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HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Substances of Human Origin and Tobacco Control

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SUMMARY OF THE 2011 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND REACTIONS FOR TISSUES AND CELLS (DATA COLLECTED FROM 01/01/2010 TO 31/12/2010)

Article 7 of Directive 2006/86/EC provides that Member States (MS) shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events (SARE) received by the competent authority using the formats in Part A and B of Annex V.

This document intends to provide a summary report of the data collected during 2010 (from 1st January to 31st of December) received from the Member States, including preliminary conclusions.

1. DATA COLLECTION METHODOLOGY

Starting with 2008, when the first SARE reporting exercise was launched, DG SANCO together with a group of National Competent Authorities for Tissues and Cells participating in the EU-funded projects EUSTITE[1] and SOHO V&S[2] have been working together to refine the SARE reporting tools. These reporting tools include:

1) An electronic reporting template to be filled in by the Member States with their data from the previous year, from 1st January to 31st December. Once completed, the information is sent in html format to a DG SANCO hosted database. The template used in 2011 (for 2010 data) was version 1.2.

2) A Common Approach document which provides recommendations for the completion of the electronic reporting template for SARE, as required by the EU Directive 2006/86/EC, but has no legally binding status for Member States. This is a working document that was initiated in 2009 and has been updated annually in the light of the reports received in the previous years; its main aim is to clarify points that were ambiguous or interpreted inconsistently, thus gradually increasing the quality of the data collected from 27 different national sources. The version of the Common Approach document used in 2011 (for 2010 data) was 1.1 and guidelines from this document on reportable SARE are presented in Annex 1.

[1] http://ec.europa.eu/eahc/projects/database.html?prjno=2005204
[2] http://www.sohovs.org/soho/

2. MAIN FINDINGS OF THE 2010 DATA COLLECTION

2.1. General comments

The first reporting exercises have shown that data collection is still a difficult task. Even though MS have transposed and implemented the legal requirements of the 2006/17/EC Directive, at national level there are various approaches on how and when data collection is performed. Even though the quality of data has improved over the years due to the guidance provided in the Common Approach document, the data presented within this report should be considered as partial data and interpreted with appropriate caution.

The reporting template was sent to the EU27 MS as well as to Liechtenstein, Norway and Croatia. All the above mentioned countries send back answers.

It has to be noticed that in many cases the reports submitted had gaps and clearly missing or flawed information. As agreed by the Tissues and Cells National Competent Authorities, a quick quality check was performed for the first time; the submitted data (anonymized reports) were analysed by an expert working group from the SOHO V&S project. The results were sent back to the National Competent Authorities, who, based on this feedback, could fine-tune their submissions accordingly.

In 2011, the possibility to discriminate between missing/non-available data and 0 (no reactions, no events, no tissues/cells distributed or processed) was introduced. For most of the MS, the number of SAR/SAE was reported, but in many cases the number of tissues/cells distributed or processed was not included, raising questions about availability/accuracy of data. These latter numbers not only give indication about the national tissue banking activities, but are also used as denominators for SAR and SAE respectively. Moreover, some MS noted that not all TEs and end-users (hospitals, clinics) provided their data, which is another argument for interpreting the current data with appropriate cautiousness.

Although the last Common Approach document addressed many issues raised during the previous reporting exercises (e.g. measuring units, reporting in the area of Assisted Reproductive Technologies, etc) ensuring already a certain level of standardisation of the information format, it has proven to be misunderstood and/or inappropriately used by a certain number of respondents, thus impacting ultimately the quality and reliability of the information in the database. Therefore, the Commission decided to revise both the template and the Common Approach document (wording of questions, adequate definitions, improvement of the structure of the document) in advance to the next SAR/E reporting in 2012 (see section 3).

2.2. Serious Adverse Reactions (SAR)

2.2.1. Information by country

All MS, as well as Liechtenstein, Norway and Croatia submitted replies to the questionnaire and therefore complied with the annual report submission established by Article 7.

A total number of 329575 units of tissues and cells were distributed by tissue establishments in EU and EEA countries. It has to be highlighted that there are clearly

missing data linked to this information, and in some cases data reported had to be excluded because of atypical measurement units (e.g. skin expressed in m^2 and cm^2, and not in containers; cycles of artificial insemination instead of units of oocytes/sperm distributed) or non-compliance with the definition of the requested parameters (e.g. cord blood units procured and stored without distribution have been included in the category of tissues and cells distributed, etc.).

