TECHNICAL GUIDELINES FOR OCULAR TISSUE*

GENERAL.

The following Guidelines take into account the following European Directives which are mandatory in those countries that belong to the European Union:

- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC with regards to certain technical requirements for the donation, procurement and testing of human tissues and cells.
- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC with regards to certain technical requirements for the coding, processing, preservation, storage and distribution of human cells and tissues.
- Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells
- Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.

Suitably trained, designated and authorised personnel, following national legislation and requirements, should perform all tasks according to validated, up-to-date, document-controlled standard operating procedures (SOPs) in relation to:

1 Ocular tissue retrieval
2 Processing and storage of corneal tissue including tissue lamella preparation for surgery techniques (e.g. DSAEK, DMEK etc.)
3 Corneal tissue evaluation and selection for transplantation
4 Scleral tissue
5 Amnion tissue
6 Tissue distribution and follow-up

1 OCULAR TISSUE RETRIEVAL.

The following should be carried out in compliance with EEBA Minimum Medical Standards:

1.1 Retrieval of the tissue should be performed by qualified and trained personnel.

1.2 Prior to the actual retrieval procedure:

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* Guidelines reviewed by the EEBA Technical Guidelines Special Interest Group in September 2018 [Andrea Gareiss-Lok (Chair, München), Stefan Ek (Mölndal), Lisa Dahlström (Örebro), Wessel Vermeulen (Beverwijk), Sabine Salla (Aachen)]. Revisions to be submitted to the EEBA Business Meeting on 19 January 2019 for approval.

** In the EU, the Responsible Person has the role and responsibilities as defined in EU Directive 2004/23/EC. The term 'Responsible Person' for eye banks in non-EU countries shall refer to the person with overall responsibility for the quality and safety standards and may be a Medical Director or other suitably qualified person.

- Identify the donor according to national legislation and the eye bank's standard operating procedures which have been approved by the Responsible Person**/ her/his designee[SS1].
- Where required, ensure that consent or no objection to donation has been properly obtained and documented.
- Check donor's medical records, charts/interviews etc. for any contraindications for donation according to guidelines and/or recommendations [SS2]for further risk assessment which may rule out the donation. New and emerging diseases including those that have spread to new geographical areas (e.g. Ebola, Zika, West Nile Virus etc.) need to be taken into consideration and a careful screening of donors travel history becomes necessary (for further information see https://ecdc.europa.eu/en and www.transfusionguidelines.org for the UK Blood Services Geographical Disease Risk Index and http://www.notifylibrary.org for serious adverse reactions caused by disease transmission).
- Perform an inspection of the donor's body to check for any signs of medical contraindications according to actual guidelines and recommendations.
- If possible, perform an inspection of the ocular globe with special focus on the corneas with a view to the medical contraindications. If not possible prior to retrieval this should be done as soon the globes arrive to the eye bank.
- Document all significant, suspicious and pathological findings.

1.3 Blood sample:

- While drawing/collecting blood sample, make sure correct tube sample (e.g. tube for plasma) is taken in accordance with samples of required test-kits. Correct labelling of all samples is mandatory.
- Draw a post-mortem blood sample, recording the date and time of sampling, within 24 hours post-mortem (EU-Directive requirement) and in accordance with national legal requirements (e.g. time frame of refrigeration of donor body). Be aware that ~~used~~ test-kits for donor testing has to be suitable/validated for usage of cadaveric blood samples.
- A suitable ante-mortem blood sample obtained just before death (or taken up to max. 7 days before death) may be used for donor testing provided identification can be ensured (see EEBA Minimum Medical Standards – Donor Medical Assessment and Laboratory tests for donors, EU Directive). The date and time of sampling should be recorded to indicate that it is an ante-mortem sample and taken within the time-frame.
- If a donor has been transfused with blood, blood products, colloids or cystalloids in the 48 hours before death, the risk of haemodilution must be assessed in accordance with national requirements/legislation (see also EEBA Minimum Medical Standards page2 *Testing of Donor* and Council of Europe *Guide to the Quality & Safety of Tissues and Cells for Human Application, 3rd edition* [EDQM *Quality & Safety Guide*]).

1.4 Retrieval.

Ensure that the retrieval is performed within the post mortem time limits approved by the Responsible Person / her/his designee *(*EDQM *Quality & Safety Guide* recommends a maximum post-mortem time of 48 hours*)*. Details of post mortem time limits for EEBA member eye banks can be found in the EEBA Annual Directory.

