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Conference Opening
Artur Kaminski welcomed the conference participants to Warsaw on behalf of the hosts, the National Centre for Tissue and Cell Banking which is based in the Medical University of Warsaw. On behalf of Dr Alessandro Nanni Costa, Director of the Italian National Transplant Centre and leading partner of the EUSTITE project, Deirdre Fehily thanked the hosts for their work in organising the conference. She explained that the conference represented a merging of three planned project activities: an Exploratory Workshop, a Vigilance and Surveillance (V&S) Medical Advisory Committee meeting and the final meeting of the project partnership. She thanked the partners for their flexibility, which had allowed these events to be combined in a way that facilitated the dissemination of the project outcomes to a significantly wider audience.

Dr Fehily informed the audience that the conference participants included representatives of all project partner organisations, large numbers of inspectors and vigilance officers from EU Competent Authorities, both project partners and non-partners. She welcomed many experts and regulators from outside the EU who had contributed to various project activities during its three-year duration and made major contributions to the development of project deliverables. Representatives of key professional societies in Europe and the US were also welcomed. The partnership regretted that the European Commission had not been able to send any representative due to events taking place in Brussels that week that prevented officials from travelling; it was noted that the team working on safety and quality of substances of human origin at the Commission had been exceptionally supportive of the project and had sent greetings to the group for a very successful conference.

A full list of conference participants is provided in Annex 1.

Deirdre Fehily presented the Conference Programme (Annex 2), explaining that the aim was to present the work of the project and to explore some of the unresolved issues that had arisen in the course of the three years. The group would be asked to contribute to identifying future work priorities for the field of tissue and cell regulation.

The participants had each been provided with a removable drive containing all the key project outputs to date (some deliverables would be finalised and submitted after the conference). A wall-chart of the EUSTITE V&S tools was also provided to each participant.
1.1 EUSTITE Inspection Guidelines

Deirdre Fehily presented an overview of the process of development of the EUSTITE Inspection Guidelines. The Inspection Guidelines are now in a second edition. The first edition, delivered to the European Commission in September 2007, was based on existing related guidelines from regulatory authorities (ABM, AFFSAPS, Belgian and CNT guidelines, EMEA-GMP, FDA,) and from professional societies and other relevant organisations (e.g. AABB, AATB, JACIE ISO). Partners, professional stakeholders and Competent Authorities had participated by commenting on the first edition and on the draft second edition, during an open consultation.

Early in the project, an exploratory workshop was hosted by the Irish partner, IMB, in Dublin in May 2007 with the purpose of clarifying what worked well in inspection practice and what principles should be incorporated in the Inspection Guidance. Many Member States (MS) did not have an actual system in place at that time. Experts and regulators from many MS attended and presented the strengths and weaknesses of their systems. Rapporteurs and facilitators were appointed, who captured the points raised and the consensus reached and produced a detailed report from the workshop. The documented discussions, key points and recommendations were central to the subsequent development of the inspection guidelines.

A Questionnaire Survey on inspection systems in the EU was led by Spain (ONT), and received very good feedback (87%). This survey report was published in the journal “Organs, tissues and cells” in 2008, and provided an important basis for the further development of the draft guidelines. It demonstrated that inspections systems were at an early stage of development in most EU MS and that the organisations which had been delegated the responsibility for inspection had widely varying experience and competencies.

A series of exchanges between partners to observe inspections in other Member States (9 in total) also provided very good information for the development of the guidelines. During these exchange visits, organised jointly by IMB and HF EA, agreed written procedures were followed by the observers and observations were documented in a structured way using standard forms. A long list of key points of good practice was collated for use in the development of the inspection guidelines.

Some of the key contents included in the final version of the Inspection Guidelines (edition II) were presented:

- Qualification and training of inspectors, inspection criteria and frequency, (it was difficult for many Member States to have the inspection every 2 years, EUSTTIE recommended a
full on-site inspection every 4 years with the possibility of organising thematic inspections in between).

- Defining types of inspections (full inspection, re-inspection, process-related or 3rd party inspections) - the inspection of 3rd party should be risk based, and according to specific guidance and criteria.

- Describing the Criteria for the scheduling of routine inspections.

- Establishing the need for planning of the inspection, and the reporting that followed (deficiencies: Critical/Major/Other)

- Stressing the need for evaluation of the inspection system performance.

It was noted that there remained some unresolved areas where further work was needed. For example, the verification of procurement conditions, verification of adequate air quality, coding and traceability and handling of fraudulent or illegal activities were all areas that were considered to require further work.

Deirdre Fehily informed the participants that the final version of the guidelines had been used by the European Commission during 2009 as the basis for the agreement with all MS Competent Authorities on inspection practice. Key elements of the text had been used as the basis of an EU Decision, which will be legally binding in the EU, and is likely to be adopted in 2010. The remaining guidance has been incorporated into a ‘Manual for Competent Authorities’ which will be issued as an Annex to the Decision and will not be legally binding.

Deirdre Fehily thanked all those who had contributed to the development of the document, which had become an important instrument for the standardisation of the inspection of tissue and cell procurement and tissue establishments in the EU.

1.2 EUSTITE Training of Tissue and Cells Inspectors  
- Johann Kurz, Ministry of Health, Austria

Johann Kurz described the training programme that had been developed during the course of the project. The purpose of the training courses was to promote harmonisation of inspection procedures in the EU, on the basis of the EUSTITE Inspection Guidelines. It was noted that there is a wide variety in the backgrounds of the inspectors who participated in the training programme, from public health inspection to GMP and blood inspection and including some inspectors that had background in tissue and cell banking.

The training programme included a 3-day residential course which was preceded by 7-weeks of e-learning, during which participants were expected to dedicate at least 1 hour/day. A tutor was
allocated to each week to collate the documents and to be available to answer questions and join in discussions on the weekly forum. A total of 61 documents were provided for review by participants. The subjects addressed related to inspection techniques, EU provisions, disease transmissions, vigilance management, import/export situations and risk assessments. From week 2 to week 7, participants were required to complete at least one self-assessment quiz each week. It was noted that the backgrounds of the inspectors did not influence their success in completing the quizzes.

Johann Kurz presented the e-learning platform. It was clear that it had improved with each edition of the course. The platform will be maintained by the University of Applied Sciences in Vienna so that all those who participated in the courses can continue to communicate with each other in the discussion forum.

It was reported that 71 participants from 26 Member States and 2 EEA countries had completed the training course under the guidance of 7 facilitators.

The first residential course was held in Austria in September 2008, which was followed by courses in Bulgaria in 2008, in Denmark and in Italy in 2009. During the courses, participants took part in discussions of case studies which had been designed to highlight many of the key issues where a common approach was necessary and sometimes challenging. Behavioural aspects of inspection and questioning techniques were explored in role-plays and participants worked in small groups to classify deficiencies identified during inspections.

The training programme had been evaluated very positively by the participants and at the end of the 4 courses there were still 25 inspectors waiting for a place on the training programme. Johann Kurz thanked the tutors and congratulated all 71 inspectors who had completed the programme.

During the discussion that followed the presentation, it was agreed that the objective of the training programme was not to fully educate an inspector, as further training would always need to be provided within the Competent Authority in the Member State and there would always be the need for continuing education. The idea was rather to promote a common approach to the implementation of the regulatory requirements of the tissue and cells directives. It was noted that there are some options for continued training, including the annual meeting of the Expert Circle for Blood and Tissues of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

1.3 NorPEP –The Nordic partnership for the EUSTITE project
–Michael Cox, Danish Medicines Agency

Mike Cox, of the Danish Medicines Agency, presented an overview of the role and activities of NorPEP (the Nordic Partnership of the EUSTITE Project) which had representatives of the different regulatory Agencies from Denmark, Finland, Iceland, Norway & Sweden. The first of three annual meetings was held in September 2007 and their principal objectives were to:
• provide a useful forum for exchange of national systems and practices;
• provide mutual support in the implementation of the relevant Directives;
• support the outcomes and principles of the EUSTITE project;
• provide input to the working groups of the EUSTITE project;
• collaborate in survey schemes for national healthcare practices.

The representatives and inspectors of the Agencies shared views and national approaches on the implementation of regulations and site inspections, the management of procurement sites, serological testing of obligatory biological markers, the systems for the management of “direct distribution” and the data set for the obligation for public registers of tissue establishments.

At other meetings the focus was directed towards risk assessments by responsible persons, the fate of tissues and cells stored prior to the adoption of the Directives, environmental standards for processing sperm cells within IVF clinics, the interface with newer regulations for advanced therapy medicinal products, and the approach to management of distributors of human tissues (e.g. DBM’s).

One important difference between the countries in the group was that some countries had more than one agency controlling the roles of inspection and certifications, which might make it more complicated to move implementation forward.

Meeting notes and abstracts of the meetings have been placed at the EUSTITE website and submitted to the dissemination work package leader for inclusion in the project dissemination reports. The NorPEP scheme continues to be a beneficial forum for exchanging views on interpretations and regulations. It has an informal communication network between the countries with direct links and access to the activities/work programmes of EUSTITE.

At a prior meeting held in Oslo, Norway the NORPEP partners fully supported the continuance of this self funding Nordic forum into 2010 and beyond.

Session 2
Challenges of Implementing the Tissues and Cells Directives in Decentralised Inspectorates
Chair: Jacinto Sanchez Ibanez – Competent Authority, Galicia, Spain

Jacinto Sanchez Ibanez opened the session by describing the situation in 2000 where some European partner countries had little or no regulation. When the European directives for tissues and cells were published there has been a real need for harmonization of both practice and inspection across the EU community.

The different organisational and authority structures in various countries have led to a number of different ways of addressing the challenges of the transposition of the Directives and the harmonisation of inspection methodologies. Dr Sanchez Ibanez introduced three case study
presentations, each describing the particular challenges of implementing the regulations in countries where there are decentralised regulatory approaches.

2.1 Case Study 1: Spain - Harmonising Regulation in the Autonomous Communities  
- Gregorio Garrido Cantarero, Spanish National Transplant Organisation (ONT).

Gregorio Garrido Cantarero began by explaining the demographics of Spain. Spain has a population of 46 million people; it is a constitutional monarchy and is one of the most decentralised countries in Europe. There are 17 autonomous communities, each with their own parliament, government, public administration, budgets and resource management and their own health and educational system. Within this system there are three levels to the network of transplant coordination: National, Regional and Hospital. Dr Garrido Cantarero went on to describe some of the transplant statistics, including that there have been over 70,000 organ transplants over the last 15 years and that over 300,000 patients had received tissue transplants between 1997 and 2008. There are 165 Tissue Establishments in Spain.

It was into this complex network that the European Directives on tissues and cells were introduced. In 2006 a Royal Decree regarding the quality and safety of human tissues and cells was issued to transpose the Directives. The main challenges were how to register the authorised centres; how tissue activity was to be reported, traceability of the tissues and cells, biovigilance and how to inspect the tissue establishments.

There has been a requirement for all centres to be registered with the Competent Authority of each autonomous community, including the submission of an annual report of activity and progress. Biovigilance is conducted at a national level via the transplant coordination network. A tissue activity report is published annually and sent to the European Commission.

The health authorities of the 17 autonomous communities form the 17 competent authorities for tissues and cells. The Organizacion Nacional de Transplantes (ONT) has the responsibility for approving the inspection plan and harmonising the inspection criteria and for establishing the required qualifications of inspectors. At the time of this conference the ONT had succeeded in carrying out a survey regarding inspections in the autonomous communities, had produced guidelines for inspection and developed a training course for inspectors, based on the EUSTITE inspector training course. In conclusion, Gregorio Garrido Cantarero presented an outline of future plans: to develop a national programme of inspections and to carry out inspections at all the Tissue Establishments using the established guidelines.

There are further plans to develop the Tissue Establishment working group into a formal committee, to improve the guidelines using the inspectors’ experience and comments, to provide an annual training course for inspectors and to extend the inspections to transplant centres.

A delegate from the audience asked how the traceability registry worked across country borders and how tissues are registered. Dr Garrido Cantarero responded by saying that all tissue coming from
outside Spain is required to be imported via a tissue establishment. The traceability and quality issues then become the responsibility of that tissue establishment.

2.2 Case Study 2: Germany – Harmonising Regulation by the Laenders.

- Isabel Astner, Chairperson ZLG - Expert Group, Biotechnology and Tissues.

Isabel Astner began the session by describing some of the challenges to the harmonization of regulation in Germany. Germany has a federal system of government and there are a number of differences Competent Authorities. Although the EU Tissue Directions have been transposed into German law, each Lander has a different way of working, individual administration and structure of inspectorates. There are joint inspections between inspectorates, such as clinical and pharmaceutical inspectorates, but further work is required for harmonization of inspection.

The Zentralstelle der Länder (ZLG) has the task, via working groups and committees, of creating a harmonised quality assurance system for the German inspectorates, bringing together tissue vigilance and pharmacovigilance inspections. Members of the expert group have joined inspectors on inspections to support their understanding of the role and to help in the development of standard operating procedures, quality assurance documents and inspection documentation. The working group has developed training programmes and workshops for inspectors and tissue establishment staff.

The ZLG has a comprehensive website providing, in both English and German, information about: medicinal products; expert groups (EFG); a directory of authorities and institutions; pharmaceutical legislation; quality assurance/management documents and links to all the Laender Competent Authorities. The website also provides access to all the training programmes and inspection documentation developed by the expert groups.

Implementation of European Directive 2004/23/EC - 2001/83/EC has been carried out by the Competent Authorities and through two separate but related routes or methods. Tissue establishments that provide products destined for the commercial market, and are using industrial methods of tissue manipulation, are inspected by the process of Good Manufacturing Practice (GMP) and by GMP-trained inspectors. Establishments using non industrial methods, where the product is not destined for the commercial market, use a slightly different process of GFP (Gute Fachliche Praxis). Both methods require inspection and licensing but have different licences and authorisation procedures.

A delegate asked what the difference is between GMP and GFP and further commented that there shouldn’t be any difference in the way different tissue establishments are inspected. Irrespective of the methodology of inspection there should be no difference in the standard of inspection or the expected quality of service provided at the tissue establishment. Dr Astner commented that GFP is not a “GMP lite” but a mixture of ISO and GMP using a less technical language that is more easily understood.
Isabel Astner was asked how common standards are maintained when issuing centre licences across regions or countries. Licences/certificates are issued by local Laenders but the long term goal is to have a bilingual form that references all the EU Tissue Directives for easier recognition by everyone.

In conclusion, Isabel Astner described a complex process of federal and Laender government working together with Competent Authorities developing common inspection practices, inspector training and supporting guidelines and documentation.

2.3 Case Study 3: France: Harmonisation of ART Regulation across the Regions of France; - Philippe Fourchtein, Agence de la Biomédecine.

Philippe Fourchtein began by describing the French experience by presenting the responsibilities of each organisation involved in the inspection and licensing of Assisted Reproduction Technology (ART) tissue establishments. The central coordinating organisation is the French Biomedicine Agency which has the responsibility for drafting of the inspection frame of reference; technical training of the inspectors; assisted reproduction treatment vigilance and the provision of technical support for the inspections. The Agency also publishes an annual national summary of inspection reports.

There are also 22 regional agencies in charge of inspections and granting authorisations.

Across France around 187 different ART sites must be inspected. 104 clinical and biological centres declared ART activity in 2007. The biological centres are structured in various ways: for example one laboratory can work with several different clinical centres and can be co-located or on different sites.

Philippe Fourchtein described how inspections are performed by medical doctors and pharmacists who are also public health inspectors. The inspections are carried out according to a national frame of reference. The final report highlights any variation to regulation and one copy of the report is sent to the French Biomedicine Agency.

The actual inspection process is very time-consuming and detailed. There are three evaluation levels: a risk evaluation is carried out on each individual item subject to inspection and a risk level determined for each item; a risk evaluation of a grouping of items describing whether the group reaches a satisfactory standard (acceptable; intermediate or insufficient levels of risk evaluation). Finally an overall inspection involves an evaluation of the overall organisation and the running of the centre.