111025 recipients (patients) were reported for receiving some kind of tissue/cell transplantation. As for the tissues and cells distributed, only 20 countries (11 MS: AT, BE, CY, ET, FI, FR, GR, HU, IE, IT, LT, MT, NL, PT, SK, SI, ES, SE, UK, as well as LI and HR) provided data concerning both tissues and cells distributed and the number of recipients of tissues and/or cells. Five MS provided data only about tissues and cells distributed (CZ, DK, PL, SI, UK), while other 4 MS did not provide any data for tissues and cells distributed and number of recipients (GE, LU, LV, RO) or the number reported was 0 (BG).

A total number of 460 SAR have been reported for 2010 by 14 MS and HR. According to the data collected, when compared to the total amount of tissues and cells distributed, SAR occurred only in 0,14% of cases. However this percentage should be interpreted with caution because only 20 countries provided data for the distribution of tissues and cells and in some cases it was acknowledged that data submitted were only partial data, due to difficulties in collection of information from some of the end-users (hospitals/clinics).

15 countries (13 MS, NO and LI) reported that no SAR related to the human application of human tissues and cells occurred in their countries in 2010. At this stage it is not possible to make any comparison between MS, because in some cases a high number of reported SAR indicates that a reliable and accurate reporting system is in place, while in other cases the absence/low number of reported SAR cannot be always interpreted as an impeccably functional system.

2.2.2. Information by type of tissue/cell

Out of the 460 SARs reported:

- 291 SARs were related to the human application reproductive cells and tissues (gametes),
- 108 SARs were related to haematopoietic stem cells transplantations (including bone marrow, blood peripheral stem cells, cord blood, DLI and other stem cells)
- 52 SARs were related to transplantation of replacement tissues (bone, tendon and ligaments, cornea, heart valves, amniotic membrane)
- 9 SARs were related to therapies with advanced-therapy medicinal products (ATMP) which included human cells.

No SARs were reported for the following categories of tissues and cells: cartilage and other skeletal tissues, skin, sclera and other ocular tissues, blood vessels and other cardiovascular tissues, chondrocytes, hepatocytes, pancreatic islets, other tissues (e.g. fat tissues, umbilical cord segments), embryos and other reproductive tissues (e.g. ovarian or testicular tissues).

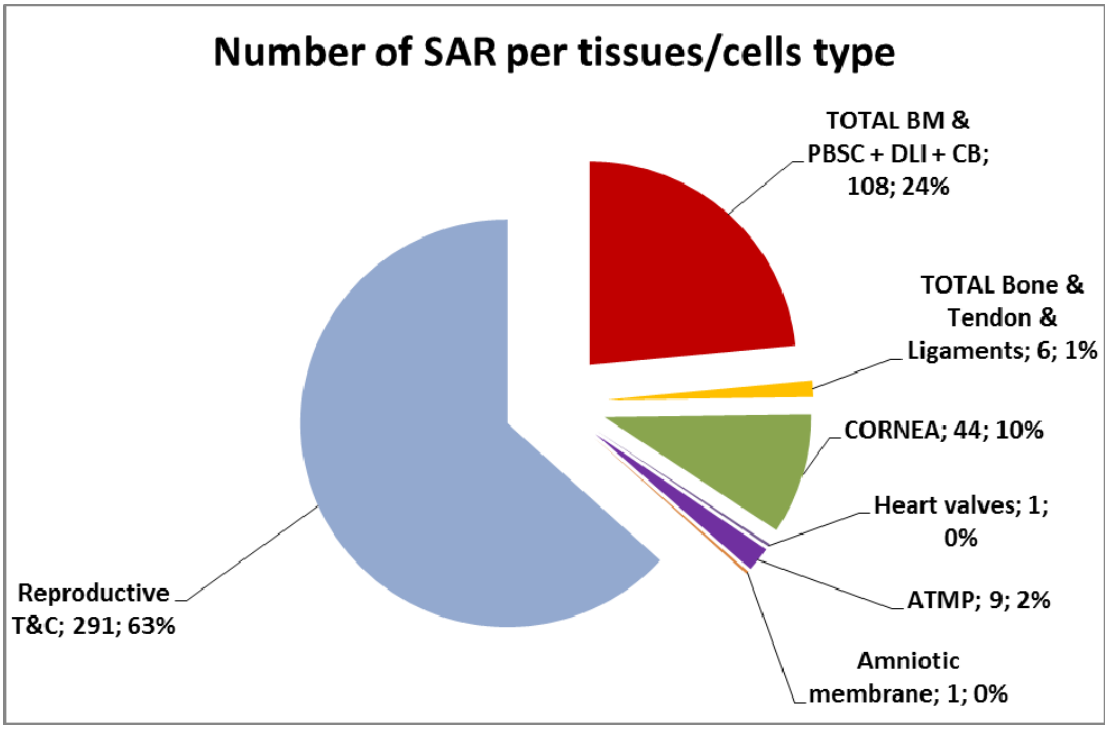

Fig.1. Number of SAR per tissues and cells type.

