue due to suspected infection
• Patient re-hospitalized 3 months after transplantation due to infection
• Evidence of infection due to unusual organism or infectious syndrome

The following algorithm is then proposed to determine whether an infectious disease episode should be considered as transplantation-transmitted:
• Recipient laboratory workup for confirmation
• Followup of other recipients
• Donor investigation
• Determination of case classification (imputability)

Conclusions of Review

This review indicates that systems for the vigilance and surveillance of tissues and cells are relatively under-developed across Europe, with a small number of exceptions. However, both in the US and in Europe, great efforts are currently underway to establish systems to ensure that safety and quality of tissues and cells applied to the human body are monitored and information is shared. This review has indicated that there are a number of basic principles and tools already in existence in related fields, such as blood transfusion, or under development for tissues and cells that can usefully be adopted or adapted in the design of new national or international systems.

The findings of this review have been discussed at two meetings during 2007. The first was a meeting of the Eustite Vigilance and Surveillance Medical Advisory Committee (V&SMAC) held in Madrid in March to which colleagues from the US and Canada were also invited. The second was a meeting hosted jointly by Eustite, the WHO and the Italian National Transplant Centre in Rome in July 2007 to which experts were invited from across the globe. The outputs of interactive discussions during these meetings, together with the findings of this report, are being used as the basis for Eustite proposals for V&S tools and guidance for the EU. The proposals which will be completed early in 2008 will form the basis of a Eustite pilot V&S programme which will run from July 2008 to July 2009. On completion of the pilot, the Eustite project will make recommendations to the European Commission.
## Appendix 1: Results from the Commission questionnaire on implementation of directives concerning Tissue and Cell safety

<table>
<thead>
<tr>
<th>Member State</th>
<th>Reporting system</th>
<th>*Definition of serious events</th>
<th>**Definition of serious reactions</th>
</tr>
</thead>
</table>
| **BE - Belgique / Belgïe** | Not in place yet, but system is ready to start as soon as the directives are transposed in Belgian legislation (end of 2007) or sooner if possible | - 1, 2, 3 are proposed to be part of national definition  
- Additional definition 'an event that might put the life of a donor in danger' added | - 1, 3, 4 are proposed to be part of national definition  
- Inclusion of 2 is to be discussed |
| **BU – Bulgaria** | There is a new Regulation concerning the issue-will be done to the end of February 2007 | - 1, 2, 3 included | - 1, 2, 3, 4 included |
| **CZ - Česká Republika** | No reporting system in place                                                   | Not applicable                                                                                     | Not applicable                                                                                   |
| **DK - Denmark** | - No, the procedural system for the reporting of serious adverse events and reactions is presently in development. It is expected to be in place early 2007. | - Will become known early 2007                                                                   | - Will become known early 2007                                                                   |
| **DE - Deutschland** | - Yes, Currently, the system for reporting adverse reactions is described in the German Drug Law ("Arzneimittelgesetz") which is fully compliant with Directive 2001/83/EC.  
- It is currently pursued to further adapt the German legislation by adopting the Tissue Act ("Gewebegegesetz") in order to meet all the requirements laid down in Directive 2004/23/EC. | - 1, 3 included  
- 2 not included | - 1 included  
- 2,3,4 not included |
### European Union Standards and Training for the Inspection of Tissue Establishments

<table>
<thead>
<tr>
<th>Member State</th>
<th>Reporting system</th>
<th>*Definition of serious events</th>
<th>**Definition of serious reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE - Eesti</td>
<td>No reporting system in place</td>
<td>- Not available</td>
<td>- Not available</td>
</tr>
<tr>
<td>EL - Elláda</td>
<td>No reporting system in place</td>
<td>- 1 included</td>
<td>1, 2, 3, 4 included</td>
</tr>
<tr>
<td>1, 2, 3 excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES – España</td>
<td>No reporting system in place</td>
<td>- 1 included</td>
<td>1, 2, 3, 4 included</td>
</tr>
<tr>
<td>FR - France</td>
<td>La biovigilance s’applique à l’ensemble des activités portant sur les éléments et produits d’origine humaine depuis l’étape du prélèvement ou de la collecte jusqu’à leur utilisation.</td>
<td>Les événements indésirables sont des incidents qui se sont produits à une étape de mise en œuvre du procédé (préparation inattendues chez le donneur ou le</td>
<td>Les réactions indésirables sont définies comme des manifestations cliniques</td>
</tr>
</tbody>
</table>
Le dispositif de biovigilance repose sur 3 pôles :