- Retrieve either the whole eye by *enucleation* or the corneoscleral disc by *in situ* excision using validated aseptic procedures.
- Place the whole eye in a fixed position in a moist chamber, or immerse the corneoscleral disc in an appropriate corneal storage solution.
- Make sure that all tissues are labelled (e.g. SEC-coding) for clear identification at every time point.
- Indicate the lot number (including expiry date) of all materials and equipment used that comes into contact with retrieved tissues.
- Single-use materials and equipment are preferred. If re-usable instruments are used, it is recommended that the identification code of the instruments or instrument sets is recorded is recorded for the purposes of traceability. Re-usable instruments must be cleaned and sterilised by a validated protocol.

1.5 Transport the tissue to the eye bank for further processing as soon as possible in accordance with a validated procedure (e.g. validated transport box etc.).

2 PROCESSING AND STORAGE OF CORNEAL TISSUE.

2.1 General.

- Use only reagents and materials from suppliers that meet the documented requirements and specifications approved by the Responsible Person / his designee. CE/pharmacopeia-labelled materials/chemicals are recommended.
- All procedures must be documented in written and periodically revised SOPs, including method and dates for decontamination, endothelial evaluation and microbiological testing of the tissue. Where necessary the time point should also be documented. Use aseptic techniques while processing the tissue in the eye bank.
- The required air quality standard of the environment (air particle/CFU-count) in which the corneal tissue will be processed should be defined and monitored routinely (usually class A equivalent in a laminar flow cabinet with a minimum of class D background).
- Considering that:
  - post-mortem eye tissue is generally contaminated,
  - the amount of remaining contaminating microbes is dependent on pre-storage decontamination procedures, antibiotics during storage, and storage procedure.

  Each bank should collect data to demonstrate and document that the defined standard of the environment achieves the required quality and safety of the corneal tissue (e.g. monitoring plan).

2.2 The following methods for preparation of the cornea are accepted:

- Excision of the corneoscleral disc from enucleated whole eyes *in vitro*.
- Excision of the corneoscleral disc from the donor eyes *in situ*.
- Lamellar tissue preparation of the corneoscleral button using manual, automated or lasers methods.

2.3 The following storage methods are generally accepted for the viable cornea:

- Hypothermic storage of the whole eye. Maximum recommended storage time is 72 hrs for selected surgeries. New surgical techniques may lead successfully to longer storage times which should be left to the discretion of the Responsible

Person / her/his designee of the individual eye bank.
A slit lamp examination is mandatory and, if possible, the endothelium examined to estimate endothelial cell density. If the latter is not possible, the cornea should be used only for procedures that do not require a viable endothelium. The Responsible Person / her/his designee must ensure that all the necessary serological and, where appropriate, NAT tests on the donor have been performed within this limited storage period. Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon.

- Storage of corneoscleral discs in a hypothermic storage solution at +2-8°C: Maximum storage time depends on the storage medium used following the manufacturer's recommendations. Longer storage times should be approved and left to the discretion of the Responsible Person / her/his designee in consultation with the transplanting surgeon (e.g. usage for tectonic graft /stromal patch).
  An inspection of the endothelium is mandatory and the cell loss during storage must be taken into account, except for tissue to be used for procedures that do not require a viable endothelium. Due to the short time of storage, it is not possible to wait for the final result of sensitive microbiological testing of the culture medium using traditional microbiological testing (e.g. blood-culture bottles) but there are alternative testing-methods available. However, sampling of the culture medium one day after the start of the storage period, or just before delivery for clinical use is recommended. The efficacy of the used microbiological testing method should be evaluated and validated due to the presence of antibiotics within the storage media, releasing tissues with 'negative-to-date' result after 48h incubation. The treating physician/receiving transplanting centre should be informed as quickly as possible in the event of a 'late' positive result. Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon (see 3.7).
- Storage of the corneoscleral button by organ culture at +28-37°C: It is recommended to keep the storage time as short as possible with a maximum of 34 days for selected surgery cases. Longer storage times should be approved and left to the discretion of the Responsible Person / her/his designee in consultation with the transplanting surgeon (e.g. usage for tectonic graft /stromal patch). [SS3]Inspection of the endothelium is mandatory and should be preferred in any case at the end of the storage period except for procedures that do not require a viable endothelium. Inspection of the endothelium also at the start of storage allows the endothelium cell loss to be determined.
  A minimum storage period is mandatory to allow for microbiological testing of organ culture medium to minimize the risk of bacterial/fungal contamination. The time period required to perform microbiological tests of the storage medium is at the discretion of the Responsible Person / her/his designee. The efficacy of this quarantine period and the microbiological testing method should be evaluated and validated considering the effectiveness of antibiotics within the storage media (see also the EDQM Quality & Safety Guide for advice and guidance on microbiological testing).
  Microbiological testing of media samples is mandatory, sole reliance on visual inspection of the medium for a change in colour or transparency is not

acceptable. Medium changes during storage using aseptic procedures is at the discretion of the Responsible Person / her/his designee and/or the recommendations of the medium manufacturer and taking into consideration that corneal endothelium might be stressed when transferred into other solutions/media. Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon (see 3.7).