Legend: BM = bone marrow; PBSC = peripheral blood stem cells; DLI = donor lymphocyte infusion; CB = cord blood; ATMP = Advanced Therapy Medicinal Products

2.2.3. Information by category of SAR

The 460 SARs reported were classified as following:

- Transmitted infections: 42 cases (9,13% of reported SARs), out of which:
  - 38 cases of bacterial infections (reported for the following transplanted tissues/cells: gametes 25, cornea 6, cord blood 3, bone 2, amniotic membrane 1 and peripheral blood stem cells 1);
  - 1 case of parasitical infection (Acanthamoeba infection following cornea transplantation) and
  - 3 cases of viral infections (one case of CMV infection transmitted via sperm; one case of HSV transmission following cornea transplantation and one case of HCV infection following treatment with donor lymphocyte infusion).
- Transmitted malignant diseases: 2 cases (0,43% of reported SAR), both reported following transplantation of haematopoietic stem cells (bone marrow and cord blood respectively).
- Other disease transmissions: 3 cases of fungal infections (0,65% of reported SAR) reported in 2 cases cornea transplantation and one case of cord blood transplantation.
- Other SAR: 413 cases (89,78% of reported SAR). In this broad and heterogeneous category, 265 SARs were associated to ART procedures, 100 SARs concerned haematopoietic stem cells transplantation procedures, 39 SARs concerned transplantation procedures with replacement tissues (bone, tendons and ligaments, cornea and amniotic membrane) and 9 SARs occurred following therapies with tissues related-ATMPs. This last category of SARs was also reported via the pharmacovigilance system.