1) L’Agence française de sécurité sanitaire des produits de santé
   Cette agence définit les orientations, anime et coordonne les actions des différents intervenants et veille au respect des procédures. Elle réalise le bilan d’activité de la biovigilance à l’attention des différents intervenants.

   ➢ Elle est destinataire des déclarations d’incident ou d’effet indésirables ainsi que des rapports de synthèse adressés par les correspondants locaux ; elle prend les mesures conservatoires qui s’imposent ainsi que les mesures appropriées visant à prévenir ou faire cesser les incidents ou effets indésirables.

2) les correspondants locaux de biovigilance
   Toutes les structures publiques et privées, autres que les cabinets libéraux, qui collectent et prélèvent, préparent, conservent et distribuent, importent et exportent des cellules, tissus, organes ou qui administrent ou greffent des produits d’origine humaine doivent disposer d’un correspondant local de biovigilance. Les correspondants sont chargés de la transmission des déclarations de tous les incidents et effets indésirables à l’AFSSAPS, de la réalisation des enquêtes et investigations nécessaires à la recherche de l’imputabilité de l’incident et de l’information des autres correspondants locaux concernés. Les correspondants n’ont pas la responsabilité de prendre des mesures conservatoires, mission qui incombe exclusivement à l’AFSSAPS. Les professionnels de santé qui exercent dans une structure ne disposant pas de correspondant (notamment en libéral) ont également l’obligation de signaler et de déclarer à l’AFSSAPS les incidents et effets indésirables.

*Definition of serious events

- qualification, stockage, etc... pourraient entraîner des effets indésirables sur le donneur ou le receveur. (contamination microbiologique)

   Les événements indésirables graves sont des incidents qui se produisent avec une fréquence anormale et qui peuvent susciter des effets indésirables graves chez le donneur ou le receveur (événement lié à un problème d’inactiveur virale)

   - 1 included (failure or delayed graft function; Risk of infectious disease (viral or bacterial infection))
   - 2 included
   - 3 included (Detection of a CJD few years after the procurement)
   - 4 included (hypocalcaemia entailed in the donor after HSC collection)

- 1 included (examples: serological screening of the donor: not done or incomplete, high percentage of non viable cells)
- 2,3 included
- Additionally: a) Perte accidentelle avant la greffe d’un greffon autologue (réactions indésirables graves chez le patient déjà conditionné pour la greffe)
- b) Mauvaise qualité d’un produit annexé découverte

**Definition of serious reactions

- 1 included (reaction allergique par exemple).

Les réactions indésirables graves sont définies comme des réactions pouvant entraîner la mort ou mettre en danger la vie du patient ou générer chez lui des problèmes de santé graves (réactions neutrophiliques par exemple)

- 4 included (hypocalcaemia entailed in the donor after HSC collection)
- 3 included (Detection of a CJD few years after the procurement)

- 1 included (failure or delayed graft function; Risk of infectious disease (viral or bacterial infection))
- 2 included
- 3 included (Detection of a CJD few years after the procurement)
- 4 included (hypocalcaemia entailed in the donor after HSC collection)

- Additionally: a) Adverse reaction which occur with an abnormal frequency, b) adverse reaction possibly linked to the ancillary product
### European Union Standards and Training for the Inspection of Tissue Establishments