Inspection is largely based on expert knowledge and experience and current professional thinking. The process normally takes approximately 5 days and includes: 1 day of preparation; 2 days of inspection; 1 day for report writing and 1 day for follow-up with the centre.
The inspectors receive 3 days training in assisted reproductive therapies and vigilance and are all doctors and pharmacists with at least 10 years experience in their field. Where required, the inspectors can co-opt other experts to advise or accompany them on inspections.

In conclusion harmonisation of inspections in France relies on a common frame of reference for inspection and common training for inspectors. The annual report of all inspections in France submitted to the French Biomedicine Agency provides an exchange of information between the regional hospital agencies and the decentralised centres which can only lead to a more consistent and harmonised level of inspection.

In summary the key points from across the three case studies include:

In all three countries there are complex levels of government. The responsibilities for implementation and regulation of the tissue establishments and ART centres have been devolved to the competent authorities in each region. The overall goal is to harmonise the way that the competent authorities inspect, accredit and license establishments through the development, implementation and evaluation of common methods of inspection and inspector competencies.

There is some cross border cooperation between smaller member states with joint training of inspectors and joint inspections and this should be expanded further. Inspectors working together across regions and countries prevent them from becoming isolated or having so few inspections that skill and competencies become stagnant. Cross border inspections can become complicated. They can be difficult to organise, there may be different laws, regulations and languages to which the inspectors need to adapt. But even with these challenges joint working can be very effective and enriching for the inspectors and tissue establishments.

Ján Koller introduced the session, explaining that small Member States face particular challenges in the implementation of the tissue and cell directives. He quoted the legal basis for inspections of tissue establishment, Article 7 of the Directive 2004/23/EC: Inspections and control measures according to which every Member State is obliged to ensure that the Competent Authority or Authorities organise inspections on a regular basis and that appropriate control measures are in place for the procurement of human tissues and cells. This is considered to be one of the more challenging requirements for smaller Member States.

Professor Koller chose to define a Small Member State as one having 5 million inhabitants or fewer. According to this criterion, a list of small European states included: Cyprus, Latvia, Denmark, Lithuania, Estonia, Malta, Finland, Ireland, Slovakia and Slovenia. (Non-Member States
but applicant countries or EEA members of this size included: Croatia, Liechtenstein, Norway and Iceland).

The 14 states above were sent a simple questionnaire concerning the following topics:

1. Competent Authority in the country
2. Authorized Inspection Authority
3. Total number of tissue establishments assigned for inspection. (total numbers of single tissue banks, multi-tissue banks, HPC banks, cord blood banks, ART centres/banks)
4. Total estimated number of inspectors needed (an optimum)
5. Total number of inspectors already trained
6. Total number of inspectors already available
7. Presence of any legal guidance for CA inspectors

Responses were received from 8 countries: Cyprus, Denmark, Lithuania, Estonia, Finland, Slovakia, Liechtenstein and Norway. In most of the countries there was one CA, in Denmark and Norway two authorities. In most of the countries, the inspection authority is identical to the CA. A separate authority is responsible for inspection in Lithuania, Norway and Liechtenstein (here an agency from Switzerland is involved). The number of tissue establishments in the countries concerned varies, e.g. the highest number was reported by Denmark (in total 121, the majority of which, 76, are tissue establishments for Assisted Reproductive Technology); a low number of tissue establishments was reported by Estonia (5) and Lithuania (6). Liechtenstein reported a lack of tissue establishments. The number of inspectors available was in most reported cases fewer than the number needed or trained. Except for Denmark, guidance for inspectors does not exist in any of the countries that reported (no data from Norway available).

To explore the challenges of small Member States in more depth, Professor Koller introduced speakers who presented a series of 3 case studies.

3.1 Case study 1: Malta
- Richard Zammit, Ministry of Health, Malta

Richard Zammit, outlined the situation of Malta as a small Member State and the current situation in the field of cell and tissue banking in this country.

Geographic and demographic data concerning Malta were presented: Malta is an island country to the south of Sicily, of 316 sq. km, with a population of about 413,000 citizens. It was stressed that apart from the permanent inhabitants, around 1.3 million tourists visit the country each year. Malta joined the EU in 2004. It was underlined that Malta, as a disproportionately small state, attaches a lot of weight to collaborating with EU partners.

Dr Zammit proposed that the best solution for small Member States like Malta to the challenge of implementing good regulation is networking with other Member States. Malta has been present in
EU structures for a short time but, on the other hand, Europe - its culture and people - have been present in Malta for ages. For example Malta used to be a strategic meeting point for the Crusaders. The cultural proximity of Malta to Europe is a fact. It was stressed that Europe sets high standards that Malta is eager to follow. This is a motivating factor for progress. At the same time, Malta needs to find its own way to handle cell and tissue banking and create its own strategy. Options considered in this respect were:

1) organic growth (this option would mean a very slow development rate);
2) outsourcing (this would result in lack of control on the national level);
3) merging (Malta would be disproportionately small to be a part of a merger);
4) strategic alliances.

Malta has opted for option 4 which essentially means that it aims to learn from partners. In this context, Dr Zammit stressed that the EUSTITE project had been a ‘God-send’.

Currently, tissue/blood establishments operating in Malta are the following: one blood establishment (public) - 20,000 units distributed yearly; two cord blood collectors (private) - <200 units collected annually; one cornea eye bank (public) - <20 corneas transplanted each year; one IVF establishment (private) - <50 IVF cycles a year. There is one CA responsible for substances of human origin of all kinds (blood, cells, tissues and organs). Malta cooperates in all of the above sectors with European countries: Ireland (blood establishments), Belgium and Germany (cord blood collectors), Scotland (cornea eye bank), Italy (IVF).

Taking into account all of the above, Malta, in spite of its size, is capable of managing the tasks in the field of cell and tissue banking within the EU for the benefit of patients.

3.2 Case study 2: Cyprus
- Carolina Stylianou, Tissue and Cell Inspectorate, Cyprus

Carolina Stylianou reported on the process of implementing legislation for tissue and cell procurement and processing in the Republic of Cyprus. Apart from implementing the safety and quality aspects of the Tissue Directives, much attention has been paid to financial and market-related issues. For example, all advertising material campaigns and material (brochures, electronic) needs to be approved by the Competent Authority; any person promoting a TE must disclose any personal financial gains to the client/patient; financial audits of T&C Centres by the Competent Authority are permitted. Cyprus also requires all centres to acquire accreditation from a recognised body in the field (if available) after the first 2 years of licensing.

The structure of supervising authorities was presented. The Ministry of Health is the Competent Authority; inspectors for Tissue & Cell Establishments supervise applications, inspections and surveillance of tissue establishments; inspectors report to the Director General, the latter reports to the Ministry of Health. A post of Chief Inspector has been created. The Chief Inspector has a special role in the system. He/she should always be present during the initial licensing inspection
Implementation of the legislation was a multi-step process. The crucial task was to appoint inspectors. Inspectors had to meet certain criteria including: 1. Experience in Tissue Establishment; 2. Academic qualifications and being in a senior post; 3. Involvement in applying quality standards in their workplace; 4. Being trained in Quality Systems 5. The right personality; 6. Willingness to undertake the work. All inspectors were familiarised with the directives, local legislation and the EUSTITE Inspection Guidelines. Healthcare professionals were informed of the new legal requirements through many channels: 1. The Official Government Gazette; 2. The press; 3. Individual Centre notifications; 4. Information on legislation, directives and application available on the Ministry’s webpage. The Customs Department was also notified of the new regulations.

Tissue establishments were invited to register with the new CA. A quick response to the changes was received from private cord blood banks and HPC centres. Both types of establishment have successfully complied with the new legislation except for two private cord blood banks, which collect locally and store in another Member State. ART Centres were slower to respond and it was necessary for the Ministry to issue two notifications, stating clearly that funding for treatments at non-licensed centres would be revoked. Four of the 5 ART Centres inspected required major premises renovation. Apart from tissue establishments, ophthalmic clinics applied too because of the need to import corneas from a non-Member State. Applications were also submitted by 9 companies interested in importing demineralised bone from the US and distributing it to other Member States. The companies are mainly pharmaceutical and medical device importers.

The nine companies raised major concerns. Firstly, they will not import for local use but for distribution in the rest of the EU. Cyprus would then be only an entry point to the EU. Secondly, verification of documents concerning tissue banks in third countries and their meeting EU standards might be impossible in practice; traceability and serious adverse event notification remain an open question in such cases as well. Carolina Stylianou expressed her personal opinion that Cyprus should be prevented from becoming just a commercial gate to the EU without any benefit for Cypriot patients.

To sum up, the audience was informed that, for the moment, a list of licensed centres is posted on the Cyprus Ministry’s webpage and among these there are two HPC donor centres, one stem cell transplantation centre, two private cord blood banks and one ART centre.

3.3 Case study 3: Estonia

- Svetlana Orlova, Ministry of Health, Estonia

Svetlana Orlova began by outlining the historical and geographical background to regulation in Estonia. The regulatory authority in Estonia, the State Agency of Medicines (SAM), was established in 1993 after Estonia gained independence. Estonia entered the EU in 2004. The authority is responsible for regulation and oversight of issues concerning material of human origin:
tissues, cells and organs. The Agency is located in the city of Tartu, which is at a considerable distance from the capital, Tallinn, but within a walking distance of a major number of the country’s TEs. Estonia has about 1.37 million inhabitants, its area is about 45,000 km². A diagram of SAM’s structure was presented. Inspectors are employed in the Bureau of Activity Licences and Inspections, which is a part of the Department of Inspections and in the Department of Biologicals. So far 3 people are employed to conduct inspections and issue licences.

Estonia has its peculiarities e.g. tissue and cell regulations are within the “Organ Transplantation Law”; quality parameters for organs are as strict as for tissues and cells; all Estonian TEs also function as POs (in practice, hospitals are POs and TEs at the same time). There are currently 5 teams involved in procurement from deceased donors (kidneys - 1; musculo-skeletal tissues - 1; blood vessels - 1; corneas - 2). Nine clinics are involved in the procurement of tissues and cells (IVF + ICSI+AUI - 4; HSCs - 2; femoral heads - 1; amniotic membranes - 2). There are 2 bone banks, 1 blood vessel bank, 2 cornea banks (that do not distribute tissue elsewhere although the same tissue is procured) and 2 sperm banks (with distribution of the material to the rest of the fertility clinics in Estonia. Donor material (sperm, kidney and HSCs) is also occasionally obtained from foreign establishments (USA, Scandinavia, Lithuania, Latvia and Germany).

The challenges for inspected establishments were outlined. Generally, procurement is performed on a non-routine basis. Procurement teams are, in many cases, the same as processing and even transplantation teams (the question is raised by them as to whether, in such situations, issuing "product" certificates is actually needed). Team members are usually medical doctors and they also have to deal with organizational tasks (quality systems, validation, qualification). Due to the number of qualified people in the country there might also be problems getting technical expertise. Inspectors are encouraged to gain knowledge very quickly.

By December 2009 all 5 TE, with 12 different procedures, were inspected and licensed. Further plans include hosting a round table regarding the vigilance of specific issues in order to establish a harmonized approach to the vigilance system, re-inspections and educating inspectors in the field of laboratory testing.

EUSTITE’s contribution was assessed as enormous. To date the following items were implemented: TE dossier templates, inspection report templates and the establishment of the principles of a vigilance system.

In the discussion following the presentation, the question of possible professional and scientific cooperation and exchanging resources between Estonia and Finland was raised. It was confirmed by Dr Orlova that such cooperation is being considered. Concern was expressed about the potential role of Cyprus as an entry site for grafts not meeting standards for the European market. Traceability of such grafts would be an issue as well. Cyprus seems to be a target for foreign companies - the taxation here is relatively low. It might be also assumed by such companies that regulations in a small country are less strict. The question of "IVF tourism" in Cyprus was also raised and how this issue is overseen.
Session 4
Challenges of Implementing Some Technical Requirements of the Tissues and Cells Directives
Chair: Patrick Costello, Irish Medicines Board

Patrick Costello introduced the session explaining that, while most of the requirements of the Directives had been implemented without difficulty, it was evident during the EUSTITE project that certain requirements had caused difficulties for regulators. He introduced a series of speakers who reviewed a selection of the most important of these requirements, explaining why they were challenging.

4.1 Case Study 1: Assisted Reproduction Technology – processing facilities and donor/patient testing – Trish Davies, Human Fertilisation and Embryology Authority, UK

The Human Fertilisation and Embryology Authority in the UK (HFEA) was the first regulator of IVF in Europe (established in 1990) and also introduced adverse event reporting in this area. HFEA performs on-site inspections of ART Centres every 2 years, and the maximum timeframe of a licence is 5 years by UK law. Inspections are performed according to a notebook which is based on risk tools representing tissue establishment’s general performance indicators, and the Centre’s Self Assessment Questionnaire (SAQ).

The SAQ is an online questionnaire that is:

- Completed by the Centre itself every 2 years
- Incorporates requirements of the EU Tissue and Cell Directives and the HFE Act
- Enables more focused inspections in specific areas.

An important question in the SAQ is related to air quality. Although Directive 2006/86/EC defines requirements for air quality with reference to GMP grades, ART activity is generally considered to fall within the exceptions described in Annex 1 paragraph 4. In the UK, national requirements have been defined and every ART clinic should have at least a grade C with a background D for processing of gametes and embryos. There is some flexibility though, and it is up to the clinics themselves to demonstrate that they control the air quality adequately via SOPs, air quality reports, particle monitoring, validations and by rating themselves in the SAQ.

Clinicians in general say that it is a problem to perform intracytoplasmic sperm injection (ICSI) in a grade A environment in a grade B room (class II cabinet in a grade B room) but according to HFEA, this is actually quite possible. Experience showed that the ART sector was quite resistant to implementing these requirements compared to other tissue establishments. The HFEA is allowing clinics time to adapt, but issues such as air quality will be enforced more stringently in the future.

A second issue in the ART field that has caused considerable debate relates to testing of donors/patients. Screening is an important topic in HFEA’s SAQ. In the UK, screening of donors of reproductive cells, is not performed in cases of partner donation (direct use). All tests are performed when it is not for direct use (storage), according to T49-T53 licence conditions. All
relevant screening applies to non-partner donations. The clinic should demonstrate their compliance via SOPs and patient records.

During the discussion, it was generally agreed that in the field of ART, air quality does not represent one of the serious risks to patients. A greater potential problem in this sector was identified as the fact that the exact composition of the media used for IVF is not known even by those using the media because of commercial confidentiality issues. The media used in the clinics is not CE-marked for ART purpose. It was stressed that inspectors would not accept that laboratories are not aware of the composition, origin and grade of solutions that come into contact with the tissues and cells.

4.2 Case Study 2: ART – Interpretation of air quality requirements (A in D) for processing of non-reproductive tissues
– Patrick Costello, Ireland

Patrick Costello presented the important factors relevant in obtaining an acceptable controlled environment for the processing of non-reproductive cells. The legislation in this area stems from the 2006/86/EC Directive in which it is stated that “An air quality with particle counts and microbial colony counts equivalent to those of Grade A, as defined in the European Guide to Good Manufacturing Practice, Annex 1 and Commission Directive 2003/94/EC), is generally required.”

Other important standards highlighted were the ISO 14664 and the FDA classification of air quality standards. The background environment should be appropriate for the tissues or cells concerned, but at least equivalent to GMP grade D in terms of particles and microbial counts. If not obtained, the following points are required to be demonstrated by the TE:

- A validated microbial inactivation or terminal sterilisation process
- Evidence that exposure in grade A is detrimental for the tissue/cells concerned
- That application of the tissue/cells to the recipient constitutes a significantly lower risk than direct transplantation
- The grade A environment renders it impossible to carry out the processing.

The different grades of environment can be defined as the following:

- **Grade A:** Local zone for high risk operations, normally achieved by laminar airflow cabinets
- **Grade B:** For aseptic filling and preparation (background for grade A area)
- **Grade C and D:** Clean areas for less stringent stages of manufacturing sterile products.