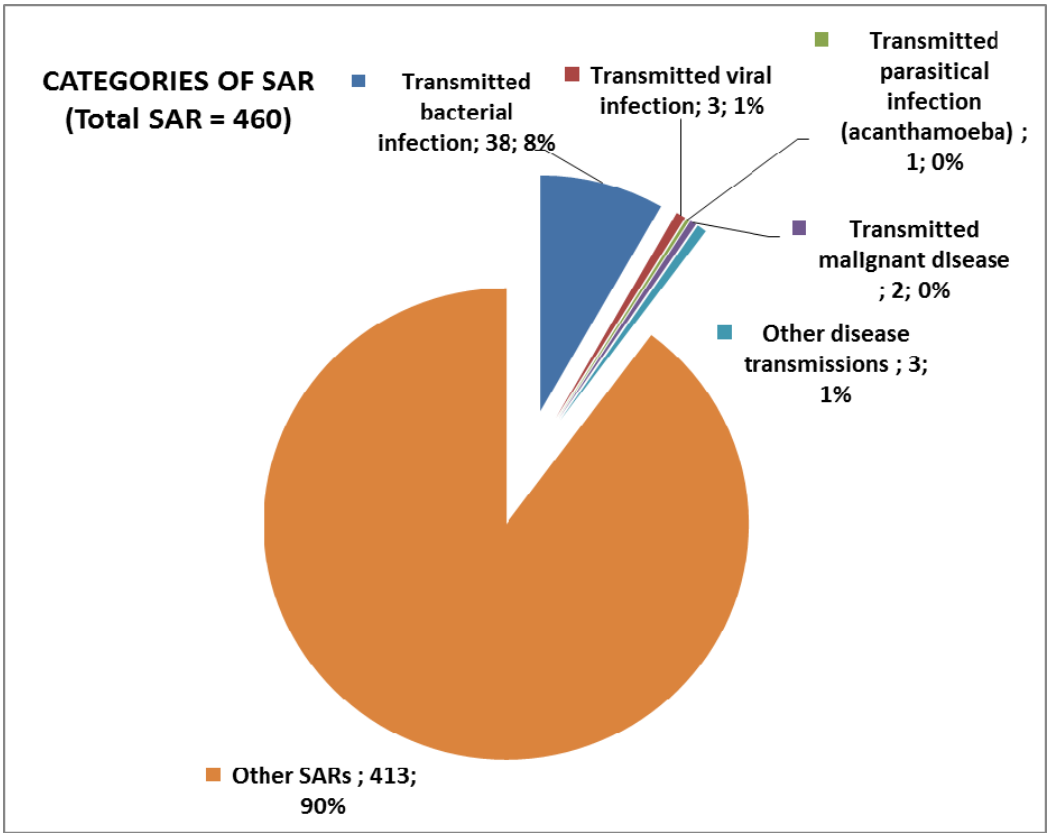

Fig. 2. Number of SARs per category

Concerning the high number of "other SAR" reported for the ART field, it has to be noted that under this category, 209 cases of severe ovarian hyper-stimulation syndrome (OHSS) were reported, which were also reported via the pharmacovigilance system. In the future such reactions should be reported only under the "SARs in donors" category.

2.3. Serious Adverse Events (SAE)

2.3.1. Information by country

A total of 30 countries (27 MS, Lichtenstein, Norway and Croatia) did answer the questionnaire and therefore complied with the annual report submission established by Article 7.

15 MS (CZ, DK, ET, GR, HU, IE, LT, MT, NL, PL, PT, SK, SI, SE, UK), as well as Lichtenstein and Croatia provided data regarding the number of tissues and cells processed in 2010. For the purpose of this reporting, the term "tissues and cells processed" refers to tissues and cells processed in the tissue establishments, but not necessarily distributed to the end-users. Overall, a total number of 477039 units of tissues and cells were processed in 2010.

SAE were reported by 17 MS (AT, BE, CZ, DK, FI, FR, GE, GR, HU, IE, IT, NL, PT, SI, ES, SE, UK) and NO. The total number of SAE reported for 2010 was 451, representing 0,095% of the tissues and cells processed in the same period of time. As in case of SAR, the percentage of SAE in relation to the total number of tissues and cells processed should be interpreted with prudence because some of the countries reporting SAE did not provide the number of tissues and cells processed at national level, in in

some cases it was mentioned that reported data were not provided for all categories of tissues/cells processed in 2010.

2.3.2. Information by type of SAE

Out of the 451 reported SAE:

- 74 SAEs (16,41%) were linked to "Procurement",
- 26 SAEs (5,76%) were linked to "Testing",
- 16 SAEs (3,55%) were linked to "Transport,
- 172 SAEs (38,14%) were related to "Processing",
- 34 SAEs (7,54%) were linked to "Storage",
- 40 SAEs (8,86%) were linked to "Distribution",
- 33 SAEs (7,32%) were linked to "Materials",
- 56 SAEs (12,42%) were included in the category "Other SAE".

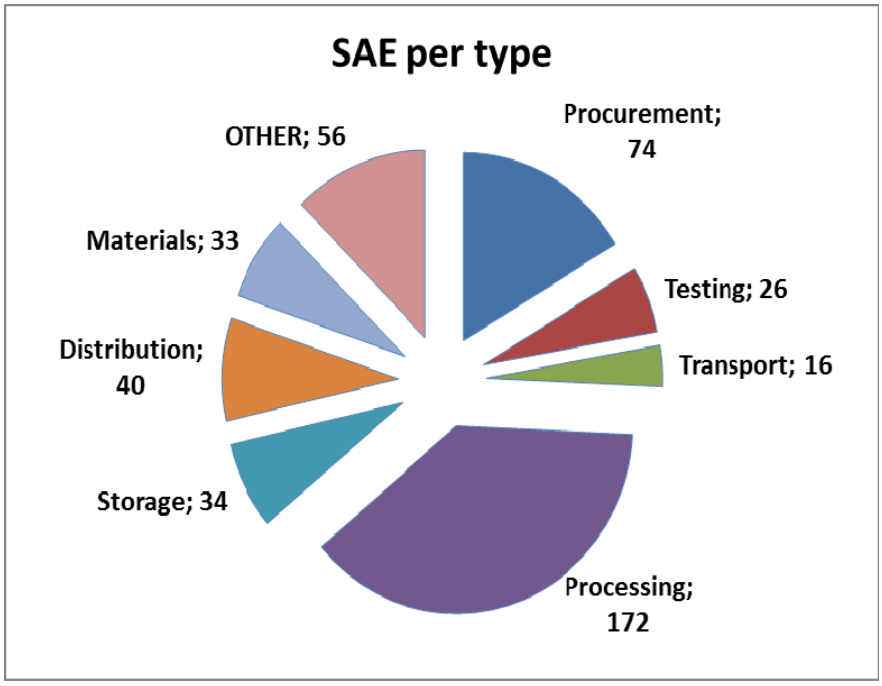

Fig. 3. Serious adverse events per type

2.3.3. Information by Specification of SAE

The 451 SAE were attributed to one of the 4 specifications:

- Tissues and cells defects: 149 SAE (33,04%)
- Human Error: 168 SAEs (37,25%)
- Equipment failure: 81 SAEs (17,96%)
- Other: 53 SAEs (11,75%).