**Member State** | **Reporting system** | *Definition of serious events* | **Definition of serious reactions**
--- | --- | --- | ---
IE - Ireland | Yes, An initial report form for SARs/SAEs is available on the IMB website. Once a report is sent to the IMB, it is reviewed in-house. Further information is requested e.g. actions taken etc. All information is logged in Excel Spreadsheet. A database is to be developed. | - 1, 2 included | - 1, 3 included
|  |  | - 3 excluded | - 2, 4 excluded
IT - Italia | - Yes, there is a local system of reporting to Regional Transplant Centres. - Tissue establishments must have systems in place to report serious adverse reactions to Regional Transplant Centres. Their procedures are checked during inspections by CNT. The CNT national guidelines for tissue banking are under revision. The new version will include instructions for reporting of adverse events and reactions following the requirements of Directive 2006/86/EC | - The term 'serious adverse events' is not specifically defined | - 1 included, but the term 'serious adverse reactions' is not specifically defined
CY - Kypros | No reporting system in place | Not determined | Not determined
LV - Latvija | No reporting system in place | - 1, 2, 3 included | - 1, 3 included

3) La commission nationale de biovigilance
Cette instance, dont le secrétariat est assuré par l’AFSSAPS, a essentiellement un rôle de réflexion et de conseil, notamment sur les mesures à adopter afin d’éviter que les incidents ne se reproduisent ; elle procédera au bilan de ces informations. Elle pourra être consultée par le ministre chargé de la santé et aura la faculté de faire appel à des experts.

Un dispositif analogue s’applique aux activités d’assistance médicale à la procréation et de don de gamètes, mais dans ce cas le pivot central du dispositif est l’Agence de biomédecine à qui les coordonnateurs de centres transmettent les fiches de déclaration d’incidents et effets indésirables.

après la délivrance ou la distribution de ce produit
Contamination bactérienne ou fongique d’un greffon
découverte après la greffe
### Member State Reporting system

<table>
<thead>
<tr>
<th>Member State</th>
<th>Reporting system</th>
<th>*Definition of serious events</th>
<th>**Definition of serious reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT - Lietuva</td>
<td>No reporting system in place</td>
<td>1, 2, 3 included</td>
<td>1, 2, 3, 4 included</td>
</tr>
<tr>
<td>LU - Luxembourg</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| HU - Magyarország | - Reporting system in place  
- Under Section 15/B of Decree of the Minister of Health No. 18/1998. (XII.27.), the NPHMOS regional office must be informed by the health service provider (e.g. tissue bank) about any adverse events that may affect the quality and safety of tissues and cells. The regional office is responsible for taking the necessary measures  
- There are two types of possible complications in case of transplanted tissues and cells: a) transferred infection b) transferred tumour. In case of any of the two, the normal procedure for nosocomial infection shall be followed: it shall be reported to the hospital hygienic doctors and the | - 1, 2, 3 included  
- Addition definition 'seropositivity' added | 1, 2, 3, 4 included |

### Definition of serious adverse events
- In the draft Regulations of the Cabinet of Ministers “Storage, preservation and distribution of human tissues and organs” serious adverse event is defined as untoward occurrence related to the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or a threat to life, disabling or incapacitating conditions for patients or which might result in a prolonged hospitalization