The limits for the maximum number of particles for each of these grades are defined in Annex 1 of the Directive. It is well recognised that most of the contamination occurring in a clean room is derived from the presence of the staff. Other factors, as potential sources of contamination, are filtration systems and associated machinery. It is therefore of great importance to minimize the number of staff and to properly train the personnel involved in the controlled environments.
Key points:
The key factors are firstly to achieve the proper design of the clean-room, followed by extensive maintenance of the filtration systems and routine particulate and microbial monitoring. The latter should not represent a once off situation. Strict controls are required (i.e. hygiene, clothing, no sinks/drains, smooth surfaces, air locks, positive pressure differentials, etc) in order to maintain the specified standards of an environment. All controlled environments must be specified, to demonstrate and document that the environment achieves the required standards of quality and safety. According to GMP, one can not have a grade A with a background D, because you would not obtain grade A unless you have a background B or C at least. One grade of controlled environment can not exist in isolation and maintaining the standard adjacent to the operational grade is essential for the processing environment. This presents difficulties in inspecting against the Directive requirement.

Dr Costello stressed that while the Directive provides a minimum standard, in the future it is expected there should be a consensus on the appropriate environmental standards for different tissues and cells and that these may be higher than the minimum defined in Directive 2006/86/EC. Perhaps stem cells and heart valves should be processed in an A environment with surrounding B grade and a cascade to C and D outside it. Perhaps it is adequate to process corneas in C or D environments. Perhaps it is adequate for ART processes to be conducted in grade D. He stressed that it should not be left to each tissue establishment to decide this but should be agreed internationally if possible.

4.3 Case Study 3: Inspecting Tissue and Cell Procurement
– Emyr Harries, Human Tissue Authority, UK

The HTA has been licensing storage under the Human Tissue Act 2004 since 2006, and in July 2007 the HTA’s remit was extended through the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) to include the procurement, testing, processing, storage, distribution and/or import/export of tissues and cells for human application. The Directives do not require that all procurement sites be inspected and licensed, but rather that the ‘conditions of procurement’ be authorised/licensed/certified. However, since 2008 in the UK, under the Q&S Regulations, procurement establishments have had to apply for a HTA licence or enter into third party agreements with a HTA licensed establishment. In total, 127 HTA licensed procurement sites were active in 2008.

All HTA licensed procurement organisations are inspected on-site. In many other cases, tissue establishments manage procurement via third part agreements. Third party procurement sites are not inspected directly, but the agreements between the tissue establishment and the third party procuring on their behalf are evaluated during the tissue establishment inspection.

Important points to be assessed during a procurement site inspection are the visual examination of operating theatres and post mortem rooms, compliance with HTA standards, interviews with key staff, audit trails and document review.
During the discussion it was noted that there is a general problem when procurement sites in other countries are not licensed, when tissues/cells are crossing borders and when a tissue establishment wants to use a procurement site in such a country.

4.4: EuroGTPs Project – Developing Technical Guidance for Tissue Establishments

- Jaime Tabera, Transplant Services Foundation, Barcelona, Spain

Jaime Tabera presented the EuroGTPs project, which is funded by the European Commission. The project seeks to develop common Good Tissue Practices (GTPs) for the European tissue establishments, in order to increase the safety and quality of tissues recovered and used for transplantation. It is important to harmonise the techniques used in different countries to achieve the highest quality of the tissues and cells, and thereby reducing the risk of disease transmission.

The three EU Directives, together with the directives concerning advanced therapies (GMP), define regulations and guidelines. In addition, there is a need to have a one regulation based on clinically proven practices. EuroGTPs will combine the requirements of these different regulations. The development of the generic EuroGTPs should include:

- General TE aspects/activities
- Donor selection and evaluation
- Multi-tissue donor procurement.

The goal is a minimum quality criterion for tissues and cells, as the Directive does not regulate tissue evaluation in very specific cases, and therefore might not be strict enough to guarantee minimum standards. Also GMPs are not always applicable to tissue practices.

It is planned to develop a training model and accreditation process for the tissue establishment personnel based on the GTPs.

The project involves 12 partners from 7 different countries. It aims to provide guidance in areas where it is lacking or where the Directives are difficult to interpret, such as the cases that have emerged during the EUSTITE project. It is intended that EuroGTPs that will be developed by the project should be regarded as a tool for inspectors as well as Tissue Establishments.

Initially, only 4 types of tissues are included in the scope of the project (ocular, cardiovascular, musculoskeletal and skin). There will be a second phase of the project (other tissues/cells/ATMPs). The first draft to the European Commission is due in January 2010. Jaime Tabera referred attendees to the EuroGTPs website: www.eurogtps.eu.
### Session 5
**International Tissue and Cell Distribution**
- Chair Johann Kurz

Johann Kurz introduced the session which would highlight the importance of international collaboration in the regulation of tissues and cells.

#### 5.1 International Distribution of Tissues – Scott Brubaker, AATB, USA

Scott Brubaker, Chief Policy Officer of the American Association of Tissue Banks (AATB)

Scott Brubaker outlined the situation in the field of tissue distribution in the United States. He began by providing some context. According to the AATB Annual Survey, there were 30,380 tissue donors in 2007, of which 29,799 were deceased and 581 were living. The information was reported by 55 AATB-accredited and 22 non-AATB accredited tissue banks. 48 tissue banks reported that they distribute tissues. These tissue banks greatly vary in the range of their involvement in tissue distribution: four of them distributed more than 200,000 grafts in 2007; six distributed between 50,000 and 150,000 and the vast majority of tissue banks distributed fewer than 20,000 grafts each. Using the example of bone grafts, Scott Brubaker showed that the number distributed is rising: in 1994 distribution of approximately 208,000 grafts was reported, in 2000 approximately 675,000 and in 2007 approximately 1.28 million were distributed. However, the fact that tissues might be redistributed by intermediaries could also be responsible for part of the growth. Musculoskeletal grafts constituted the majority of distributed grafts - over 1 million - with cancellous bone and tendons common among bone and soft tissue grafts, respectively. The number of distributed soft tissues was highlighted because of their impact on the potential transmission of infectious agents. This type of graft may undergo only decontamination with antibiotics, however, other processing treatments are also used.

Various methods can be applied in order to decrease the risk of transmission of infectious agents. A review of methods applied for bone and soft tissues was presented, based on the AATB Annual Survey in 2007. Most distributed grafts are treated by a proprietary method only (about 800,000 grafts). Other methods applied were: proprietary methods combined with Gamma irradiation (over 600,000), antibiotics and Gamma-irradiation (about 174,000), antibiotics only (over 121,000), irradiation with E-beam only (about 87,000). In this context, a chart illustrating disease transmission by allografts since 1974 was presented (information supplied by Dr. Ted Eastlund). Transmission of infectious agents and diseases such as HIV, HBV, HCV, CMV, EBV, HTLV-1, Rabies, Tuberculosis, Herpes simplex, CJD, yeast, fungi and bacteria had occurred by the use of fresh, frozen and cryopreserved allografts (and, in the case of dura mater, also freeze-dried allografts).

U.S. participation in international tissue graft distribution is considerable. Tissue grafts/devices are exported to 45 countries outside the U.S. (e.g. 80% of the tissue grafts used in Canada are imported.
from the U.S.). 29 of 56 U.S. tissue banks export tissues. The destination countries are: Argentina, Austria, Bahamas, Bermuda, Canada, Chile, Columbia, Costa Rica, Cyprus, Dominican Republic, Ecuador, El Salvador, Finland, Germany, Greece, Guam, Guatemala, Hong Kong, India, Israel, Italy, Japan, Korea/S. Korea, Lebanon, Mexico, Netherlands, New Zealand, Nicaragua, Panama, Peru, Philippines, Poland, Portugal, Puerto Rico, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom and Venezuela.

AATB Standards make reference to the question of graft distribution (in Section H - Distribution and Dispensing). Standards explicitly describe that tissue distribution intermediaries are a part of the system and as such they shall meet certain requirements. But it is the tissue bank's (the processor's) responsibility to establish recipient follow-up data collection protocols.

A new educational tool was presented, a handbook called "Hospital Tissue Management", a result of a joint initiative of the AABB (formerly known as the American Association of Blood Banks), the American Association of Tissue Banks and the Eye Bank Association of America. This handbook already contains a chapter related to tissue distribution and so disseminates the information on the topic discussed in this presentation for clinical practitioners.

In the discussion following the presentation, the question of the definition of "proprietary methods" was raised. Scott Brubaker explained that tissues treated by "proprietary methods" can be understood to be tissues minimally manipulated. These methods should be available to the public by accessing patent files. In the discussion it was also agreed that the transport environment (e.g. packaging configuration and shipping protocols) should be validated. One of the future aims is to introduce uniform methods of processing and culture method validation.

5.2 International Distribution of Gametes and Embryos
- Angela Sutherland, HFEA, UK

Angela Sutherland presented the issue of the movement of gametes and embryos within Europe and worldwide, as seen from the UK perspective.

First, the audience was provided with a short overview, which included information concerning: background, HFEA Direction 0006, the UK process for import and export, a summary of movement, two case studies and discussion.

In the UK, the issues related to the use of gametes and embryos are regulated by the Human Fertilisation and Embryology Act (HFE Act). In 2007, the European Union Tissue and Cell Directives (the EU Tissue and Cell Directives) were embedded within the HFE Act. It was pointed out that the initial HFEA policy allowed movement within the European Economic Area (EEA) to countries that had implemented the EU Tissue and Cell Directives under General or Special Directions (SD). However, subsequent legal guidance recommended that the Authority should only issue SD where premises are “accredited, designated, authorised or licensed…” to the standards required by the the EU Tissue and Cell Directives (Section 24(3A) of the HFE Act 1990). Therefore the key issue now for the HFEA is that the wording of section 24(3A) of UK legislation prohibits
the issue of Special Directions for movement between the UK and clinics within the EEA that have not been licensed by an accrediting body. It has been underlined that this created a comparatively restrictive policy that allows General Directions to be issued for the import from or export to virtually any country outside of the EEA but does not permit movement of gametes or embryos to countries where it is known that the standards are high.

Miss Sutherland detailed information on the requirements to be met for the import and export of gametes under HFEA General Direction 0006. This information was divided into four sections as follows:

- **import** of gametes or embryos into the UK **from the EEA** under General Direction (GD);
- **export** of gametes or embryos from the UK under GD **to an EEA country**;
- **import** of gametes or embryos to the UK **from countries outside the EEA** under GD;
- **export** of gametes or embryos from the UK **to countries outside the EEA** under GD.

An algorithm was presented summarizing the alternative process steps for compliant movement of gametes and embryos.
In the period April 2008 - March 2009, the vast majority of gametes and embryos were imported and exported under the General Direction. In the past year, three applications for Special Directions to export and one to import have been declined.

Two case studies were presented, illustrating the complexity of the issue of embryo movement and the application of Special Directions in this field.

In the discussion the question of systematic registering of embryo and gamete donors and, consequently, of having a Europe-wide overview, was raised. It was stated that neither in Europe nor in the United States is such a general register established. This issue will need to be resolved in the future.

5.3 International Distribution of Haematopoietic Stem Cells
- Per Llungman, EBMT

This presentation was cancelled due to unforeseen personal circumstances. Luc Noel, WHO, gave a short presentation on the subject of haematopoietic stem cells. He underlined the importance of this transplantation field and of the strong and effective international network that had been established to support this global objective. The contribution of scientists and professionals was highlighted. The audience was informed that the World Bone Marrow Transplantation Network was created in 2007. This should help to further enhance international co-operation in stem cell donation and transplantation and would provide an important partner to WHO.

5.4 Ensuring Equivalent Safety of Imported/Exported Tissues and Cells - the US Perspective
- Anita Richardson, FDA, USA.

Anita Richardson, Associate Director for Policy, Office of Compliance and Biologics Quality, CBER, at the FDA, outlined issues concerning the import and export of human cells, tissues and cellular and tissue based products as seen from the FDA perspective. The presentation covered two main topics: a general overview of the United States’ import process; importation of Human Cells, Tissues and Cellular and Tissue Based Products (HCT/Ps), regulated solely under section 361 of Public Health Service Act.

It was explained that the FDA’s objective is to ensure that imported FDA-regulated products meet the same level of protection as domestically produced products. In order to achieve this objective the import process was systematized and generally follows the pattern below:

- A customs broker or self-filer submits entry information to Customs and Border Protection (CBP) on behalf of the importer
- CBP provides entry information electronically to the FDA to enable the FDA to make the admissibility decision
FDA’s electronic system (OASIS) screens the entry against FDA admissibility criteria, and determines whether further evaluation is needed. If no further review or action is required, the entry gets a “may proceed” note and an electronic message is sent to the broker. In case further evaluation of an entry is needed, the FDA staff review it and determine the steps to be taken.

FDA entry information contains the following items: FDA manufacturer, FDA shipper, FDA country of origin, FDA product code, article description, quantity and affirmation of compliance. Reference was made to two of the above entry descriptors and their meaning explained:

- **FDA Product Code** is an alphanumeric code that identifies the specific product and must agree with the invoice description of the product. Product codes (for all products) are available via the FDA’s website at http://www.fda.gov/ora/import/default.htm

- **Affirmation of Compliance (AofC)** is a code indicating or affirming compliance with a specific FDA regulatory requirement. Submission of this code is voluntary, but it may shorten initial screening and further review of the entry. Examples include STN (biological product licence application #), BLN (U.S. biological product licence #).

More detailed information about FDA Detention and Refusal Process was provided. Detention can occur if the FDA discovers a violation under 21 U.S.C. 381(a) or 42 U.S.C. 264. In this case the FDA will issue a Notice of FDA Action, giving adequate notice of the reasons for the detention. The owner or consignee can respond by providing testimony or by applying for reconditioning of the product. Detention does not mean that the article is being physically held. It is under bond, but it is generally still moving at this point.

In case of refusal, the FDA sends out a Notice of Refusal and will ask CBP to issue a Notice of Redelivery. This allows CBP to put the goods under bond if these are not appropriately disposed of. At this point, the articles must either be destroyed or re-exported.

Further details concerning the importation of HCT/Ps in general terms or HCT/Ps for further processing and for research/testing/educational purposes were given. The following general requirements were presented:

- Responsibilities of the importer (the importer is obliged to notify the FDA District Director for the applicable port of entry and provide sufficient information for FDA to make an admissibility decision). While the FDA is determining admissibility, HCT/Ps are permitted to travel to the consignee under quarantine.

- If no AofC is provided or questions arise about the entry, the FDA may request additional information and documentation such as:
- Accompanying records (distinct identification code affixed to the HCT/P container relating the HCT/P to the donor and all records, a statement of donor eligibility and a summary of records)

- Labelling.

In the case of importation for further processing and not for distribution in the U.S. it was stated that the products must be under pre-established criteria to prevent transmission of communicable diseases and in compliance with all applicable requirements (e.g. notification, labelling), and shipped in quarantine (21 CFR 1271.265(b)).

It was underlined that the import requirements do not apply to imported reproductive HCT/Ps if donated by a sexually intimate partner of the recipient for reproductive use, imported Peripheral Stem/Progenitor Cells regulated solely under 361 of the PHS Act, unless they present an unreasonable risk of communicable disease transmission.

Reference was also made to the on-going activities by the FDA which are routine monitoring of imported HCT/Ps, foreign inspections, outreach to the industry & import community, efforts to improve entry data quality (preparation for implementation of PREDICT, the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting, a method of data screening).

Further, the basics and objectives of the PREDICT method were outlined. Implementation of this is expected to improve import screening, prevent the entry of non-compliant goods and expedite the entry of compliant goods. This method should replace the admissibility screening portion of the FDA’s legacy electronic system for processing import entries.

After the presentation, numbers were given to allow everyone to see the importation of tissues and cells in the context. There are about 75,000 entries per year, which fall into the category of biological products. HCT/Ps constitute about 2,200 of these entries.