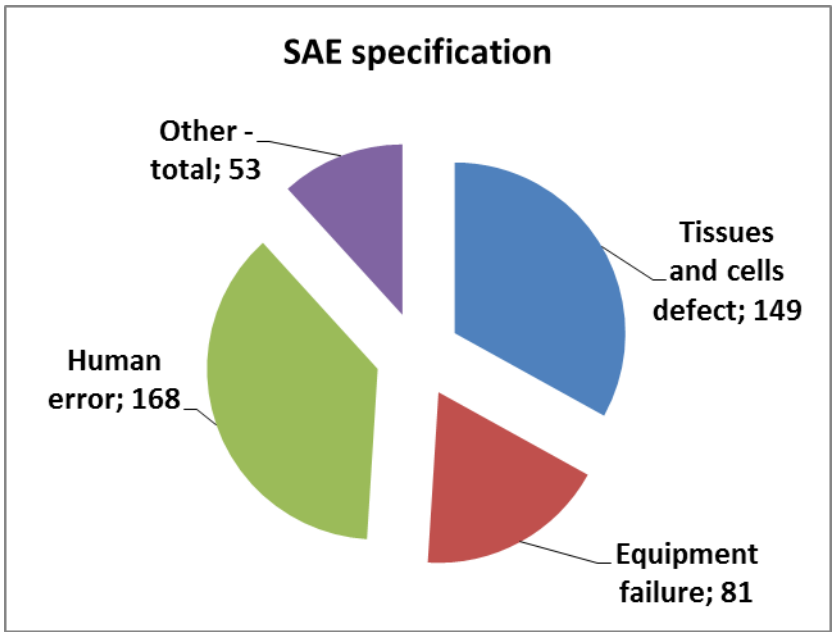

Fig. 4 Serious adverse events per specification

2.4. Serious Adverse Reactions (SAR) in donors

Serious adverse reactions in donors were also included in the annual report because definition of SAR in the Directive 2004/23/EC refers also to donors. However, Article 11 of that Directive specifies that only those reactions that 'influence the quality and safety of tissues and cells' should be reported. It was noted that many Member State competent authorities currently collate, or will soon begin to collate, information on donor adverse reactions not influencing the quality and safety of tissues and cells. Reactions such as OHSS and reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection, or reactions which result in harm to the donor i.e. cardiac or neurological episode, might impact on the willingness of donors to donate and therefore on the supply for patients needing treatment. In general, these reactions fall outside the scope of the tissues and cells Directives and should be reported to pharmacovigilance systems where appropriate. Conversely, the Commission recognizes the value of this data in the context of tissue and cells regulation, and invited Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template. The declared figures were calculated separately, and were not included under the total number of SARs.

For 2010, a number of 50 SAR in donors were reported. Eight MS provided data related to SARs in donors (AT, BE, FR, IE, IT, ES, SE, UK) and HR, as following: 30 were related to activities in the field of ART, 16 were connected to the haematopoietic stem cells transplantation procedures, and 4 were associated to procedures involving other tissue types. It has to be noted that 209 cases of severe OHSS were reported under SAR, but in the future such reactions should be reported only under the "SARs in donors" category.

3. TOWARDS AN IMPROVED REPORTING IN 2012

A revised version of Common approach for definition of reportable serious adverse events and reactions was developed by the Commission together with NCAs participating in the EU-funded SOHO V&S project and was provided before the launch of the 2012 SARE reporting exercise.

The PDF reporting template for the 2012 reporting exercise (for data reported in 2011) has been technically revised, and semantic and structural gaps were corrected.

Two hands-on training sessions for inspectors/professionals in National Authorities involved in the collection and reporting of SARE data at national and EU level were be organised by the SOHO V&S project (June and September 2012). The training sessions were open to all EU MS and provided both theoretical and practical guidance for the SARE submission.