### Definition of serious reactions
- 2,4 excluded

In the draft Regulations of the Cabinet of Ministers “Storage, preservation and distribution of human tissues and organs” serious adverse event is defined as untoward occurrence related to the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or a threat to life, disabling or incapacitating conditions for patients or which might result in a prolonged hospitalization
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</thead>
<tbody>
<tr>
<td>National Public Health and Medical Officers’ Service.</td>
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</tr>
<tr>
<td>MT - Malta</td>
<td>No system in place</td>
<td>- 1, 2, 3 included</td>
<td>- 1, 2 included</td>
</tr>
<tr>
<td>NL - Nederland</td>
<td>Reporting system in place</td>
<td>- The Inspectorate has to be informed. (the system is partly already electronically). Depending on the report the Inspectorate can take immediate measures. Besides that there is an optional system in place where all adverse reactions and events can be reported, so statistics can give more detailed results, etc.</td>
<td>- 1, 2 included</td>
</tr>
<tr>
<td>AT - Österreich</td>
<td>No reporting system in place</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>PL - Polska</td>
<td>- In case of SAR, transplantation team has an obligation to report to tissue establishment. Tissue establishment must report SAR and SAE to NCTCB. - For tissues and somatic cells by National Center of Tissue and Cell Banking - For stem cells (blood marrow, circulating blood) by Pol transplant</td>
<td>- 1, 2, 3 included</td>
<td>1,2,3,4 included</td>
</tr>
<tr>
<td>PT - Portugal</td>
<td>No reporting system in place</td>
<td>Not defined yet</td>
<td>- Not fully defined yet</td>
</tr>
<tr>
<td>RO – Romania</td>
<td>No reporting system in place</td>
<td>The terms “serious adverse effects and serious adverse reactions” are not yet defined in the Romanian legislation, an official regulation is now in legislative process to be approved on this issue.</td>
<td>The terms “serious adverse effects and serious adverse reactions” are not yet defined in the Romanian legislation, an official regulation is now in legislative process to be approved on this issue.</td>
</tr>
<tr>
<td>Member State</td>
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</tr>
</tbody>
</table>
| SI - Slovenija | - No reporting system in place  
- Governmental mandatory system of reporting adverse events or reactions is in preparation | 1, 2, 3 included | 1, 2, 3, 4 included |
| SK - Slovensko | Yes, all serious adverse events/reactions shall be reported to the competent authority and corrective actions shall be taken | 1, 2, 3 included | - 1, 2, 3, 4 included  
- Additional items 'disease transmission, serious infection' added |
| FI - Suomi/Finland | - No reporting system in place  
- Specified regulations and administrative provisions concerning procedures and notification of serious adverse events and reactions will be given after the Act has been approved | All serious adverse events mentioned shall be notified according to the proposal | All serious adverse reactions linked to the quality and safety of tissues and cells (points 1 and 3) shall be notified according to the proposal |
| SE - Sverige | Serious adverse reactions and events can always be reported according to Regulations by the Board (SOSFS 2005:12) and SOSFS 2001:12, but not necessarily in a way as in the directive | 1, 2, 3 included | - 1, 3 included  
- 2, 4 not included |
| UK - United Kingdom | - Yes, Reports of all adverse events/reactions are in place since 2004  
- Verbal report must be made within 12 hours of discovery of incident, followed by a written report within 24 hours. | - 1, 2, 3 included  
- Additional definition 'any incident (or near miss) that may impact of the quality and/or safety of reproductive cells' added | - 1, 2, 3, 4 included  
- Additional definition 'any incident (or near miss) that may impact of the quality and/or safety of reproductive cells' added |
### Member State Reporting system

<table>
<thead>
<tr>
<th>Member State</th>
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<th>*Definition of serious events</th>
<th>**Definition of serious reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Yes, Currently establishments inform us of any adverse events and reactions that occur by e-mail. We also have a system for issuing regulatory alerts to our establishments and other competent authorities – please see annex 1- regulatory alert. - We are currently working with representatives from the sector and other regulators to develop an online reporting system. In April we will put in place an online reporting system for serious adverse events and reactions – please see annex 2 - project initiation document. We have defined an adverse event or reaction as it is defined in 2004/23/EC. - During the 2005 to 2006 period, 41 of the licensed tissue establishments reported adverse events or reactions, 27 of these establishments reported more than 1 adverse event or reaction, and 17 of the establishments reported more than 3. We are currently conducting a more detailed analysis of these reports.</td>
<td>- 1 included - 2 excluded - When the new reporting system is in place, we will collect information on a wide range of serious adverse events and reactions - (information unavailable for 3)</td>
<td>- 1, 3 included - 2, 4 excluded - When the new reporting system is in place, we will collect information on a wide range of serious adverse events and reactions</td>
</tr>
</tbody>
</table>
Détermination de la criticité des événements indésirables

-Assistance médicale à la procréation-

Objectif : Associer un niveau de criticité aux différents événements indésirables survenant au cours du processus d’AMP.