- The procedure and technique used to prepare lamellar tissue in the tissue bank should be evaluated, validated and regularly reviewed and, if possible, including microbiological testing (e.g. testing of transport media and/or lamella/remaining piece of tissue after preparation) intervals decided by the Responsible Person / her/his designee. Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon (see 3.7). NOTE: some EU countries require separate/specific 'allowances' for lamella preparation in the eye bank.
- [SS4]Cryopreservation may be used for non-viable tissue for tectonic grafting. Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon (see 3.7).

Details about tissue storage time within EEBA member eye banks can be found within EEBA annual Directory.

3 CORNEAL TISSUE EVALUATION AND SELECTION FOR TRANSPLANTATION[1].

3.1 General.

The findings of the specific layers may relate to contraindications if tissue is planned to be used for full-thickness graft (PKP). Due to the variety of different and new surgical techniques such tissues can be also used for transplantation of only specific and intact layers. Therefore communication between surgeon and eye bank is very important in order to release tissue for specific purposes with the necessary recommendation from the eye bank. Nevertheless, the final decision of usage and suitability always remains at the responsibility of the transplanting surgeon.

To be able to select the tissue for the specific purpose for which it is intended, it is necessary to check and document the conditions of:

- The epithelium (full-thickness graft, superficial or deep anterior lamellar graft, limbal graft) – taking into account that the epithelium may slash out/fall off, the duration of storage is crucial.
- The corneal stroma (full-thickness graft, superficial or deep anterior lamellar graft); transparency is crucial.
- The endothelium [SS5](full-thickness graft, posterior lamellar graft) - cell density is crucial (see 3.6).
- The corneal thickness may give additional information and therefore an evaluation is recommended before and after storage/deswelling – taking into

[1] GOD Rosenwasser, WJ Nicholson. Introduction to Eye Banking: A Handbook and Atlas Proforma 2003, pp 83-127

account that thickness below 400µm may indicate unusual thinning (e.g. keratoconus, refractive surgery, wearing of hard contact lenses); thickness above 700µm may indicate unusual stromal oedema within corneal layers caused by endothelial dysfunction (e.g. 'weak pump-activity' within endothelial, contamination).

- If a corneoscleral disc is distributed for a limbal tissue transplant (eg, keratolimbal allograft, KLAL) or used for extraction of limbal stem cells, the same donor selection criteria used for non-ocular tissue donors apply (eg, malignancies, not just haematological, are a contraindication to transplantation).

3.2 Macroscopic inspection.
Without optical aid inspect the donor eye for corneal transparency and document corneal pathology such as:

- Abnormalities of the external globe (e.g. hypotonic globe/phthisis bulbi, suspicious signs of conjunctiva/scleral tumour)
- Signs of previous surgery of the anterior segment.
- Epithelial abrasions, retention of excessive orbital tissue, laceration of the globe.
- Epithelial defects.
- Stromal opacities (size, location) and arcus lipoides/senilis (Gerontoxon) should be documented including size of diameter of clear zone. The minimal diameter of the clear zone is at the discretion of the Responsible Person / his designee and/or the surgeon's requirements.
- Abnormal corneal shape (keratoconus, micro- or megalocornea).
- Condition of the anterior chamber (shape, evidence of gross blood).
- Abnormalities such as pterygium extending to the optical zone.

3.3 Slit lamp examination, performed when whole eyes are enucleated or when corneoscleral buttons are excised, is recommended because it provides additional and/or crucial information.
Inspect the cornea and limbal area for features which may preclude use of tissue e.g. signs of corneal pathology or post mortem artefacts, taking into account:

- The state of the epithelium and epithelial irregularities.
- The presence of stromal opacities (e.g. macula, nebula or signs of dystrophies).
- The presence of folds in the Descemet's membrane (increasing with post mortem time, e.g. categorize into mild/medium or moderate/severe).
- Endothelial precipitates.
- Corneal guttae.
- Abnormal corneal shape (keratoconus, micro- or megalocornea).
- Attention should be paid to the following items (in case of corneoscleral button excision, this is difficult to detect):
  - Condition of the anterior chamber (shape, evidence of gross blood).
  - Signs of prior surgery in the anterior segment (e.g. glaucoma, cataract extraction).
  - Signs of any refractive surgery (PRK, Lasik etc.) [see also EEBA Minimum Medical Standards].
  - The presence of synechiae (anteriores, posteriores).
  - Signs of tumours or metastasis in the anterior ocular segment (especially at donors with diagnosis of cancer), [see also EEBA Minimum Medical Standards].