The material FDA inspectors work on and the impact of European Tissue Directives and the EUSTITE Project on the tissue and cell exchange in the United States attracted interest from the audience. During the discussion, it was explained that the FDA investigators base their work on the electronic entry data provided to the FDA and the instructors provided in FDA Compliance Programs and other policy documents. The FDA supports legislative regulation of cell and tissue grafts and initiatives like EUSTITE. These are highly appreciated because such legislative and organisational frameworks give to the U.S. authorities and users confidence that material and products from Europe are of high quality and free from communicable disease.
5.5 Ensuring Equivalent Safety of Imported/Exported Tissues and Cells - the EU perspective, - Patrick Costello, IMB, Ireland

Patrick Costello, Blood and Tissues Manager from the Irish Medicines Board, outlined the main aspects of the international exchange of tissues and cells from the European perspective, i.e. the legal basis of the exchange, differences between distribution, transport and import, specificity of import/export within and outside of the European Economic Area and the role of the Responsible Person in the exchange of tissues and cells.

Firstly, Article 4 of the Directive 2004/23/EC was cited. This article states that an EU Member State may introduce prohibition of or restriction on the importation of human tissues and cells to ensure a high level of health protection. Further, definitions of basic terms found in an application to import/export were quoted, according to the above Directive. These included: ‘storage’, ‘distribution’, ‘traceability’, ‘serious adverse event’ (SAE), and ‘serious adverse reaction’ (SAR). Next, Article 9 was cited. This article obliges Member States to take all necessary measures to ensure that all imported and exported tissues and cells from/to third countries are undertaken only by tissue establishments that are accredited, designated, authorised or licensed for the purpose of those activities. Furthermore, Article 9 states that Member States and tissue establishments that receive such imports/send such exports shall ensure that these meet standards of quality and safety equivalent to the ones described in this Directive. The crucial role of the competent authorities in enabling international movement of tissues and cells is also laid down in this article.

It was underlined that movement of tissues and cells between countries within European Economic Area actually falls within the definition of transport and distribution and not import and export:

• **Transport** (if between tissue establishments)
• **Distribution** (if between a tissue establishment and a site of human application).

Examples of transport and distribution were presented.

In the case of movement of tissues and cells across an EEA border the terms import and export are applied. Examples of import and export were presented.

With regard to the movement of tissues and cells within the EEA, the validation of and responsibility for transportation can be in two ways:

1. It can be agreed between tissue establishments (movement from one tissue establishment to another);
2. It resides with the tissue establishment (movement from a tissue establishment to the site of human application).

Next, the role of the Responsible Person (RP) in the importation process was outlined. It was stressed that the responsibility for importing tissues and cells resides with the RP. The RP must be
aware of the differences between tissues and cells sourced outside and inside the EEA. It was underlined that if a tissue establishment imports tissues and cells and supplies other tissue establishments, the responsibility resides with this first establishment as the original place of entry.

The audience was reminded that importation and exportation can be carried out in two ways, routine (if a tissue establishment imports/exports to/from particular sites on an ongoing basis) and non-routine/emergency (if a tissue establishment needs to import on an ad-hoc basis). Routine imports/exports can be listed on the tissue establishment authorisation and reviewed during inspection; Non-routine imports/exports must be notified to a local competent authority and approved by it prior to being carried out.

In the discussion the particular circumstances surrounding the international movement of autografts and embryos were stressed as was the role of the Responsible Person as a decision-maker in this respect. It the possibility and usefulness of joint European-American inspections of tissue establishments (since cell and tissues are exchange between Europe and North America) was also touched on. Doubts were raised concerning funding of such inspections.

Session 6
Reporting Serious Adverse Events and Reactions
Chair: Izabela Tyszkiewicz

6.1 EUSTITE Vigilance and Surveillance Tools
   - Luc Noel, WHO, Geneva

Luc Noel, Coordinator of HTP/EHT/CPR at the World Health Organization, outlined the issues of vigilance and surveillance, and summarized the results of activities undertaken within the EUSTITE project in this respect.

Firstly, he referred to the terms vigilance and surveillance (V&S). It was stated that the words are in common use already. The presentation focused on the European Tissue Directives: 2004/23/EC, 2006/17/EC, 2006/86/EC, which have provided certain definitions. It was underlined that harmonization demands a clear understanding of terminology as step one in any process that would lead people to work together. The definitions of ‘Serious Adverse Event’ (SAE) and ‘Serious Adverse Reaction’ (SAR) were quoted as the ones forming the basis of the concept of V&S.

One of the basic tasks within EUSTITE was to survey what actually existed in the field of V&S. The situation in January 2007 was not satisfactory. In Europe, only 10 Member States had a reporting system in place, whilst the other 17 Member States had none. However, both in the Americas and in Europe, great steps had been undertaken to establish systems to ensure the safety and quality of tissues and cells applied to the human body. It was highlighted that the WHO decided to participate in the EUSTITE project because of the global nature of S&V. Any system that would be applied only in part of the world would be simply a misleading solution. Because of the need for
a globally applicable tool, experts from non-European regions were invited to cooperate. External experts from the US FDA, CDC, Health Canada, the Public Health Agency of Canada and other institutions and regions participated in the activities of the EUSTITE Medical Advisory Committee. Their contribution was acknowledged. It was stressed that the fact that the S&V systems are just being developed globally means that there is an opportunity to standardise and to enhance communication and common responses globally and thereby to reduce the risk globally. Again, the role of terminology as the starting point for harmonization was stressed.

In May 2008, EUSTITE Deliverable 10 was issued - ‘Tools for Vigilance and Surveillance of Human Tissues and Cells’. The document included the following tools and guidance:

- Roles and responsibilities in the Management of SAE/R
- Triggers for SAE/R Reporting
  - Communication with stakeholders
- The Tool Box
  - The Severity Grading Tool
  - The Imputability Assessment Tool
  - The Impact Assessment Tool
- Competent Authority Responses and Notifications
  - Rapid Alerts
  - Regulatory Action Notices
  - Routine Responses to SAE/R Reports
- Evaluation of V&S Systems and Performance Indicators
- Annexes
  - Categories of Events and Reactions to Notify (Adapted from AFSSAPS)
  - Examples of SAE/R
  - Glossary.

With regard to Roles and Responsibilities in the Management of SAE/R in the EU, the key role of Tissue Establishments and the Competent Authorities was underlined. Still, the system can only function correctly if awareness and compliance of the staff involved in the processing stages at all levels and of the clinicians is guaranteed. TEs, POs and ORHAs, together with CAs, should foster a culture of reporting and notifying SAE and SAR.

The V&S Information Flow within an EU Member State was presented in the form of the following graph. It was underlined that a central role is played by Tissue Establishments.
Lists of tasks and responsibilities for the Competent Authority, Tissue Establishments and sites of SAR/E detection were presented.

The V&S Information Flow within the EU was presented in the form of a graph. Here the key role is played by competent authorities.

It was highlighted that while the Directives describe responsibilities for functional entities (TE, PO or ORHA and Responsible Persons), the efficacy of V&S relies on professionals and their reporting of adverse events and reactions and of the management of these. Examples of types of reactions...
were enumerated (infection – donor or tissue/cell, hypersensitivity, malignancy, failure, toxicity, mismatch, undue risk, genetic abnormality or other transmission).

The necessity for monitoring reactions in living donors was stressed. This can have implications for the safety of other living donors. It should also be taken into account that a serious threat to the supply could result from the loss of public willingness to donate. CAs should include reporting of such donor adverse reactions in their tissue and cell vigilance programmes and in their annual reports to the EC. Since living donors are in some cases treated pharmacologically (in order to enable donation) links with pharmacovigilance should be considered (examples of reactions to pharmacological agents were given: reactions such as OHSS associated with egg donation and reactions to GCSF administration for peripheral blood stem cell collection).

The criteria for SAE reporting to Competent Authorities were presented. Deviations should not be reported as SAEs to CAs unless:

A. Inappropriate tissues or cells have been released for clinical use, even if not used
B. The event could have implications for other patients or donors because of shared practices, services, supplies or donors
C. The event resulted in the loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells
D. The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

The tools elaborated within EUSTITE for SAR/E reporting were presented in detail (see figures below).

1. Proposed SAR Severity Grading Tool

<table>
<thead>
<tr>
<th>1</th>
<th>Non serious</th>
<th>Mild clinical consequences which do not necessitate hospitalisation and/or result in long term disability or consequences for the recipient or living donor</th>
</tr>
</thead>
</table>
| 2 | Serious     | Adverse reaction resulted in: 
- hospitalisation or prolongation of hospitalisation and/or 
- persistent or significant disability or incapacity or 
- medical or surgical intervention to preclude permanent 
  damage or impairment of a body function or 
- there is evidence of a serious transmissible infection 
- ART child serious genetic illness with non-partner donation |
| 3 | Life-threatening | The living donor or recipient required major intervention following procurement or tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death or there is evidence of a life-threatening transmissible infection. 
  ART child life-threatening genetic illness with non-partner donation |
| 4 | Death       | Death |
2. Proposed SAR Imputability Assessment Tool

<table>
<thead>
<tr>
<th>NA</th>
<th>Imputability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Excluded:</td>
<td>When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.</td>
</tr>
<tr>
<td></td>
<td>Likely,</td>
<td>When the evidence is clearly in favour of attributing the adverse reaction to causes other than the tissues/cells.</td>
</tr>
<tr>
<td></td>
<td>Certain</td>
<td>When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the tissues/cells.</td>
</tr>
<tr>
<td></td>
<td>Definite,</td>
<td>When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the tissues/cells.</td>
</tr>
<tr>
<td></td>
<td>Certain</td>
<td>When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the tissues/cells.</td>
</tr>
</tbody>
</table>

It was underlined that the descriptions ‘excluded’ and ‘unlikely’ were applied in order to keep the terminology uniform. These descriptions have been already used in the Directive 2005/61/EC implementing Directive 2002/98/EC which was setting the rules for traceability requirements and notification of serious adverse reactions and events (SARE) in the field of blood and blood products. Still, there is some ambiguity in them and some thought should be given to modifying the terminology to separate these terms.

3. Impact Assessment Tool (for SARE)

Step 1: Probability of Recurrence

<table>
<thead>
<tr>
<th>Probability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Rare</td>
<td>Rare, difficult to believe it could happen again</td>
</tr>
<tr>
<td>2 Unlikely</td>
<td>Unlikely, not expected to happen but possible</td>
</tr>
<tr>
<td>3 Possible</td>
<td>Possible, may occur occasionally</td>
</tr>
<tr>
<td>4 Likely</td>
<td>Likely, probable but not persistent</td>
</tr>
<tr>
<td>5 Almost Certain</td>
<td>Likely to occur on many occasions</td>
</tr>
</tbody>
</table>
Step 2: Consequences

<table>
<thead>
<tr>
<th>Level</th>
<th>Impact Description</th>
<th>Impact on individual(s) Actual (SAR) Actual (SAR) Potential (SAE)</th>
<th>Impact on Transplant or Fertility System</th>
<th>Impact on Tissue/cell supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Insignificant</td>
<td>Insignificant</td>
<td>No affect</td>
<td>Insignificant</td>
</tr>
<tr>
<td>1</td>
<td>Minor</td>
<td>Non-serious</td>
<td>Minor damage</td>
<td>Some applications postponed</td>
</tr>
<tr>
<td>2</td>
<td>Significant</td>
<td>Serious</td>
<td>Damage to system – services will be affected for short period</td>
<td>Many applications cancelled or postponed</td>
</tr>
<tr>
<td>3</td>
<td>Major</td>
<td>Life threatening</td>
<td>Major damage to system – significant time needed to repair</td>
<td>Significant no. of procedures cancelled - importation required to make-up short-fall</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Death</td>
<td>System destroyed – need to rebuild</td>
<td>All allogeneic applications cancelled</td>
</tr>
</tbody>
</table>

Step 3: Risk Matrix

<table>
<thead>
<tr>
<th>CONSEQUENCE</th>
<th>Rare</th>
<th>Unlikely</th>
<th>Possible</th>
<th>Likely</th>
<th>Almost certain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insignificant 0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Minor 1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Significant 2</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Major 3</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Severe 4</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>
Step 4: Response

The response of a TE or CA to a specific SAR/SAE should be proportionate to the risk indicated by the incident as assessed by the risk matrix. According to the zone: red, yellow, green, the reaction should be as follows:

- **RED** - major active response (possibly including involvement of policy makers)
- **YELLOW** - active response (e.g. approval of corrective, preventive actions, a review of data, a non-routine inspection)
- **GREEN** - e.g. file and a follow up at the next routine inspection, possible thematic review.

The proposed tools should have a didactic impact. They are expected to help the users to stay in line with the objectives. They are transitional steps towards improvement with the benefit of feedback from real situations.

Luc Noel expressed his gratitude to Deirdre Fehily and Stephanie Sullivan for their particular contributions to the project.

6.2 The EUSTITE Vigilance and Surveillance Pilot
- **Stephanie Sullivan, Pilot Co-ordinator, UK**

Stephanie Sullivan outlined the EUSTITE Vigilance and Surveillance Pilot and reported on its outcomes. This pilot has enabled participating Member States to assess, test and comment on tools for the reporting of Severe Adverse Reactions (SARs) and Severe Adverse Events (SAEs) in respect of tissues and cells. A lot of invitees and experts from all over the world have contributed to this Pilot.

The aims of the Pilot (as defined in the 3rd meeting of V&S Medical Advisory Committee) were recalled and these were:

- validation and improvement of the tools
- reduction in the likelihood of disease transmission
- improved quality and safety by sharing information learned from incidents
- demonstration of the value of data
- support from the added value of consolidated data
- promotion of patient safety advocacy and donor motivation for human Cells & Tissue Vigilance and Surveillance
- promotion of openness, transparency and learning
- support for implementation of the EU Directives.

The Vigilance & Surveillance Pilot began on 01 July 2008 and finished on 30 June 2009. Initially, the number of countries involved was limited to Project Partners (Austria, Bulgaria, Denmark, Italy, Poland, France, Ireland, Spain, Slovakia and the United Kingdom). Later, due to the enthusiasm for the Project in other countries, it was suggested by the EC to let others join in. In the end, the following countries were also participating: Belgium, Croatia, Lithuania, Netherlands, Portugal, Estonia, Germany, Greece, Slovenia and Switzerland.
The process of the Pilot was presented in the form of a diagram:

The final number of participating Competent Authorities was 22. CAs reported quarterly on SARs and SAEs. The number of submitted reports was fewer than that of the CAs. In total, 306 cases were reported (152 SARs and 149 SAEs). These concerned the following cells and tissues: reproductive (122), HPC (104), ocular (39), skeletal (17), cord blood (12), vascular (5), amniotic membrane (4) and skin (3). The above numbers had to be "filtered" and categorized according to EUSTITE’s criteria for SARE and the Directive reporting requirements.

Following the filtration process, the SAR cases fell into the following categories: hypersensitivity (19), infection - tissue & cells (18), failure (11), infection of the donor (5), toxicity (1), mismatch (1) and other (22). Concerning SAR severity, most of the cases were categorized as serious and there were also life-threatening and death cases. Examples of cases graded as ‘life-threatening’ or involving death were listed: long epileptic seizure following autologous PBSC infusion; haemorrhage post retrieval of oocytes; pulmonary haemorrhage in a sibling bone marrow allograft recipient leading to death of the patient; respiratory insufficiency; hypertensive crisis following PBSC infusion. Examples of SARs graded as serious were quoted: Acanthamoeba transmission by both corneas from one donor; cutaneous rash after cord blood infusion; Enterococcus and later Staphylococcus & Streptococcus cultured from a wound following femoral head grafting. The above examples were then presented in detail, i.e. information concerning the following items were given: description, classification, severity, impact, whether reported to the CA and learning points.

It was recommended that attention be paid to the fact that many reactions to DMSO after HPC transfusion were reported, as well as to the toxicity cases and complications resulting from the use
of reproductive cells and tissues. The consequences of most cases reported were considered significant and their recurrence as possible or unlikely.