L’évaluation de la criticité sert d’outil de tri afin de déterminer la priorité des actions à mener en hiérarchisant les événements constatés.

La criticité d’un risque est une de ses caractéristiques. C’est un paramètre de décision de la gestion des risques.

Elle intègre deux paramètres :

- la gravité : importance des conséquences directes et indirectes en termes de dommages ou de préjudices, relatives à la survenue d’un événement redouté (cf. échelle de gravité)
La gravité de l’événement indésirable est appréciée dans un premier temps par les professionnels de santé.

- la vraisemblance (ou fréquence ou probabilité) : évaluation qualitative (ou quantitative) de l’occurrence d’un événement au niveau national. Elle ne pourra être déterminée qu’après une mise en place généralisée du dispositif de vigilance et au moins un an de fonctionnement (cf. échelle de vraisemblance)
La probabilité d’occurrence des événements sera déterminée par l’agence de la biomédecine.

La criticité est fonction de l’évaluation de la gravité et de la vraisemblance :

Criticité C = (gravité) x (vraisemblance)
**Echelle de gravité**

<table>
<thead>
<tr>
<th>Classe de gravité</th>
<th>Intitulé de la classe</th>
<th>Nature des conséquences</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Mineure</td>
<td>Diminution de la performance du processus, sans conséquence sur son résultat, et/ou source de contrainte opérationnelle acceptable</td>
</tr>
<tr>
<td>G2</td>
<td>Significative</td>
<td>Dégradation de la performance du processus susceptible ou ayant altéré de façon tolérable son résultat et/ou source de contrainte opérationnelle non acceptable</td>
</tr>
<tr>
<td>G3</td>
<td>Grave</td>
<td>Dégradation de la performance du processus ayant altéré de façon intolérable son résultat.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perte de l’embryon et/ou des gamètes sans disparition des chances de procréation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Altération de la qualité des gamètes et/ou des embryons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complications modérées liées au processus d’AMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risque de transmission d’affection(s) à morbidité modérée accessibles à un traitement</td>
</tr>
<tr>
<td>G4</td>
<td>Critique</td>
<td>Acte ou procédure sur un patient autre (erreur de patient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perte de l’embryon et/ou des gamètes avec disparition des chances de procréation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complications sévères liées au processus d’AMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risque de transmission par les gamètes d’affection(s) à morbidité sévère : affections transmissibles mortelles à long terme</td>
</tr>
<tr>
<td>G5</td>
<td>Catastrophique</td>
<td>Décès au cours du processus d’AMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>incapacité fonctionnelle permanente</td>
</tr>
</tbody>
</table>

**Echelle de vraisemblance**

<table>
<thead>
<tr>
<th>Vraisemblance</th>
<th>Classe de vraisemblance</th>
<th>Ordre de grandeur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basse</td>
<td>V1</td>
<td>Moins d’une fois en 2 ans</td>
</tr>
<tr>
<td>Moyenne</td>
<td>V2</td>
<td>Plusieurs fois en 2 ans</td>
</tr>
<tr>
<td>Haute</td>
<td>V3</td>
<td>Plusieurs fois par an</td>
</tr>
</tbody>
</table>
• **Échelle de criticité**

L’échelle de criticité est à usage interne au sein de l’Agence de la biomédecine

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>V3</td>
<td>C2</td>
<td>C2</td>
<td>C3</td>
<td>C3</td>
<td>C3</td>
</tr>
<tr>
<td>V2</td>
<td>C1</td>
<td>C2</td>
<td>C2</td>
<td>C3</td>
<td>C3</td>
</tr>
<tr>
<td>V1</td>
<td>C1</td>
<td>C1</td>
<td>C1</td>
<td>C2</td>
<td>C3</td>
</tr>
</tbody>
</table>

- **C1** Acceptable en l’état
- **C2** Acceptable sous contrôle
- **C3** Inacceptable