4. CONCLUSION

Based on the reported data, the number of SAR and SAE reported for 2010 is low (460 and 451 respectively), especially when compared to the number of tissues and cells distributed and processed at EU level (0,14% and 0,095%). Nevertheless, these data need to be interpreted with caution due to the fact that in many MS it is still difficult to collect accurate data for both SAR/SAE and the two denominators (tissues and cells distributed and tissues and cells processed).

Due to the improvements in the template and Common Approach Document, the 2011 reporting exercise included more data than in the previous years, and the majority of submissions followed the definitions provided in the Common Approach Documents. However, both the Commission and National Competent Authorities for Tissues and Cells acknowledge that there is an under-reporting due to various causes which need to be further addressed (e.g. different periods for data collection in the MS, different definitions used for data collection at national vs. EU level, raising awareness of end-users of the importance of reporting SARE for the benefit of the entire professional community working in the area of tissues and cells for human application).

Overall, the SARE annual reporting exercises show that there remains much work to be done to improve data collection and accuracy. Based on this learning by experience process, it is expected to have information of better and better quality in the next couple of years, which will help in drawing trends in the safety of tissues and cells, and improve the safety of European patients in Europe.

ANNEX 1

A. GUIDANCE ON REPORTABLE SERIOUS ADVERSE REACTIONS (SAR)

The electronic report template includes a number of terms from Annex V, part A of Directive 2006/86/EC (Annual notification for serious adverse reactions). The following definitions/interpretations are proposed to ensure a common approach to reporting this data.

1. Number of tissues and cells of this type distributed

According to Article 3 (k) of Directive 2004/23/EC distribution "means transportation and delivery of tissues or cells intended for human applications". 'Human application' is defined in the same article as follows: "means the use of tissues or cells on or in a human recipient and extracorporeal applications'.

In the annual report, the number of tissues and cells of this type distributed should be understood to mean 'the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or the same floor'**.** If tissues and cells are returned to the Tissue Establishment (TE) without use and for subsequent redistribution, they should be counted only when subsequently redistributed. Where tissues or cells pass from one TE to another TE before distribution, they should not be included in this total until finally distributed for clinical application.
The quantity of tissues and cells distributed by a TE could be extracted from the annual activity report that all TEs submit to the CA in accordance with Article 10 of Directive 2004/23/EC.

This field should be completed for each type of tissues or cells distributed in the Member State, even if no SAR was reported for that tissue or cell type. This is the national distribution activity that provides a denominator for the frequency of reactions for this type of tissue or cells. These data will allow the calculation of SAR rates in relation to numbers of tissues distributed in the European Union. Where data regarding the number of tissues or cells distributed is not available to the competent authority they should leave this field blank. The '0' option should only be chosen when it is known by the competent authority that no tissues or cells of that type have been distributed in the Member State.

The understanding of "Number of tissues and cells of this type distributed" can vary depending on the organisation of the transplant or Assisted Reproductive Technologies (ART) system in a given country, in particular regarding certain types of tissues and cells that can be processed and packaged in a wide range of different ways. The following is a proposed common approach to counting units distributed:

- Skeletal Tissues**:** One unit is one individually packaged graft (e.g. one femoral head, one unit of demineralised bone, one container of bone chips, one femoral strut, one osteochondral allograft, one individually packaged tendon or part of a tendon).
- Haematopoietic Stem Cells**:** One unit is one single bag or container of cells.
- Ocular Tissues**:** One unit is one individually packaged or contained graft (e.g. one cornea, one piece of sclera).
- Cardiovascular Tissues**:** One unit is one individually packaged or contained graft (e.g. one valve, one package containing one or more lengths of vessel).

- Reproductive Tissues and Cells: One unit of sperm is one individual straw, the contents of which will be applied at once or one individual embryo or one individual oocyte.
- Skin: One unit is one container of skin, regardless of the area of skin it contains.
- Amniotic Membrane: One unit is one container of tissue, regardless of the area of tissue it contains.

2. Total number of recipients for this type tissues and cells (number of recipients affected)

This should be understood to mean the total number of patients who received applications with this type of tissues or cells in the country in the reference year, regardless of whether they had a reaction or not. This is the national activity that provides a denominator for the frequency of reactions for this type of tissue or cells. These data will allow the calculation of SAR rates in relation to numbers of tissues or cells clinically applied in the European Union. It is acknowledged that not all Member States currently collect data on the total number of patients treated with each type of tissue or cells. If this information is not available, it should be noted in the comments space provided.