Analysing the results of the report one should be aware of the possibility of under- and over-reporting. This is especially important in the case of countries with small number of inhabitants (SAREs numbers are calculated per 1 million inhabitants, so even a few cases might cause a considerable shift in this calculation). Results concerning SARE numbers/population were presented. France was highlighted as an experienced V&S country (about 0.5 SAR per 1mln inhabitants). Croatia (an example of a small country) turned out to have the highest number of SAREs per population (about 2.25 for each SAR and SAE) this might represent over-reporting in the early stages of the system’s development.

Cases of SAEs reported to CAs during the Pilot were discussed according to the EUSTITE reporting criteria:
1. inappropriate tissues/cells distributed for clinical use, even if not used (54 cases) e.g. lymphoma found in a donor by pathology after a cornea had been transplanted
2. the event could have implications for other patients or donors because of shared practices, services, supplies or donors (37 cases) e.g. a sample of donor sperm contaminated with fungal infection (Penicillium)
3. the event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched allogeneic tissues or cells (48 cases) e.g. stored bags containing autologous blood stem cells burst in nitrogen tank
4. the event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells (11 cases).

Also analysed were:
- the stage at which SAE took place: processing (43), procurement (34), distribution (28), storage (26), testing (10), transport (4) and other (5), and
- the classification of the event: tissue & cell defect (29); equipment failure (35); human error (70); other (16).

Examples of events of each type were given:
- Tissue/cell defect - e.g. heart valve thawed for implant unusable due to tear at the sinus
- Equipment Failure - e.g. incubator breakdown, temperature dropped, loss of embryos
- Human Error - e.g. femoral heads lost due to freezer accidentally being switched off
- Other e.g. illegal activity – cord blood collected on unlicensed premises.

The Risk Matrix Scores revealed that most cases of SAEs were graded as having significant consequences and of being possible to recur with 2 cases as having severe consequences.

Several issues have arisen from the analysis concerning grading SARs (how to grade suspected transmitted infections, how to define the terms "excluded", "unlikely", "without delay").
In the summary, the importance of collective awareness and evaluation, and of the exchange of information, were underlined. Benefits arise from shared expertise and experience. There is a need for common definitions/nomenclature. It was stressed that the main aims of the Pilot had been achieved. Expertise and experience from across Europe were utilised in a very successful networking experiment. Three of EUSTITE’s tools are now incorporated into EC Guidance for MS for annual reporting of SAREs (SAE criteria, Severity and Imputability of SAR). Many EU countries use the tools as a basis for their tissue and cell V&S process. Global interest was attracted by the issues raised in the Pilot.

Points arising from the Pilot for further discussion were presented:

- the application of the tools to ART was challenging and may need to be addressed in more depth,
- the reporting of Ovarian Hyperstimulation Syndrome (OHSS)
- corneal infection
- reactions resulting from the use of DMSO
- donor harm – differentiation of severity level
- establishing links with scientists and clinicians
- the role of the CA in oversight
- the need for collective work across Europe in reporting but also investigating SAREs.

Stephanie Sullivan thanked all of the vigilance officers who had participated in the pilot. She finished by quoting Dr Luc Noel:

‘Vigilance is an attitude, Surveillance a method’.

6.3 Rapid Alerts Tissues & Cells (RATC) in the EU
- Mike Cox, Danish Medicines Agency, Denmark

Mike Cox from the Danish Medicines Agency, reported on the Rapid Alerts Tissues & Cells (RATC) system. The starting point was the Conference of the European Association of Tissue Banks in Edinburgh in 2008 when the first draft was worked out. The system is currently in the consultation phase. It had already been presented at the Meeting of Competent Authorities for Tissues and Cells, called by the Commission of the European Communities, Health and Consumers Directorate-General in October 2009.

The legal basis of the need for a system of effective recalls was presented. According to the Technical Directive (2006/86/EC), tissue establishments should implement an effective recall procedure for human tissues and cells. Also the tissue establishment is to notify their relevant Competent Authority of any serious defect that could result in a recall and to indicate, as far as is possible, the specific countries. On the other hand, the Directive obliges the Competent Authorities for human tissues and cells to: “communicate to each other and to the Commission information as is
appropriate with regard to serious adverse reactions and events”. The purpose is the need to guarantee that adequate actions are taken.

The purpose of the RATC system was outlined: to ensure the transmission of information to Competent Authorities of the EU/EEA “when urgent remedial or precautionary action is needed due to a serious public health threat”. There are two groups of such threats: it can be related to tissue/cell defects or to epidemiological outbreaks. The currently operated procedure focuses on the first group - related to tissue/cell defects. Examples of recent events requiring a rapid action and actions undertaken were presented.

There are definite criteria for a rapid alert. Member States issuing these rapid alerts should ensure each of the following criteria is satisfied:

- quality defects of a serious or potentially serious nature,
- known risk to patients in one or more other Member States (also a risk to patients in other countries: Australia, Canada, USA etc., should be taken into account),
- with wider public health implications.

The Rapid Alert is to be coordinated by the Competent Authority of the Member State in which the tissue establishment responsible for the tissues/cells is situated. In another scenario, when the tissues/cells are imported from outside the EU, the country responsible for the “first point of entry” fulfils the role of the co-ordinating Competent Authority. Of course, the question arises as to who decides on the need for the recall. In most cases this will be the staff of the establishment responsible for the tissues/cells. In a few cases it might occur after consultation with the national Competent Authority of the tissue establishment responsible for the tissues/cells. In rare instances it may be “requested” by the national Competent Authority.

Rapid Alerts are to be issued at the European level where the defined criteria are fulfilled. Diagrams representing the activities to be undertaken for a recall in two scenarios were presented: within a Member State and involving more than one Member State.

1. Recall in a Member State
2. Recall in other Member States

The responsibilities of the CA for the issue and management of the RATC were enumerated:

- to include a recommendation, where possible
- to consult with tissue establishment at all times
- to investigate circumstances which led to the defect
- to assist the tissue establishment with their recall process
- to advise other sectors (medical devices, medicinal), if relevant
- to issue a summary to all CAs and the European Commission at 6 months
- to contribute to the annual review of RATC’s.

In the summary, the key points of the RATC system were presented:
- RATC’s are managed, issued and coordinated by the CA where the TE is situated
- Common Data Sets assist the TEs to perform an effective recall and where necessary, the Member States to communicate with each other and the Commission (COM)
- Periodical summaries of all these Rapid Alerts should be made available to healthcare professionals and regulatory organisations
- RATC is a secure communication network between CA’s & COM to ensure remedial and precautionary actions have been taken
- The Pilot phase of the RATC system is to start January 2010.

6.4 Horizon Scanning for Risk or Remember the Titanic...
- Richard Tedder, Health Protection Agency, UK

Richard Tedder, from the UK Health Protection Agency, gave a presentation concerning preparedness for emerging risks in the field of transplantation. Transplantation as such will bring risks and since we cannot afford to give up the benefits of this treatment, risks are unavoidable. Still, there should be awareness of the fact that risk exists and also an active approach should be adopted which will enable us to foresee at least some threats. This approach was metaphorically described as ‘horizon scanning’. The notion of "horizon" perfectly illustrates the situation in which certain phenomena appear but are not precisely perceived and identified but, in the end, they may have a great impact. Examples of phenomena in the field of transplantation/transfusion were given:

- vCJD (as a totally new phenomenon)
- HCV (first misjudged and described as non-A non-B hepatitis, NANB)
- Chikungunya virus and West Nile virus infections (not recognized and underestimated at first because of their apparently local character, which turned out to be absolutely false).

Hazards can be predicted, as could have been the case for the Titanic. The areas in which hazards arise are basically the following:

- they can be inherent in the “product” (cells, tissues, blood; example - pooled blood samples)
- inherent within the “process” (example - intravascular injections)
- they can come from external influences (example - bacteria, viruses)
- they can result from human error (example - false assumptions).

This active approach is currently used in the UK in the form of a system of information flow which has an impact on decision-makers and results in the introduction of preventive measures by health authorities. The diagram below outlines the structure of the system:
NHS Blood and Transplant (NHSBT) is responsible for providing a safe, reliable supply of blood, tissues and organs to the NHS. Fundamental to maintaining a safe supply is the appropriate selection and testing of donors. The organisation has been working jointly with the Health Protection Agency (HPA) to collect and analyse data on markers of infections in donors and possible transfusion and tissue transmitted infections. HPA is an independent UK organisation that was set up by the government to protect the public from threats to their health from infectious diseases and environmental hazards. It carries out the task by providing advice and information to the general public, to health professionals and to national and local governments. The Epidemiology Unit within the HPA issues Monthly Emerging Infections Reports. These reports are prepared after analysing data from a defined period. The data sources are various, e.g. Pubmed and the ECDC website. The report is then sent to, and reviewed by, the Transfusion Microbiology Unit. Some data is then forwarded to the Joint Professional Advisory Committee (JPAC) of the 4 UK blood services (England, Scotland, Wales and Northern Ireland) where policy decisions for these services are made. The main objective of the system is to increase awareness of the risk and react before the danger becomes significant.

The system has been proven to work e.g. in the recent cases of West Nile Virus and Chikungunya Virus. Examples were provided of documents in the information flow, including e-mails and the front page of the monthly report. In addition, a summary report on an action undertaken in connection with the new human retrovirus, Xenotropic Murine Leukaemia Virus (XMRV), was presented. Within one day of the first information on the virus becoming available, JPAC were able to provide ratified advice.

An investigation was presented as an illustration of how apparently obvious hazards can easily be overlooked. The investigation concerned a series of HBV infections among several autologous bone marrow recipients. Unexpectedly a linkage was made in the cases; the virus was genetically identical. So a search for a common source was undertaken that failed to identify any likely point source. The only linkage that could be found was that the bone marrow harvests from the cases involved had all been stored in the same liquid nitrogen tank. The results of the investigation showed that the preservation bags allowed the passage of liquid N₂ into and out of the bag. The first
case of the series had an acute infection at the time of harvest. The patient's virus had contaminated the liquid N2 and each of the other cell harvests.

In summary, the importance of risk management, as a day to day process, of predicting new risks and taking preventive action and of learning from mistakes was stressed.

6.5 Responsive Safety Measures - Responding to Risk
- D. Michael Strong, Past President AABB, USA

Michael Strong discussed reacting to sentinel events. He recalled the anniversary of the establishment of the first tissue bank in Bethesda and the founding of the American Association of Tissue Banks. It was stressed that, from the very beginning of tissue banking in the US, professionals from outside America were also involved.

In responding to risk, responsibilities are shared by the regulatory and the professional fields. Apart from regulations and professional standards, Good Tissue Practices, traceability and biovigilance are important parts of the system. It was felt that there is still room for progress in the field of traceability.

Several cases (donor- and tissue-related, at a national and international level) were presented to illustrate the process of responding to sentinel events. In 1985, HIV was transmitted from an anti-HIV negative organ & tissue donor. This was discovered very early in the case of an organ recipient but it took a few years to find out that tissue recipients were affected as well. An investigation carried out in 1990 revealed that the virus was transmitted by unprocessed frozen tissues. The gap between organs and tissues in this respect is still present. This particular case also brought about a better understanding of transplants. It was discovered that processed transplants (freeze-dried and irradiated tissues) had not transmitted the disease agent. The event resulted in an early response by regulators – the FDA issued an Interim Rule in 1993 (Fed. Reg. 58 (238) 65514/Dec. 14, 1993/21 CFR, Parts 16 and 1270) imposing an obligation of:
- infectious disease testing (HIV 1/2, HBsAg, HCV)
- donor screening for risk factors and infection
- record keeping (10 year retention).

In 2002, a 23-year-old patient died because of Clostridium sepsis, which, in turn, was linked to the application of a tissue graft. The CDC & the FDA investigated that case and found out, among other things, that:
- terminal sterilization had not been carried out at the tissue processing facility
- the procedures used were not validated to ensure sterility and
- residues from antibiotic soaks had interfered with the final sterility test in detecting Clostridium.

The FDA responded immediately by stopping further tissue processing and distribution by the implicated tissue bank. It also resulted in issuing a guidance document that required written,
validated procedures for infectious disease prevention and cross contamination and maintaining current records for each step. Additionally, validation data needed to demonstrate reliable prevention of infectious disease contamination.

In 2005, Biomedical Tissue Services (BTS) acquired body parts without donor permission and appropriate testing. Tissues were distributed throughout the United States and internationally. A recall took place, but a large number of tissues had been implanted and a significant amount was difficult to trace. This case showed that security must be ensured also at the international level. The year prior to this occurrence, FDA issued a Final Rule for Current Good Tissue Practice which includes requirements such as:

- a distinct identification code must accompany recovered or distributed tissue and be affixed to its container
- the code must be associated with all key records
- the tissue must be tracked from recovery, through shipping, processing, storage and distribution to the consignee or final fate
- procedures for investigating/reporting adverse reactions must exist.

Responses at a professional level (by standards organizations) were described. In 2005, in response to identification of more transmissions of disease by organ transplantation, a workshop was organized by the CDC, gathering specialists from the fields of tissue and organ transplantation, in order to work out solutions for better communication (Safety Workshop Priorities, 2005). Several recommendations were proposed:

1. A better communication network within and between organ and tissue community
2. A Unique donor ID linking organs and tissues
3. Clear mechanisms for adverse event reporting by healthcare facilities
4. Stronger information dissemination to a broad array of clinicians, health professionals and patients
5. A notification algorithm, for trace-back and trace-forward tracking.

Also in 2005, the Joint Commission, that accredits hospitals in the US, recognized the problem and issued standards concerning tissue handling, including storage and tracking (TJC Standard QC.5.300).

Other activities were undertaken and are continuing, in response to risks, and new solutions are being proposed. The CDC and the AABB carried out a survey concerning the use of tissue grafts in hospitals. It was found that, except for surgical departments, it is the blood banks that deal with tissue grafts the most. Gaps in existing standards were identified and standards were appropriately updated. The AABB also published a handbook on tissue management for hospital practitioners. The American Association of Tissue Banks has the responsibility of publishing Standards for Tissue Banking (the last, 12th, edition was issued in 2008, the first one published in 1984). The Standards are updated in accordance with advancements and experiences.
Dr Strong moved to the question of traceability. Labelling of tissue grafts has not yet been clearly regulated in the US. A uniform system is needed. A definition is still being discussed. So far the ISBT 128 system has become the standard in blood banking. Standard setting organizations such as JACIE/FACT are expected to require the use of ISBT 128 for professional accreditation in Cellular Therapies. With regard to tissues, an advisory body was established, called the North American Tissue Technical Advisory Group that is investigating the application of ISBT 128 (for 4 years now). There is a need to come to a common approach to coding. ISBT 128 finds application also in Europe. The system has been implemented for tissues in England, North Wales, Finland, Poland and Denmark. Implementation is planned in Austria. The CEN Workshop Agreement recommends the use of ISBT 128 throughout the European Community.

A recent analysis (2009) of Blood, Organ, Cell and Tissue Safety Reporting carried out by the US Department of Health and Human Services revealed that in all of the above fields, some systems for adverse event reporting are applied, but they are passive, with multiple pathways and these are regulated by various authorities. Adverse event reporting systems do not provide for the participation of clinicians or outcome reporting and coordination is needed.

On biovigilance, the EU appears to be more advanced in this respect (blood transfusion reaction reporting). In the USA, four separate modules are being generated: Blood Recipient System, Blood Donor System, Tissue/Organs and Cellular Therapies.

The guidelines "Inspection of Tissue and Cell Procurement and Tissue Establishments Guidelines for Competent Authorities" submitted to SANCO in May 2008 were mentioned as an example of Europe’s reaction to risks.

Session 7
Engaging Clinical Users in Vigilance and Surveillance
Chair: Trish Davies, Human Fertilisation and Embryology Authority, UK

The session was introduced by Trish Davies who considered the necessity of engaging clinicians and clinical users in vigilance and surveillance systems. It was emphasized that the participation of clinical users is an essential component of the success of any vigilance system. She introduced the first speaker of the session who would present the longer experience of vigilance for blood and blood products.