<table>
<thead>
<tr>
<th>Classe de criticité</th>
<th>Niveau du risque</th>
<th>Élément de décision associé</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Accepté en l’état</td>
<td>Pas d’action à entreprendre dans l’immédiat</td>
</tr>
<tr>
<td>C2</td>
<td>Acceptable sous contrôle</td>
<td>On doit organiser un suivi en termes de gestion du risque</td>
</tr>
<tr>
<td>C3</td>
<td>Inacceptable</td>
<td>On doit refuser la situation et prendre des mesures de réduction des risques</td>
</tr>
</tbody>
</table>

L’acceptabilité du risque est une notion subjective liée à la perception du risque qu’a l’entité qui prend la décision. Elle est également dépendante du contexte socio-économique et culturel. Elle peut varier en fonction des différents cas qui se présentent et relèvera d’une décision politique par l’autorité compétente. Tous ces éléments constituent un facteur k qui peut parfois influer sur le niveau de criticité.

**Criticité C = gravité x vraisemblance x k**
## Fiche de BIOVIGILANCE

**Direction de l’évaluation des médicaments et des produits biologiques**  
**Département de l’évaluation des produits biologiques**  
**Cellule de biovigilance**  
**Téléphone : 01.55.87.35.16**  
**Fax : 01.55.87.34.92**

1. Déclarant(s)

1.1 À remplir par le signalant  
1.1.1 Identité du signalant  
Nom :  
Prénom :  
1.1.2 Qualité :  
1.1.3 Coordonnées du signalant  
Téléphone :  
Fax :  
E-mail :  
Adresse :  

1.1.4 Tampon du service signalant

1.2 À remplir par le correspondant local de biovigilance  
1.2.1 Identité du correspondant local de biovigilance  
Nom :  
Prénom :  
1.2.2 Qualité :  
1.2.3 Coordonnées du correspondant local de biovigilance  
Téléphone :  
Fax :  
E-mail :  
Adresse :  

2. Produit(s) concerné(s)

2.1 Nature du greffon ou du produit mis en contact avec le greffon  
2.2 N° identification (référence ou n° de lot)

3. Patients impliqués

3.1 Donneur  
3.1.1 Statut :  
Vivant  
PMO  
PPM  
Inconnu  
3.1.2 N° identification :  
3.1.3 Sexe :  
M  
F  
3.1.4 Âge :  
3.1.5 Date du prélèvement :  
3.1.6 Lieu de prélèvement :  

3.2 Receveur  
3.2.1 N° identification :  
3.2.2 Sexe :  
M  
F  
3.2.3 Âge :  
3.2.4 Date de greffe :  
3.2.5 Lieu de greffe :  

(1) PMO : prélèvement multi-organes ; (2) PPM : prélèvement post-mortem (« à cœur arrêté »)
4. Description de l’incident et/ou de l’effet indésirable

4.1 Date de survenue : 

4.2 Description :

4.3 Conséquence(s) effective(s) ou possible(s) :

5. Autre(s) receveur(s)

5.1 Autre(s) receveur(s) d’organe et/ou de tissus et/ou cellule : 

5.1.1 Nature du greffon
5.1.2 N° identification
5.1.3 Date de greffe
5.1.4 Site de greffe

5.1.5 Pour les tissus et/ou cellules : indiquer les coordonnées de la banque de tissus ou de cellules :

6. Action(s) mise(s) en œuvre

6.1 Description des actions mises en œuvre

6.2 Autre(s) correspondant(s) de biovigilance informé(s) :

6.3 Autre(s) ) vigilance(s) informée(s):

6.4 Autre(s) équipe(s) de greffe informée(s):

6.5 Date d’information à l’ABM inter-régional (ex EfG) :
Appendix 4: HFEA Incident Matrix

Incident reporting protocols: Appendix II

Risk matrix used to assess the severity of incidents and near misses, and the likelihood of a recurrence:

STEP1: Taking account of the current controls in place and their adequacy, how likely is it that this particular incident will occur again? Is this at this particular centre or all centres?