If this information is available, it should be understood as the number of individual patients who had at least one unit of tissues or cells applied as a transplant or during assisted reproductive therapy during the year concerned in a given country. It should be completed, even if there was no SAR associated with this type of tissues or cells. The goal of this definition is to aggregate the number of individual patients to whom tissues or cells were applied over a year in the country, i.e. not specifying whether they received single or multiple applications during the period. If it is impossible to trace patients/persons at national level (e.g. no unique national ID/reference number or no national collation of these data), calculation should be done as a minimum at hospital or clinic level, in order to limit statistical bias or possible overestimations caused by some patients having several tissue or cell applications in different places during a year. If this information is not available at a national level, the field should be left blank. '0' should be selected only if it is known by the competent authority that no tissues or cells or this type were clinically applied in the Member State.

3. Nature of Serious Adverse Reaction(s) reported

3.1. The annual report template previously included 5 categories of disease transmission (bacterial infections, viral infections, parasitic infections, malignant disease and other disease transmission). Prion, immunological and genetic disease transmissions could be included in the 'other disease transmission' category. The following category has been added: "Other Adverse Reactions" to allow the reporting of serious adverse reactions that do not involve a disease transmission, e.g. structural graft failure, toxicity of excipients such as dimethyl sulfoxide (DMSO), allergic reactions or unnecessary repeat surgery due to the provision of an incorrect or unsuitable tissue or cells (referred to as 'undue risk'), that would fall under the definition of SAR in the Directive.

3.2. **Serious adverse reactions in donors** should be included as the definition of SAR in Directive 2004/23/EC includes serious reactions in donors. However, Article 11 of that Directive specifies that only those reactions that 'influence the quality and safety of tissues and cells' should be reported. It is noted that many Member State competent authorities currently collate, or will soon begin to collate, information on donor adverse reactions not influencing the quality and safety of tissues and cells. Reactions such as

Ovarian Hyper-Stimulation Syndrome (OHSS) and reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection, or reactions which result in harm to the donor i.e. cardiac or neurological episode might impact on the willingness of donors to donate and therefore on the supply for patients needing treatment. In general, these reactions fall outside the scope of the tissues and cells Directives and should be reported to pharmacovigilance systems where appropriate. The Commission recognizes the value of this data, in the context of tissue and cells regulation, and invites Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template. The declared figures won't be calculated as part of the total number of SARs.

4. Number of serious adverse reactions

4.1. A common approach to this definition is required to clarify whether, for example, a defect in a tissue processing batch or a multiple donation by a sperm donor should be considered as 1 adverse reaction or multiple adverse reactions, where multiple tissue recipients or multiple children born following ART are adversely affected by the defect. Each individual who has an adverse reaction following the application of human tissues or cells, and where the reaction is 'serious' and can be linked to the tissues or cells applied, should be counted as 1 adverse reaction report.

4.2. Reactions should be included in this number only if they were serious in nature. Directive 2004/23/EC defines serious as "fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity."
The following severity assessment tool is proposed:

Insignificant	No harm to the recipient therefore considered as reportable as an event according to the EU Directives
Non-serious:	Mild clinical consequences which do not necessitate hospitalization and/or result in long term disability or consequences for the recipient or living donor.
Serious:	Adverse reaction resulted in: - hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity and/or - medical or surgical intervention to preclude permanent damage or impairment of a body function and/or - there is evidence of a serious transmissible infection and/or - evidence of a transmission of a communicable disease and/or - evidence of a genetic abnormality in a child born following ART with gamete donation and/or - disabling or incapacitating conditions
Life-threatening:	- The living donor or recipient required major intervention following procurement or the tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death and/or - There is evidence of a life-threatening transmissible infection and/or - There is evidence of a life-threatening genetic abnormality in a child born following ART with gamete donation.
Death:	Death

It should be understood that "Serious", "Life-threatening" and "Death" categories are reportable.

4.3. It should be understood that, as stated in Article 6(2) of Directive 2006/86/EC, 'in the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered as a serious adverse event.' Therefore, even if such an event causes serious psychological damage, it should not be reported as a serious adverse reaction. However, if a SAR occurred as a result of gamete or embryo misidentification i.e. disease transmission, then it should be reported as an adverse reaction.