7.1 The Experience with Haemovigilance
- Rene de Vries, the International Haemovigilance Network and TRIP

The International Haemovigilance Network (IHN) has developed a system of haemovigilance that spans the safety of the whole of the blood transfusion chain. The Transfusie Reacties in Patienten (TRIP) is a reporting system of vigilance that has been created by professionals for professionals in the Netherlands. It has multiple stakeholders including the Healthcare Ministry, the European
Union blood component safety office, the Sanquin blood supply foundation and participating hospitals.

Founded in 2001, the TRIP system is independent of blood suppliers and hospitals and, being run by professionals, it has a wealth of experience and expertise. TRIP is also responsible for the reporting of haemovigilance and surveillance issues and also manages public reporting of anonymous information.

There has been a gradual increase in the number of hospitals reporting incidents to the present day where 95% of all hospitals regularly report to TRIP. The numbers actually reported have risen from 862 in 2002, one year after inception, to 2030 in 2006. Each of these is reported to the Healthcare inspectorate at the Ministry. As a result of the transposition of the EU Directive hospitals and blood banks were already reporting directly to the Ministry but TRIP provides a single system connecting all the different stakeholders.

The TRIP system has a number of advantages and strengths including the fact that it is relatively inexpensive to run. It has strengthened international ties, promoting mutual learning. All the scientific data has been validated and there is agreement amongst professionals on definitions and reporting requirements. The findings are available to professionals throughout the whole transfusion field and are expected to lead to the further development of professional standards.

Some of the weaknesses that need to be addressed for further development were described. As in most vigilance and surveillance systems, it relies on the willingness of professionals to report. Historically this has proved to be a challenge but as the professionals reporting receive feedback and see the benefits of the system reporting is improving. Some of the reporting of incidents can be too late to do anything about the issue (cold-vigilance). Sometimes it is difficult to fund the staff in hospitals and, as there are so many people involved in the whole system, it can take considerable time for decisions and action to be taken.

TRIP deals with much more than the requirements of the Directive. Its remit is across the whole blood transfusion chain, with the main purpose being to collect and assess information on the undesirable effects of labile blood products with the goal to improve the safety of blood transfusion. The Directive demands traceability of blood products from donor to recipient and reporting of SARs and SAEs. During the first year of reporting 2201 SARs were reported to the European Commission of which only 22 were attributable to the quality and safety of blood components.

Haemovigilance was started in France in 1994 emerging from the recognition of the impact of HIV in the health sector. Its aim was to develop and maintain a common structure with regards to the safety monitoring of blood and blood products and the haemovigilance of blood transfusion. It retains the objectives of an exchange of valid information between the members, rapid alert and early warning between the members, facilitating joint activities between the members of the Network and providing educational activities in relation to haemovigilance.
Haemovigilance now has an international dimension, with each participating state or country having its own structure and methodology for participation but the conclusion is clear: irrespective of the structure of the system, haemovigilance works and provides quality data for priority setting and the evaluation of risk preventive strategies.

7.2 Engaging Tissue Users in Vigilance: An NHSBT & possible EATB perspective
- Ruth Warwick, Past President EATB, NHSBT, UK

Ruth Warwick began her presentation by saying that there is a real need to raise awareness of surveillance and vigilance among surgeons and other relevant clinicians. Clinicians may not always be aware of the risks associated with the human origin of the tissues and cells that they apply and of just how complicated and complex the chain is from procurement to application. Tissues and cells frequently cross national boundaries and there are differences between the legal requirements and the professional reporting schemes in different countries. It is important that clinicians understand the importance of statutory vigilance and of the reporting requirements of SAERS to Competent Authorities (CA) through to reporting procedures for suspected SAERs to Tissue Establishments.

Prompt reporting of SAERs can prevent other recipients of tissues or cells or organs from being affected by an event or from suffering a reaction that has happened with the index case. Effective quarantining of material from the same donor or from tissue processed using the same reagents or clean rooms can also prevent multiple recipients being affected by an incident. The rapid identification of risks with public health implications can escalate to alert competent authorities in other Member States and beyond.

The UK National Health Service Blood & Transplant (NHSBT) is responsible for optimising the supply of blood, organs, plasma products, haematopoietic cells and tissues. It is also responsible for raising the quality, effectiveness and efficiency of blood and transplant services. Tissue Services sits within the organisational structure of NHSBT.

NHSBT has developed a number of surgeon user groups to provide a forum for professional interaction between the major providers of tissues and the UK’s major clinical users of tissue allografts. In each tissue-specific case, the Chair is a nominee of the appropriate surgeons’ professional association and the group is managed by an NHSBT Tissue Services medical consultant.

The terms of reference for the groups include the collection and reporting of data on allograft implantation, including feedback mechanisms for providing outcome data. The group oversees the introduction of new tissue allografts, conducts monitoring and reporting on novel technologies and recommends risk reduction strategies. By reviewing the relevant published literature, the group can help prioritise research and development in the sector.

NHSBT is not the sole supplier of tissues and cells in the UK and cannot easily influence the relationship of surgeons with other suppliers but the organisation has a long standing close
relationship with other providers and users of ocular tissues and cells. The relationship between Tissue Services and the Ocular Tissue advisory group was described. The mechanism for providing advice and sharing information was outlined, as well as the process for analysing patterns of SARE and the management of the consequences and outcomes. Part of this mechanism includes some cooperation with the UK’s CA for Tissues, the Human Tissue Authority and a potential structure for professional overview was outlined, which again would require considerable professional input to be fully effective.

7.3 Engaging Ocular Surgeons in Tissue Vigilance:

- Ruth Warwick, on behalf of Esteve Trias of the European Eye Banking Association.

The European Eye Bank Association (EEBA) is an organisation comprising technical and scientific individual members from 83 eye banks in 22 European countries. Its role is to collect and exchange detailed information from European Eye Banks. The association has been responsible for the definition of minimum quality standards and has actively encouraged banks to produce Standard Operating Procedures. At the present time, the EEBA does not have any recommendations related to adverse reaction reporting but the topic has been discussed in the past and developed to the stage of drafting a project proposal to SANCO. The action plan includes selecting and characterising data from SARs and SAEs, identifying common and rare reactions or events and the rate of reporting. Discussions have taken place on how data would be collected and analysed as well as the categorisation and classification of SARE. This would be analysed and results published amongst the participants to improve the services each eye bank provides.

Designated individuals in each eye bank would be provided with password protected access to a central database and be asked to provide information about any actual or potential SAR or SAE, including a determination of the possible causes, consideration and implementation of necessary preventative actions and their results. An e-mail based rapid response system will be introduced to alert tissue establishments and regulatory authorities of any suitably identified and analysed SARs and SAEs.

The goal for the plan is an overall improvement in healthcare performance and levels of safety and quality through evidence-based root cause analysis for system breakdowns, management effectiveness, equipment malfunctions and human error, to prevent event recurrence.

7.4 Engaging Assisted Reproduction Therapy (ART) Clinicians in Vigilance

- Luca Gianoroli, President, ESHRE

The European Society of Human Reproduction and Embryology (ESHRE) was founded in 1985 and represents over 5,300 professional members in reproductive medicine and science from 114 countries. More than 50% of all members are from Europe. ESHRE’s aims are to promote an understanding of reproductive biology and medicine, to facilitate research and the dissemination of
research data to the public, scientists, clinicians and patient associations and to inform policy makers in Europe.

The demographics of ART practice across Europe were presented, showing the increasing number of cycles per head of population and per unit gross domestic product of individual countries across all Member States.

ESHRE has developed 11 special interest groups reflecting the scientific leanings of the Society’s membership. It brings together members of the Society in sub-fields of common interest. Seven Task Forces have also been established, to work on a single defined task or activity, covering subjects such as fertility preservation in severe diseases, developing countries and infertility, cross border reproductive care and infertility & society.

In November 2007, in response to Directive 2004/23/EC, Technical Directive 2006/17/EC and Technical Directive 2006/86/EC, ESHRE produced an official position paper concerning the specific application of these directives to ART. It was emphasised that this paper cannot ensure equal regulation in all countries, however, it can be a useful instrument for professionals when dealing with national authorities in the implementation of the EU Tissue and Cell Directives.

Considering its commitment to good practice, safety and the harmonization of the implementation and certification, ESHRE sees its initiatives as complementary to the requirements of the EU Tissue and Cell Directives, including the revision of the “ESHRE Guidelines for good practice in IVF laboratories” and the development of the European Assisted Conception Consortium (EACC), which aims to understand all the implications of the EU Tissue and Cell Directives, identify areas problematic to the ART community, provide interpretations to be used locally in European countries and to establish a good dialogue among EU, professionals and local regulatory authorities.

Some of the clearly defined areas of the the EU Tissue and Cell Directives that impact on ART units were outlined, including the requirement that all units will have to be licensed or accredited according to national regulations, all units must implement a quality management systems with written standard operating procedures, units must ensure full documentation of all activities carried out in the clinic and that all units must ensure full documentation of traceability for all materials used in each treatment and keep these for 30 years.

There are a few issues that require further clarification, including the screening of all patients, which will lead to a clear distinction between infected and non-infected patients. It was noted that testing positive for HIV or Hepatitis does not automatically exclude patients from treatments. As far as this point is concerned, ESHRE recommends that the national authorities clearly define how and where positive patients should be treated to minimize the organizational and financially negative impact of the EU Tissue and Cell Directives on many centres.

Further issues include the fact that the cost of the implementation of the directive will be extremely high for the involved units. ESHRE estimates that increased financial support will be mandatory,
both in the public and in the private systems, to avoid an increase in the cost to patients. The the EU Tissue and Cell Directives defines the standard of air quality but ESHRE asserts that there is no evidence of transmission of infectious diseases due to poor air quality in ART.

The wide scope of the Directive, in comparison to the specific nature of ART, which involves numerous repeated procedures on the same patient and long duration of treatment, leads to some anomalies. For example, the requirement for screening for HIV and hepatitis at every gamete procurement would be a serious problem for both units and patients. It is not specified whether it is required to re-test the patient prior to each treatment or if a specified interval is acceptable. ESHRE suggests a system where, in the case of partner donations, patients should be tested no more than 30 days before the initial treatment. If the test is negative the result should be valid for at least 24 months. If the test is definitely positive the couples will be considered positive in all future treatments.

It was concluded that ESHRE has enormous experience in ART and it is important that ESHRE works together with EUSTITTE and other relevant projects and groups to ensure that the implementation of the EU Directives is a beneficial one and that cross-sector and cross-border communication is optimal.

7.5 A new US initiative - Hospital Tissue Management
- Scott A Brubaker, Policy Officer, American Association of Tissue Banks (AATB) USA

Scott Brubaker began his presentation by describing two significant events that resulted in recalls, which in turn led to the development of hospital tissue handling requirements in the form of 2 documents: an AATB guidance document (in preparation) and a new handbook for use by hospitals developed jointly by the AABB, EBAA, AATB, FDA and the Joint Commission.

The first recall procedure resulted from a single donor in 1985, from which 53 tissues and 4 organs had been made available. 44 tissues were implanted and subsequently 7 recipients (4 for organs and 3 for tissues) tested positive for HIV. During the ensuing investigation it was discovered that 5 tissue grafts were totally unaccounted for by the hospitals that received them. Nine % of the total tissue availability was not traceable to recipients.

The second recall resulted from 3 HCV seroconversions in tissue recipients. The key issues identified in this case were that 84% of implant cards had been returned to the tissue banks. This card return system is voluntary and is used by the implant centre to inform the tissue bank of the use of the tissue and the outcome. Also key in this case was that 7% of the grafts were completely unaccounted for.

In 1993, the first incident led to the AATB proposing new hospital standards for tissue handling, including the use of standard operating procedures, traceability records, investigating adverse incidents, outcomes and results of recalls. This proposal by the AATB was accepted by the Joint
Commission on Accreditation of Healthcare Organisations, which is headquartered in Chicago, and they began work on development and implementation of tissue handling standards.

Continued work and consultation with key stakeholders in the tissue banking sector led to the development and publication of a section in AATB Standards for tissue dispensing services (hospitals) and for tissue distribution intermediaries (distributors). Various sections of the AATB Standards were described, including requirements for storage, issue of products, distribution, recall procedures and the need for detailed traceability of tissues. A further case study reinforced the concern that there are a substantial amount of tissues that are unaccounted for and not traceable when a recall occurs (i.e., BTS).

The expectations of the accrediting bodies were described (i.e., AABB, College of American Pathologists, The Joint Commission). There is a clear definition of responsibility and a need for clear and documented procedures for tissue handling that include: ordering and supplier qualification, receipt, storage and issuance, allograft preparation, records maintenance, graft tracking, recalls and adverse event recognition and reporting.

The AATB is developing, for end users, guidelines on the proper recognition of tissue recipient adverse reactions, and describing best practices for tissue banks to follow when performing an investigation through to proper closure as well as best practices for handling recalls and market withdrawals. When these guidelines are completed, the AATB plans to gather support for this guidance from professional associations and key stakeholders and go on to develop specific “brochures” for clinicians using the EUSTITE terms and tools.

The Hospital Tissue Management handbook is for practitioner’s and describes in some detail the structure and function of a hospital tissue service, an overview of Tissue Transplantation in the United States and a number of other relevant and useful pieces of information for the hospital and clinician.

The AATB’s “Healthcare Facility” Tissue Services Committee has been formed and continues to grow. It includes members from key stakeholder committees. The committee will continue to look at ways of revising and improving guidance and promoting membership with stakeholders from the end user/clinician clients across the USA.

7.6 Engaging Hematopoietic Progenitor Cell (HPC) Transplanters in Vigilance
   - Carolina Stylianou, on behalf of EBMT

HPC transplantation is a multifaceted “jigsaw” of events, all having an impact on outcomes. Pieces of this jigsaw include:

- the disease and its extent or status
- the patients age, type and the availability of the graft,
- graft rejection and
- any contributing infections.
Putting all the pieces in place is a complex procedure and involves many stakeholders and there can be a variation in the expectation of the quality of the graft and how the quality is measured.

Transportation and graft receipt procedures at each tissue establishment include the requirement for labelling of the tissue, using a transport container and the accompanying documents as required in the Directives.

The Serious Product Event and Adverse Effect Registry (SPEAR) has highlighted a number of events including: donor blood group being incorrect, the incorrect product collected by the courier (as two products had been harvested on the same day) and a unit of cord blood arriving at the centre partially thawed with a resultant substantial drop in viability. There have also been two donor derived malignancies reported via the SPEARs.

There are a number of places where these events can be reported: to the Competent Authority (CA), The World Marrow Donor Association (WMDA) or the Centre for International Blood and Marrow Transplant Research (CIBMTR) and this may be causing some confusion. It has been noted that nurses are more motivated to report to SPEARs and are incentivised if there is feedback about the outcome of any investigation. A number of tissue establishments have voiced concerns about being accused of malpractice, although attitudes are beginning to change and more work needs to be done to encourage people to participate in the SPEARs.

A delegate commented that it is a real challenge to get people to report when there are so many organisations to report to and that sometimes we ask for too much data. Perhaps there should be a minimum data set and minimal documentation requirements?

### Session 8

**Electronic vigilance reporting**

Chair: Ewa Olender, National Centre for Tissue and Cell Banking, Poland

#### 8.1 Simultaneous reporting to professional and regulator systems

- David Mold, SHOT, UK

David Mold presented the system for haemovigilance reporting in the UK. SHOT (Serious Hazards of Transfusion) is the professional and independent haemovigilance scheme for reporting of SAR in recipients. The system has existed since 1996 and collects and analyses SARE in blood transfusions from healthcare organisations. Some of the incidents reported to SHOT includes:

- Incorrect blood component transfused
- Inappropriate and unnecessary transfusion
- Storage errors
- Incidents related to autologous transfusions
- Acute transfusion reactions
• Haemolytic transfusion reactions.