Probability of recurrence:

<table>
<thead>
<tr>
<th>Level</th>
<th>Descriptor</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Almost Certain</td>
<td>Likely to occur on many occasions</td>
</tr>
<tr>
<td>4</td>
<td>Likely</td>
<td>Probable but not persistent</td>
</tr>
<tr>
<td>3</td>
<td>Possible</td>
<td>May occur occasionally</td>
</tr>
<tr>
<td>2</td>
<td>Unlikely</td>
<td>Not expected to happen but possible</td>
</tr>
<tr>
<td>1</td>
<td>Rare</td>
<td>Difficult to believe it could happen again</td>
</tr>
</tbody>
</table>
**European Union Standards and Training for the Inspection of Tissue Establishments**

**Document Type:** Minutes Deliverable Other: (Specify) Report  
**Version:** First Draft Draft no.: 2 Final approved  
**Drafting Date:** 04 December 07 Approval Date:  
**Status:** Confidential – level 1 (partnership only) Confidential – level 2 (partnership and key collaborators) Consultation Public

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**RC(06)15**

**STEP2:** Again, taking account of the conditions and current controls in place and their adequacy, how severe would the consequences be if this incident occurred again?

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Actual or potential impact on individual</th>
<th>Actual or potential impact on organisation</th>
<th>Numbers affected</th>
<th>Potential for complaint or litigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Severe</td>
<td>Death of patient/staff, loss of ALL samples for many patients</td>
<td>Multi-agency investigation, adverse publicity, prosecution, loss of HFEA licence</td>
<td>One (e.g. death) or many e.g. minor deviation failure</td>
<td>Litigation expected/certain Possible prosecution</td>
</tr>
<tr>
<td>4</td>
<td>Major</td>
<td>Major harm, professional misconduct, loss of all samples for few patients, recurrent significant breach of COP</td>
<td>Costs, reputation damage, impact on staff morale, disciplinary hearings, loss of HFEA licence or conditions on practice</td>
<td>Smaller numbers 2-5</td>
<td>Litigation expected/certain. Action taken by professional organisations e.g. HSE, MHRA or GMC</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Semi-permanent harm, loss of all samples for one or loss of most samples for some patients, significant breach of COP</td>
<td>HIXIDOR or MHRA reportable, compensation costs (complimentary cycle)</td>
<td>1-2</td>
<td>Litigation possible but not certain. High potential for complaint</td>
</tr>
<tr>
<td>2</td>
<td>Minor</td>
<td>Short term injury, minor breach COP, avoidable risk, loss of 1 of many samples for a patient</td>
<td>Minimal risk to organisation</td>
<td>1</td>
<td>Complaint possible, litigation unlikely</td>
</tr>
<tr>
<td>1</td>
<td>Insignificant</td>
<td>No injury or adverse outcome</td>
<td>No risk to the organisation</td>
<td>1</td>
<td>Complaint and litigation unlikely</td>
</tr>
</tbody>
</table>
**European Union Standards and Training for the Inspection of Tissue Establishments**

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**RC(06)15**

**STEP 3: Risk Level Estimator**

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Almost Certain 5</th>
<th>Likely 4</th>
<th>Possible 3</th>
<th>Unlikely 2</th>
<th>Rare 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe 5</td>
<td>23</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Major 4</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Moderate 3</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Minor 2</td>
<td>19</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insignificant 1</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Green 1-5 Grade C**
- Information only incident.
  - Add to database as grade ‘C’ & save report form to TRIM.
  - Acknowledge & close, no paper records required.

**Yellow 6-12 Grade B**
- Incident investigation required.
  - Add to database as grade ‘B’ & save report form to TRIM.
  - Request details to examine adequacy of risk precautions, management controls & revised protocols.
  - Site visit & incident inspection if appropriate.
  - Equipment quarantined if appropriate.
  - Liaise with external agencies & internal stakeholders.
  - Maintain contact with reporter until risks adequately controlled and file closed.
  - If presented to LC peer reviewed report required.
  - Incident & trend analysis. If appropriate, dissemination of information to other centres via HFMA Alert process, quarterly publication (Update) and/or centre’s external.