4.4. It should be understood that only SARs for which the investigation has been completed should be included in the annual report. SARs which are still pending should remain for the report of the following year and should only be included once they have been investigated and closed. The annual report to the European Commission aims to monitor the actual reactions which have occurred during the past year in the European Union. At this stage, it is not part of any EU wide tissue and cell vigilance system e.g. a large scale rapid alert mechanism. Therefore only the confirmed cases of serious adverse reactions which were submitted within the reporting year shall be included in the annual report template. Suspected serious adverse reactions must be communicated to the competent authority but those should not be included within the annual report to the European Commission unless they have been fully confirmed at the date of submission of the report.

4.5 Where implicated tissues or cells have been distributed to more than one EU Member State, the CA in the Member State where the tissues or cells originated and where the reactions occur should communicate and include in their respective reports the affected recipients and reactions occurred in their respective country, so as to ensure that recipients affected are included in just one report.

4.6. It is further proposed that where national Competent Authorities accept SAR that fall outside the strict interpretations of the EU Directives, the Commission encourages these to be indicated separately on the report template, in the space provided. This will allow Member States to evaluate the added value of extending the definition on a voluntary basis.

4.7. According to Article 11(1) of Directive 2004/23/EC, SAR should be reported "which may be attributable to the procurement, testing, processing, storage and distribution of tissues and cells as well as any serious adverse reactions observed during or after clinical application which may be linked to the quality and safety of tissues and cells". This link between a reaction in a recipient and the tissues and cells applied can be referred to as 'Imputability'.

Only reactions that are reasonably considered to have been caused by the tissues or cells applied, or the procurement process in the case of a donor, should be included in the annual report.

The following imputability assessment tool was proposed:

Not assessable	When there is insufficient data for imputability assessment

NA	
Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes
Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
Possible 1	When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells, to the donation process, or to alternative causes
Likely, Probable 2	When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)
Definite, Certain 3	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)

In general, reports which fulfil the reporting criteria and where imputability is 1 to 3 should be included.

B. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAE)

The electronic report template includes terms which are taken from Annex V, part B of Directive 2006/86/EC (Annual notification for serious adverse events). The following definitions/interpretations are proposed to ensure a common approach to reporting this data.

1. Total number of tissues and cells processed:

1.1. It should be understood that this term refers to tissues and cells processed in TEs but not necessarily distributed**.** It should be completed, even if there was no SAE associated with this type of tissues or cells reported. These data will allow the calculation of SAE rates in relation to numbers of tissues or cells processed in the European Union. If this information is not available at a national level, the field should be left blank. '0' should be selected only if it is known by the competent authority that no tissues or cells or this type were processed in the Member State.

Article 3(g) of Directive 2004/23/EC defines processing as 'all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications'.

1.2. The units for reporting in this section should be the same as those proposed for finished tissues and cells at the end of distribution.

2. Total number of serious adverse events which may have affected quality and safety of tissues and cells due to a deviation in: Procurement, Testing, Transport, Processing, Storage, Distribution, Materials, Others (specify)

Only those adverse events which indicate a serious risk should be reported. Quality systems aim to maintain a consistently high quality in the processes and actions undertaken within a TE. Quality systems are based on standard operating procedures (SOPs) and methods to detect variation, deviations, or breaches of these SOPs, namely "events". In other words, a quality system aims intrinsically to detect events and to ensure that corrective and preventive actions prevent them from causing harm to patients. Not all these events are adverse; nor are all adverse events serious. Therefore, it is important to clarify when an adverse event becomes serious and reportable.

The following criteria are proposed for the evaluation of SAE which are reportable to Competent Authorities and, subsequently, to the Commission:

1. Inappropriate tissues/cells have been distributed for clinical use, even if not used;
2. The event could have implications for other patients or donors because of shared practices, services, supplies or donors;
3. The event resulted in a mix-up of gametes or embryos;
4. The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;
5. The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

3. Specification of SAEs:

The following categories are provided in Annex V, part B of Directive 2006/86/EC and in the electronic annual report template:

- Tissues and cells defect (specify): this should be understood as a defect in the quality or safety of the tissues and cells due to an inherent unpredictable safety or quality deficit, e.g. a defect due to an undiagnosed illness or genetic factor or an unknown exposure to a toxic agent.
- Equipment failure (specify): this should be understood as a defect in the quality or safety of the tissues or cells due to a fault in critical equipment used in procurement, processing, storage or distribution.
- Human error (specify): this should be understood as a defect in the quality or safety of the tissues or cells due to an error by a member of personnel during procurement, processing, storage or distribution.
- Other: this should be understood as a defect in the quality or safety of the tissues or cells due to any other cause during procurement, processing, storage or distribution.