SHOT identifies risks and problems, and the information obtained contributes to improving the safety of the transfusion process. Recommendations made by SHOT are gathered in an annual report which is circulated to all relevant organisations.

Reporting to SHOT is voluntary, but it is mandatory for some of the incidents to be reported to the national CA. The EU Blood Safety Directive defines the legal requirements for reporting SARE to the relevant CA. Therefore MHRA introduced SABRE (Serious Adverse Blood Reactions) which is an online reporting system that provides a single reporting route for UK haemovigilance. In this way, SABRE allows blood establishments and blood banks/transfusion teams to meet, not only their legal obligations, but also to report to SHOT electronically. Although SABRE provides a single system for reporting both to the MHRA and to SHOT, the reporter is also able to choose to submit a report to only one organisation i.e. a “SHOT only” report which is not visible to the MHRA.

From 2010, reporting to the MHRA will be made using the SABRE system. If the reporter wishes to share this report with SHOT or wishes to make it a “SHOT only” report, then a message is sent to the SHOT Dendrite database and a record is created. The reporter is then e-mailed automatically by the SHOT Dendrite database and asked to complete the record that has been created.

8.2 US Transplant Transmitted Sentinel Network (TTSN)
- Matthew J Kuehnert, M.D. USA

Matt Kuehnert gave an introduction to the US organ and tissue safety programme, as reflected in the TTSN project (Transplant Transmitted Sentinel Network). There is an important link between biovigilance in the areas of blood, organs and tissues, and the balance between availability and safety is a key factor.

In the US, the Health Resources and Services Administration (HSRA) oversees the transplantation of solid organs through the Organ Procurement and Transplantation network (OPTN), administered by the United Network for Organ Sharing (UNOS). The FDA regulates the reporting of certain adverse reactions related to implantation, transplantation, infusion or transfer of a HCT/P (Human Cell and Tissue Product). The FDA requires that all HCT/P establishments report serious infections following graft transplantation, but healthcare professionals are not required to report.

In the US, the use of tissue allografts has exploded over the past few years. More than 2,000,000 tissue transplantations (musculoskeletal, skin, heart valves, vascular tissue and corneas) occur each year. As a consequence, this increasing availability has further increased the risk of disease transmission. Other factors contributing to the potential risk of disease transmission in this area are that many allografts can be processed and distributed from one donor, and that a donor’s tissue can be sent to multiple tissue banks for processing. Therefore a national biovigilance network is
The system is important for discovering trends and the aim is an improved communication network and to reduce the risk of disease transmission.

The aim of the TTSN project was to detect and prevent disease transmission from organ and tissue allografts for transplantation. Through improved communication among people in the organ and tissue community, healthcare facilities and public health officials, it is hoped to improve patient safety. The TTSN comprised the following tasks:

- Identification of donor
- Tracking of organs or tissues
- Recognition of infections among recipient or donor
- Data feedback and education for improved communication.

There has been a developmental phase of the system leading to a “pilot phase” in 2008 which tested the actual system. Institutions from both the organ and tissue sectors attended the pilot. The pilot phase was successful and showed the further need for improvements in certain areas (bar coding of organs/tissues, the implant data should be easier to enter and the importance of everyone down the transplant chain participating to avoid missing events and thereby obtaining useless data). A RFI (Request for Information) has been issued to gather experiences, opinions and other comments on the system. Feedback is to be submitted by December 2009.

Dr Kuehnert stressed that it is very important to keep a focus on tissue and organ safety and the link between these areas. The need for both a regulatory system and a surveillance system that adequately detects and responds to adverse events and reactions is needed. This need is further stressed by the fact that many tissues are distributed worldwide, which makes global data sharing the key to biovigilance.

8.3 Tissue and cell vigilance reporting to the FDA
- Laura St Martin, FDA, USA

Laura St. Martin gave an overview of the current practices to prevent the introduction, transmission and spread of communicable diseases, and heighten the safety and quality, of tissues and cell donations in the US.

Human cells or tissues intended for implantation, transplantation, infusion or transfer into a human recipient are regulated as human cell, tissue and cellular and tissue base products (HCT/P). The Center for Biologics Evaluation and Research (CBER) at the FDA, regulates HCT/Ps under 21 CFR, parts 1270 and 1271. The FDA’s revised regulations are contained in Part 1271 and apply to tissues recovered after 2005, which are the current tissue rules. Examples of tissues regulated are musculoskeletal tissue, skin, corneas, heart valves, hematopoietic stem cells and reproductive cells. Examples of tissue not included are vascularized organs, blood and blood products and minimally manipulated bone marrow.
In 1997, the FDA published a set of 3 rules in order to implement its proposed approach to the regulation of HCT/Ps. The first rule on registration and listing was finalized in 2001 and the second, on donor eligibility, and the third, on current good tissue practice, followed in 2004.

The first rule – **Registration and Listing** - requires tissue establishments to register and list their HCT/Ps with the FDA. This includes the types and uses of the products that will be regulated by these rules. Also, all foreign establishments importing HCT/Ps into the US must register and list such HCT/Ps.

The second rule – **the Donor Eligibility Rule** - requires HCT/P establishments to screen and test tissue and cell donors for relevant communicable disease agents or diseases. All HCT/P donors are screened for HIV-1 and 2, hepatitis B and C, human TSE and syphilis. In addition, donors of viable, leukocyte-rich cells are also tested for HTLV-1 and II. For reproductive cells, anonymous and direct semen or oocyte donors are screened and tested for Chlamydia, gonorrhoea, HTLV and CMV. Donors who are sexually intimate partners are not required to be screened or tested, neither if they later decide to donate their embryos. Furthermore, tissue and cells for autologous use are not included in the donor eligibility rules. Once a donor eligibility determination has been made, the record must include a distinct identification code that tracks the HCT/P to the donor and to the tissue establishment.

The third and final rule establishes **Current Good Tissue Practices (CGTPs)** for HCT/Ps. CGTPs are the requirements that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including all steps in recovery, donor screening and testing, processing, labelling, packaging and distribution. Also included are the requirements for process validation, labelling, tracking, complaint files and adverse reaction reporting. In general CGTP ensures that HCT/Ps do not contain communicable disease agents, are not contaminated and that they do not become contaminated during manufacturing.

Certain areas of the CGTPs are not implemented for reproductive cells. This means that the regulations for adverse reactions and HCT/P deviation reporting, and for labelling, are not included. Manufacturers must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution. Only serious reactions are required to be reported to the FDA, and must be sent to the FDA within 15 days. In 2009, 98 reactions were reported to the FDA.
The goals to ensure tissue and cell safety can be summarized as:

- Enhancement of adverse reaction reporting and processes for investigation and evaluation.
- Increasing collaboration with organisations and Authorities.
- Improved outreach to healthcare providers to encourage reporting of reactions and to heighten the education in the area of tissue safety.

### 8.4 V&S Annual reporting to the EC – long term trending and monitoring,
- Deirdre Fehily, National Transplant Centre, Italy

According to Directive 2006/86/EC, there is a legal requirement for an annual report to be submitted by each Member State to the EC on the notification of SARE received by the Competent Authority. It was stressed that the purpose of gathering these reports was not so that the EC could manage the SARE, but rather to allow an EU level overview of the different kind of SARE, their numbers, changes in trends and to support the development of guidelines through the provision of consolidated data.

The EU Commission developed a document to support Member States in the submission of their annual reports for blood vigilance. That document was entitled “Common approach for definition of reportable serious adverse events and reactions”. The decided to develop an equivalent document for tissues and cells. This was done in collaboration with representatives from the EUSTITE V&SMAC working group and the document was issued to Competent Authorities in July 2009. The approach for tissues and cells is a guidance document, not a legal requirement. Only serious reactions and events should be reported, and should only be reported if they influence the quality and safety of the involved tissues or cells. The document proposes the application of the EUSTITE severity and imputability grades to decide which SARE should be included in the report.
The project’s proposal for criteria for reporting of SAE was also incorporated in the guidance document.

She presented the electronic reporting form supplied by the Commission for submission of the annual data.

An important point to highlight is the fact that many Member States are beginning to collect data on donor adverse reactions. Those reactions fall out of the scope of legal requirements, but still are valuable information. Therefore, the Commission is welcoming any reporting of these reactions on a voluntary basis.

Session 9
Developing Key Recommendation for Effective V&S in the EU and Globally:
Chair: Deirdre Fehily, CNT, Italy

In a series of facilitated workshop discussions, groups of delegates were asked to consider what key recommendations could be made for effective V&S in the EU and globally. The discussion groups were facilitated by

- Dagmar Doerman, Paul Ehrlich Institute, Germany
- Jacinto Sanchez Ibanez, Health Authority, Galicia, Spain
- Caterina Delvecchio, National Transplant Centre, Italy
- Richard Zammit, Ministry of Health, Malta
- Arnaud Deguerra, Agence de la Biomedecine, France

Deirdre Fehily asked the groups to consider the following questions:

- What will an effective EU/Global V&S system for tissues and cells look like? (What will be its key elements?)
- What needs to be done by regulators to make it happen?
- What are the barriers to building effective V&S?
- How can they be overcome?

The following is a consolidated summary of the points raised in the discussion groups:

1. **Role of Regulators**: Regulators and accrediting authorities have a mandate to ensure quality standards are raised and maintained in tissue and cell procurement, processing and storage. There are a number of mechanisms and tools that empower this mandate, including effective vigilance and surveillance. A great deal of work by regulators and accredited authorities has already gone into the development and implementation of mechanisms and processes for the recognition, management and reporting of adverse incidents.
2. **Engagement of Clinicians**: A key point raised is the need for engagement by clinicians and professional bodies to take the work forward. The more benefit that the clinicians derive from the system, the more they will engage with the concept of vigilance and surveillance. Reporting requirements should be proportionate to risk and not too onerous for the clinician. Regulators and accrediting authorities should provide feedback on cases reported and their outcomes so that clinicians can see the benefit of their participation.

3. **Role of Professional Societies**: Vigilance is an area where regulators should work closely with professional societies to ensure that appropriate technical expertise is available for the evaluation of risk and the communication of recommended corrective or preventive actions.

4. **Clarity in Reporting Requirements**: Although progress has been made in the clarification of what should be reported to regulators, professionals would benefit from having further detailed guidance on this issue. Case studies could be used as tools for ongoing training and for validation of the clarity of guidance provided. It was suggested that penalties, including financial, should be considered for non-compliance with reporting requirements.

5. **Openness, Transparency and Non-punitive Culture**: Vigilance and surveillance represent very important learning opportunities. Attributing blame is secondary to the opportunity for learning. Empowering the practitioners to carry out self assessment, being open and transparent in reporting incidents and events and, more importantly, disseminating outcomes and lessons to be learned will encourage good practice. This will improve the quality of services and ultimately patient care and outcomes.

6. **Effective Communication**: It is recognised that sharing of information regarding risk, outcomes and corrective actions is central to ensuring that vigilance systems achieve the intended improvements in patient safety. Communication needs to be effective:
   
   a. across tissue and cell specialities,
   b. between procurement organisations, tissue establishments, clinical users and regulators,
   c. between EU Member States and between the EU and third countries.

7. **Patient Focus**: V&S should be patient–oriented; making high quality tissue and cell products through a good process will give good patient outcomes. Clinicians should appreciate their role in improving product safety by participating in vigilance reporting.

8. **Terminology/nomenclature**: Commonality of language, definitions and tissue/cell nomenclature are essential for effective V&S systems. Common global coding for product identification and description was also considered to be a fundamental tool to improve traceability and communication, both essential to good vigilance.
9. **Adaptation for ART**: The ART sector finds it difficult to match some of the terms for tissue establishment reporting. Many of the incidents reported to the UK CA for ART don’t “fit” the reporting criteria of the Directives, thus they don’t get reported as part of the European wide system. The group suggested that any mix up of ART material should have a separate definition.

10. **Denominators**: There is a need for a series of common, consistent activity denominators in order to allow frequency of SARE to be monitored. Not all national regulators collect data relating to the numbers of human applications. For example, the US has traceability procedures from procurement and processing to distribution but not through to implantation. In contrast, some regulatory systems, such as HFEA in the UK, capture all human application activity and can therefore express SARE in relation to numbers of procedures.

11. **System Standardisation**: The development of a common, international system (perhaps with a single reporting form) would provide a global understanding of issues in different countries. A question was raised as to whether all SARE should be reported through the World Health Organisation (WHO), as a central repository of information. Tissue Establishments should be reporting to Competent Authorities using a unique incident code, to prevent duplication of reporting. The group recognised that there could be some commercial sensitivity, particularly in the US, but this could be addressed to some extent through education, anonymisation of information and confidentiality, where appropriate.

12. **Education of Stakeholders**: It was considered that education of all stakeholders is essential to achieving success when establishing a vigilance system.

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**Session 10**
**Measuring Success**
**Chair: Samuel Arrabal, Agence de la Biomedecine, France**

10.1 **Evaluating the EUSTITE Project**
**Samuel Arrabal, Agence de la Biomedecine, France**

Samuel Arrabal opened the session, describing the EUSTITE project evaluation work package that was led by the Agence de la Biomedecine in Paris. The objective of the work package was to ensure that high quality deliverables were produced and that outputs were applicable and fit for purpose.

External Peer Review had been provided by two organisations during the project: FDA in the USA and RIVM in the Netherlands. The work of Claes Wasenaar (RIVM) and Anita Richardson (FDA) was much appreciated by the project. They had reviewed the Inspection Guidelines and the Vigilance and Surveillance Tools providing written reports. In summary, the Inspection Guidelines
The document was considered to be ‘high quality, complete, appropriate’ and the Tools and Guidance for Vigilance and Surveillance document was considered to be ‘Excellent, clear and realistic and, although quite complex at first sight, to have a practical approach’.

Project outputs were also evaluated by an internal Evaluation Committee made up of individuals from partner organisations who were mostly not personally involved in the project. The following individuals participated in the Evaluation Committee:

- Agence de la Biomédecine (France): H. Espérou, G. Lemardeley, A. Pariente-Khayat;
- Bulgarian Executive Agency for Transplantation (Bulgaria): A. Tcenkova;
- Central Tissue bank (Slovakia): J. Dragunova;
- Centro Nazionale Trapianti (Italy): L. Lombardini;
- Danish Medicines Agency (Danemark): not specified;
- Irish medicines board (Ireland): Lorraine Nolan
- Human Fertilisation and Embryology Authority (United Kingdom): D. Bloor, A. Cummings, A. Sutherland,
- Ministry of Health, Family and Youth (Austria): J. Dichtl, E. Hofbauer;
- National Centre for Cell and Tissue Banking (Poland): G. Gut;
- Organización Nacional de Trasplantes (Spain): R. Marazuela.

The Committee evaluated the Inspection Guidelines as ‘excellent’ (6/9) or ‘very good’ (3/9). They were considered to be clear, in line with the European Directives and applicable in practice across the EU although countries that already have systems in place would need to adapt them.

The Committee considered the Guidance and Tools for Vigilance and Surveillance to be ‘excellent’ (3/9), ‘very good’ (5/9) or ‘not satisfactory’ (1/9). They were considered to be applicable although not always compatible with systems already in place. In general, there were concerns that they may not be fully applicable in the field of ART.

The Vigilance and Surveillance Pilot was evaluated by the Vigilance Officers from the 22 participating Competent Authorities using a standard evaluation questionnaire. Overall appreciation of the toolkit was ‘very good’ (10/18), ‘good’ (6/18) or ‘average’ (2/18). The lower scores were given by the ART specialist regulators. The tools were considered to be practically applicable in all countries, even in countries with a system in place. They were considered to be logical and easy to apply, except in the field of ART. All participating competent authorities, except one specialist ART regulator, recommended that they be fully or partly incorporated.