**Red 15+ Grade A**
- Incident inspection required.
  - Add to database as grade ‘A’ & save report form to TRIM.
  - Notify internal stakeholders.
  - Maintain contact with reporter – ensure equipment quarantined where appropriate.
  - Arrange site visit and incident inspection.
  - Incident inspection report.
  - Incident & trend analysis. If appropriate, dissemination of information to other centres via HFMA Alert process, quarterly publication (Update) and/or centre’s external.
Appendix 5: HFEA Alert system

RC(06)15

Appendix V: The publication of an HFEA Alert

Standard procedures for the dissemination of learning outcomes following an incident(s) and/or 'near-miss'

HFEA Alerts are issued to share experience and learn from what has happened elsewhere. Alerts will provide an opportunity for all centres to develop their protocols to avoid similar situations occurring. The decision to issue an Alert is taken by the HFEA Alert Team, led by the Head of Clinical Governance and Patient Safety (HoCG) and the Inspector for Incidents.

STEP 1:
The first draft. Version 1.0 is prepared by the HoCG or the Inspector for Incidents, in consultation with the team of Inspectors and Director of Regulation.

Where appropriate, the author(s) will research the subject matter and maintain a list of references for quality control. The research exercise may involve advice from expert sources, collaboration with other agencies and consultation with professionals from different disciplines.

Alerts are prepared in a standard format and details are edited so that centres and patients cannot be identified.

If the HoCG is unavailable, decisions relating to an Alert will be taken by the Director of Regulation.

STEP 2:
The HFEA peer review process. The first draft (version 1.0) is peer reviewed by one or more HFEA Inspector(s) for accuracy and technical detail.

Version 1.1 is saved and passed to a member of the HFEA communications team for editorial purposes (spelling, grammar, sense, style etc.). The edited/proof-read version (1.2) is saved and the version is used going forward.

During the review process, the names of the HFEA reviewers and the date are recorded within the document.

<table>
<thead>
<tr>
<th>Author 1:</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author 2:</td>
<td>Date</td>
</tr>
<tr>
<td>Technical Reviewer</td>
<td>Date</td>
</tr>
<tr>
<td>Editorial Researcher</td>
<td>Date</td>
</tr>
</tbody>
</table>
Publication of an HFCA Alert, continued...

STEP 3:
Maintaining contact with the incident reporter(s) at the centres involved.
The proof read version is circulated to the PR at each centre involved for information only. The HFCA seeks confirmation that the patients involved have been informed and will offer the centre an opportunity to correct any inaccuracies in the draft.

No alert can be sent out until the HCC has received written confirmation from the centre concerned that all patients involved in the incident have been informed of the incident.

STEP 4:
The publication process:
Once comment has been received from the centre(s) and the alert modified as necessary, the draft must be circulated to the review panel, which comprises:

- Director of Regulation and Head of Inspection
- Director of Communication and Press Office
- HFCA Legal Advisor
- Sue Arery
- Debbie Barber Chair Fertility Nurses Group (Debbie.Barber@fert.org.uk)
- Andrew Rickel
- Richard Kennedy

These reviewers of the draft must be given a reasonable deadline for feeding back comments. If there are numerous revisions, a further editorial review will be undertaken by a member of the HFCA communications team.

At the same time that the draft alert is sent to the review panel, the Business Process Manager must be notified that an alert is expected to be circulated within 8 days. This gives proper opportunity to include the activity in the business and IT schedule.

The circulation is sent to:

- HFCA Members
- HFCA Directors
- HFCA Inspectors (external)
- PR at Licensed Centres
- Regulation
- Press Office
- HFCA External Advisors
- HFCA office based staff
- Where appropriate, the HCC, MHRA, HSC etc

The final version is published online (www.hfca.gov.uk) and circulated by email to the stakeholders listed above. The email communication will remind PRs of their responsibility for the dissemination of information to all staff (including transport and satellite centres) and also, a reminder on how to obtain a password to access the Internet site.

The HFCA will also notify centres of the publication via the HFCA circular UPDATE.