The EUSTITE training courses were evaluated by 69 of the 71 course participants. Overall appreciation of the course was ‘excellent’ (42/69) ‘very good’ (24/69) or ‘good’ (3/69). Participants commented that the courses were very interesting and relevant and were practically applicable.
10.2 Measuring Impact: Indicators of Inspection and Vigilance System Performance

Anne Cathrine Bollerup, Danish Medicines Agency

Dr. Bollerup introduced the topic, explaining that evaluation was a crucial step in the quality cycle. Both inspection and vigilance systems should be evaluated to ensure that they are meeting their objectives and to facilitate continuous improvement. She stressed that it was important that indicators be measurable. The EUSTITE Inspection Guidelines and the Vigilance and Surveillance Tools had each provided some recommendations for system evaluation by Competent Authorities.

The Inspection Guidelines proposed that performance be evaluated according to the following criteria:

- **System performance**
  - Number of inspections per year
  - Number of centres licensed per year
  - Average time to final report
  - Number of preparation processes authorised per year
  - Time from application to licensing

- **Inspector performance**
  - Number of inspections per inspector/year
  - Number of centres licensed per inspector per year
  - Time from inspection to final report, by inspector
  - Number of preparation processes authorised, by inspector per year

- **Inspector qualification**
  - Extent and depth of inspection
  - Ability to recognise deficiencies
  - Assessment of deficiencies
  - Actions recommended
  - Effectiveness of actions carried out.

It was proposed that the following criteria could be evaluated for Vigilance Systems:

- Publication and dissemination of core values of the system,
- Implementation Strategy and Plan for V&S systems,
- Allocation of adequate resources at EC, CA and TE levels
- Education of all stakeholders regarding their role in the system
- Development of realistic SOP’s and related documentation eg. Investigation process for SARE, universal format for reporting forms to CA’s, templates forms for corrective actions, template for ‘Dear Dr’ Letters, etc.
- Engagement of relevant parties eg. clinicians, professional societies,
- Advice given to healthcare professionals of positive benefits for reporting
- Openness and transparency
- Demonstration that a wide range of people in different places and different professional roles have received information and understand the V&S System
In conclusion, Dr Bollerup stressed that it is important that each regulator establishes a system to evaluate their inspection and vigilance system. A structured evaluation process should be part of a Quality Management System. She concluded that it was timely to review the suggested indicators in the current two documents.

10.3 Group Discussion on Performance Indicators

Samuel Arrabal asked the participants to consider the indicators presented by Dr Bollerup and to discuss the following questions:

- Are there indicators that are inappropriate or missing?
- How should we prioritise the indicators?

The groups discussions were facilitated by the same individuals who facilitated during Session 9.

The facilitators provided feedback following the group discussions. The key points are summarized as follows:

- Every competent authority should have an action plan to disseminate to stakeholders.
- In every inspection, the inspectors should review all the reactions and events that TE have recorded and check if the serious ones have been communicated to the CA and if the procedure followed was in accordance with the SOP.
- It was considered that it might be necessary to define a time limit between occurrence and communication of SARE
- Clarity and consistency were considered important indicators.

Artur Kaminski introduced the final session of the Conference, asking Deirdre Fehily to present a project which will take forward the vigilance aspects of the EUSTITE project.
11.1 Looking to the Next EU Project – SOHO V&S
Deirdre Fehily, CNT, Italy

Deirdre Fehily explained that the European Commission publishes its priorities for projects in January of each year. In 2009 they chose to focus, for tissue and cells, on vigilance and surveillance and CNT decided to propose a new project which would address many of the issues in vigilance of tissues and cells that needed further work. A consortium was formed and a project proposal submitted. The project was approved for co-funding. Dr Fehily gave an introduction to the project, SOHO V&S – Vigilance and Surveillance of Substances of Human Origin. SOHO V&S is a 3 year project, with an intended start in February or March 2010.

The project will be co-ordinated by CNT, Italy, and will involve 8 associated partners and more than 20 collaborating partners. CNT, as the coordinating partner, together with the associated partners will hold the budgets but collaborating partners will have their travel and accommodation covered by the associated partners’ budgets. The collaborating partners are not allocated a budget and are invited to events as external experts (a contact name is required for each collaborating partner).

The aim of SOHO V&S is to support EU Member States in the establishment of effective vigilance & surveillance systems for tissues and cells used in transplantation and in assisted reproduction. The specific objectives include guidance to the CAs on the investigation and management of SARE, training of Competent Authority officers in investigation of SARE, development of guidance for clinical users in hospitals, promotion of global standardisation, communication in V&S and further enhancement of awareness among regulators, professionals and the general public.

The expected outcome and results of the project, as project deliverables are:

- A Report of a survey of EU V&S systems
- A Guidance document on V&S in ART
- A Report on SARs in living donors of tissues and cells
- Guidance on illegal and fraudulent activity in tissues and cells
- A Guidance document on the investigation and communication of SARE
- A Training course module for investigators of SARE
- V&S guidance for clinical units.

The project will have three elements: Exploration, Development of Guidance and Dissemination.
It was noted that contacts who are already registered on the EUSTITE website will have their access moved automatically to the new website for SOHO V&S and will receive the regular newsletters.

11.2 Looking to the Future – Harmonised European Tools in the Global Context
Luc Noel, WHO

Dr Noel argued for the need for an agreed approach to the use of the European tools in the global context.

The procurement of human material for transplantation implies ethical and safety risks for the donor and recipient. The WHO aims to meet the requirement of the fifty-seventh World Health Assembly resolution (WHA57.18). The WHA urges Member States to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability.
WHO supports national regulatory Authorities by providing guidance on the effective oversight of transplantation to ensure harmonisation in the areas of traceability, surveillance of SARs and SAEs safety and quality of human tissue or cells and organs, and to promote global cooperation and the harmonisation of technical and ethical practices in transplantation.

To ensure national support and understanding, a key factor is the establishment of a vigilance and surveillance system. The cooperation with EUSTITE, and the development of the EUSTITE V&S tools for common reporting and management of SARE, is of high importance in developing a global system. The tools will soon be presented, at a WHO Consultation meeting in February, following which, it is hoped, they may be the basis for the development of a global version.

Another important factor in developing a global V&S system is a national system for traceability of donated tissues and cells from donor to recipient. The adoption of a global system would promote standardisation of labelling, description and coding, and provide an opportunity for working in a harmonised way before developing different national coding systems.

Key aspects:
The WHO aims to facilitate the adoption and development of a global, common system. The WHO Executive Board Resolution specifically urges Member States:

- to implement the Guiding Principles on human tissues, cells and organs
- to foster public awareness and understanding of controlled transplantation
- to oppose the seeking of financial gain related to organ trafficking and transplant tourism
- to promote equitable access to transplantation services
- to improve the safety and efficacy of donation and transplantation
- to strengthen national Authorities to provide oversight, organisation and coordination of activities related to donation and transplantation
- to collaborate in collecting data on SAREs
- to encourage the implementation of global coding systems.

11.3 Conclusions and Final Remarks

Izabela Tyszkiewicz, National Centre for Tissue and Cell Banking, Poland

Izabela Tyszkiewicz informed the participants that a communication had been received from Maria Pilar LaCruz of the European Commission Directorate-General for Health and Consumer Protection. The message highlighted the contribution of the EUSTITE project to the implementation of the tissues and cells Directives in the EU. In particular, she noted that the EU Decision and Operational Manual on Inspection, in the final stages of adoption, were based on the EUSTITE guidelines and that most of the EUSTITE vigilance tools had already been incorporated in the official guidance to Member States for SARE reporting to the European Commission. She acknowledged the achievement of the training courses and the continuing contribution of the internet platform where inspectors discuss challenging issues. She evaluated the EUSTITE outputs as ‘solid’ and ‘reliable’ and attributed the success to the thorough nature of the work carried out. On behalf of the Commission, she thanked the EUSTITE partners for the work done, the
commitment shown and for the support they gave, individually and as a group, to the Commission during the project. She expressed particular thanks to Deirdre Fehily for her dedication to the project and support to the Commission.

Johann Kurz, on behalf of the project partnership, thanked Deirdre Fehily for her role as Technical Coordinator and Caterina Delvecchio, CNT, for her invaluable work in organisation and budgeting support throughout the project.

Deirdre Fehily, in turn, thanked all of the partners for their hard work and enthusiasm over the years of the project. She also acknowledged the enormous contribution of numerous individuals and organisations from the EU and many countries outside the EU who had supported the work of the project through participation in project events, peer review and commenting on draft documents. Finally, she thanked the presenters, the chairs, the facilitators, the rapporteurs and the Polish hosts of the conference who had done an excellent job in providing a perfect close to the EUSTITE project.
### Annex 1: Participants

<table>
<thead>
<tr>
<th>Participant Surname</th>
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## European Union Standards and Training for the Inspection of Tissue Establishments

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**Drafting Date:** 17 May 2010

**Status:** Confidential – level 1 (partnership only), Confidential – level 2 (partnership and key collaborators), Consultation, Public

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<td>John Rosendale</td>
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## European Union Standards and Training for the Inspection of Tissue Establishments

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Annex 2 - Conference Programme

EUSTITE FINAL CONFERENCE

Final Draft Programme
December 1st – December 4th 2009
Warsaw, Poland

This conference incorporates the 2nd Exploratory Workshop (WP 5), the final meeting of the V&S Medical Advisory Committee (WP 4b) and the final Project Partners Meeting (WP1) of the EUSTITE project.

1st December 13.00 – 16.00 - EUSTITE Project Partners meeting – Part I

2nd December

Inspection of Tissue Establishments and Tissue and Cell Procurement
9.00 – 9.15 Official Opening of the Conference - Artur Kaminski,
9.15 – 9.30 The EUSTITE Project - Aims and Objectives - Deirdre Fehily, CNT, Italy

Session 1: A Common Approach to Inspection in the European Union - Chair: Artur Kaminski
9.30 – 10.10 EUSTITE Inspection Guidelines – Deirdre Fehily, CNT, Italy
10.10 – 10.50 EUSTITE Training of Tissue and Cell Inspectors – Johann Kurz, Ministry of Health, Austria
10.50 - 11.00 NorPEP - The Nordic Partnership for the EUSTITE Project - Mike Cox, Danish Medicines Agency
11.00 – 11.30 Coffee

Session 2: Challenges of Implementation in Decentralised Inspectorates - Chair Jacinto Sanchez Ibañez
11.30 – 11.40 Introduction – Jacinto Sanchez Ibañez, Competent Authority, Galicia, Spain
11.40 – 12.00 Case Study 1: Spain – Harmonising regulation by the Autonomous Communities – Gregorio Garrido, ONT
European Union Standards and Training for the Inspection of Tissue Establishments

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Status: Confidential – level 1 (partnership only)
Confidential – level 2 (partnership and key collaborators)
Consultation
Public

12.00 – 12.20 Case Study 2: Germany – Harmonising regulation by the Länder – Isabel Astner, Braunschweig
12.20 – 12.40 Case Study 3: France – Harmonising ART regulation nationally – Dr Philippe Fourchtein, ABM
1.40 – 13.00 Open Discussion

13.00 – 14.00 LUNCH

Session 3: Challenges of Implementation in Small Member States - Chair: Jan Koller

14.00- 14.10 Introduction - Jan Koller, Slovakia
14.10 - 14.25 Case Study 1: Malta – Richard Zammit, Ministry of Health, Malta
14.25 - 14.40 Case Study 2: Cyprus – Carolina Stylianou, Tissue and Cell Inspectorate, Cyprus

Session 4: Challenges of Implementation of Certain Technical Requirements - Chair: Patrick Costello

15.00 - 15.15 Case Study 1: ART – facilities and testing – Trish Davies, HFEA, UK
15.15 - 15.30 Case Study 2: Interpretation of air-quality requirements (A in D) for processing of non-reproductive tissues – Patrick Costello, IMB, Ireland
15.30 - 15.45 Case Study 3: Inspecting Procurement – Emyr Harries, HTA, UK
15.45 - 16.00 EuroGTPS - developing technical guidance for tissue establishments - Esteve Trias, TSF, Spain

16.00 - 16.30 Coffee

Session 5: International Tissue and Cell Distribution - Chair: Johann Kurz

16.30 - 16.45 Tissues – Scott Brubaker, American Association of Tissue Banks
16.45 - 17.00 Gametes and embryos - Angela Sutherland, HFEA, UK
17.00 - 17.15 Haematopoietic stem cells - Per Llungman, EBMT
17.15 - 17.30 Ensuring equivalent safety of imported/exported tissues and cells: the US perspective – Anita Richardson, FDA
17.30 - 17.45 Ensuring equivalent safety of imported/exported tissues and cells: the EU perspective – Patrick Costello, IMB
3rd December
Vigilance and Surveillance of Tissues and Cells

Session 6: Reporting Serious Adverse Events and Reactions - Chair: Izabela Tyszkiewicz

08.30 – 8.50 EUSTITE Vigilance and Surveillance Tools - Luc Noel, WHO
8.50 - 9.40 The EUSTITE V&S Pilot - Stephanie Sullivan, EUSTITE Pilot Co-ordinator
9.40 - 10.00 Rapid Alerts in the EU – Mike Cox, Danish Medicines Agency
10.00 - 10.20 Horizon Scanning for Risk - Richard Tedder, Public Health Agency, UK
10.20 - 10.40 Responsive Safety Measures - Reacting to Risk – Mike Strong, USA

11.00 - 11.30 Coffee

Session 7: Engaging clinical users in vigilance and surveillance - Chair: Trish Davies

11.30 – 11.50 The Experience with Haemovigilance - Renè de Vries, International Haemovigilance Network
11.50 - 12.10 Tissue and Cell Vigilance at the Hospital Level in France - Fewzi Teskrat, AFSSAPS
12.10 – 12.30 A “New” US initiative (Hospital Tissue Management) – Scott Brubaker, AATB
12.30 - 13.30 Round Table - Scientific and Professional Societies
  Engaging tissue users in vigilance - Ruth Warwick (EATB)
  Engaging ART clinicians in vigilance - Luc Gianaroli (ESHRE)
  Engaging ocular surgeons in tissue vigilance - Esteve Trias (EEBA)
  Engaging HPC transplanters in vigilance - Carolina Stylianou (EBMT)

13.30 - 14.30 Lunch

Session 8: Electronic Vigilance Reporting - Chair: Ewa Olender

14.30 - 14.50 Simultaneous reporting to professional and regulator system - David Mold, Serious Hazards of Transfusion (SHOT), UK
15.10 - 15.30 Tissue and Cell Vigilance reporting to the FDA - Laura St Martin, FDA
15.30 - 15.50 V&S Annual Reporting to the EC - long term trending and monitoring - Deirdre Fehily, CNT, Italy
Session 9: Developing key recommendations for effective V&S in the EU and globally (Coffee during session) - Chair: Deirdre Fehily

16.00 - 17.00 – 5 working groups
Facilitators: Jacinto Sanchez, Caterina Delvecchio, Richard Zammit, Dagmar Doerman, Arnaud Deguerra

17.00 – 18.00 Working group feedback

4th December
Where to from here?

Session 10: Measuring Success - Chair: Samuel Arrabal

09.00 – 09.10 Introduction - Samuel Arrabal, ABM, France
09.10 - 09.30 Impact – EUSTITE indicators of V&S and inspection performance - Anne Cathrine Bollerup, Danish Medicines Agency
09.30 – 10.30

5 working groups:
Facilitators: Jacinto Sanchez, Caterina Delvecchio, Richard Zammit, Dagmar Doerman, Arnaud Deguerra

Are there indicators that are inappropriate or missing?
How should we prioritise the indicators?
Group feedback

10.30 – 11.00 COFFEE

Session 11: Looking to the future - Chair: Artur Kaminsky

11.00 – 11.20 Looking to the Next EU Project - ‘SOHO V&S’ - Deirdre Fehily, CNT, Italy
11.30 – 11.50 Looking to the future – Harmonised European Tools in the Global Context - Luc Noel, WHO
11.50 - 12.00 Conference Closing Remarks

12.00 Conference Close

4th December 13.00 – 16.00 - EUSTITE Project Partners meeting – Part II – Project Close