These may only be detected by slit lamp examination.

3.4 Other microscopic examinations are mandatory by one of the following methods:

- Specular microscopy.
  The appearance of endothelial cells with specular microscopy varies with temperature, type and time of preservation and media. Evaluation of corneas at room temperature would be recommended.
- Transmitted light microscopy (bright field, phase-contrast).
  For light microscopy, it is necessary to make the endothelial cells visible by induction of swelling of the intercellular space with a hypotonic solution. The induction of the swelling and the swelling pattern is dependent on the type of medium and time of preservation. The use of a vital stain (e.g. trypan blue) may help to recognize severely damaged cells (necrotic / apoptotic) and denuded Descemet membrane.

3.5 Areas of interest during microscopic examination:

- Endothelium:
  - Appearance of swelling pattern of the intercellular space if applicable.
  - Quantity and extent of Descemet's folds.
  - Presence and distribution of dead cells resulting for example from trauma or post-mortem cell decay etc.
  - Density, size and shape of endothelial cells.
    - The endothelial cell density should be assessed according to a validated and regularly checked method, either counting directly with help of a graticule or afterwards on a photograph or with a calibrated software program.
      Caution is warranted for automatically obtained cell counts as in most cases interactive manipulation of the image is required for a reliable cell count and reliable results of the morphometric analysis for cell size, variation in cell size, % hexagonals and other shape parameters.
    - Cell counting should be done in different areas, centrally and peri-centrally up to 2-3 mm from the centre being aware that cell density varies from center to periphery.
    - Polymegethism refers to variation in cell sizes; it could be graded from trace, mild, moderate to severe – a common nomenclature and valuation procedure within each facility is recommended.
    - Pleomorphism refers to variation in cell shape and the deviation from the normal hexagonal shape (grading and documentation similar to polymegethism).
  - Signs of significant cell loss.
  - Presence of corneal guttae.
  - Intracellular morphological characteristics of endothelial cells (e.g. granulation, vacuolation).
- Stroma:
  presence of stromal opacities, stromal deposits, abnormal morphology of keratocytes. The assessment of stromal condition has to be considered on the basis of final usage and patients diagnosis (e.g. patient with stromal defects/scaring etc.).

- Epithelium:
  Check integrity of the epithelium, the presence of partial (vertical or horizontal) erosions, or the absence of epithelium. The valuation of epithelium condition has to be considered on the basis of final usage and patient diagnosis (e.g. patient with limbal defects etc.).

3.6 Exclusion criteria for the corneal endothelium, in case the endothelial layer is **included** as functional layer in the graft:

- Tissue where the viability is severely affected by trauma, post-mortem effects, indicated by dead cells and/or inflammation (presence of inflammatory cells).
- While the specific influence of morphometric parameters for the endothelium on graft outcome remains uncertain, cut off points are at the discretion of the Responsible Person / his designee. Based on literature a cell density of less than 2000 cells/mm², moderate to severe signs of polymegathism and pleomorphism, signs of significant cell loss during organ/tissue culture or the presence of dead cells are generally considered as contraindications for long term graft survival.

3.7 Clinical Use

A preservation and expiry date for the cornea has to be indicated. If medium changes are performed, these dates should be indicated, as well as the date and time of transfer to transport medium.
Handling instructions and suitable uses (types of graft) for the tissue must be included. Microbiological testing of tissue remaining at the end of surgery is recommended but is at the discretion of the surgeon. Follow-up-forms for surgical outcome must be included with the tissue for the surgeon to report any serious adverse reactions (e.g. primary graft failure, postoperative endophthalmitis, etc) or serious adverse events (together, SARE).

4 SCLERAL TISSUE.

4.1 Tissue selection, contraindications for sclera donation are the same as for non-ocular tissue because it is a vascularized tissue:

- Donor age is at the discretion of the Responsible Person / her/his designee
- Malignancies (especially if used as keratolimbal graft)
- Pathology of the eye: pterygium, abnormal shape, staphyloma.
- Previous surgery: Cryo-surgery (pterygium), Ablation surgery (cerclage surgery).

4.2 Processing:

Prepare the sclera after removal of the corneoscleral button; remove the remaining contents (vitreous, lens, iris, choroidal and retinal tissue) and adnexa (remnants of muscles, conjunctiva). If requested, and compliant with national legislation and the eye bank's standard procedures, cut the tissue into the required number of pieces. Use aseptic techniques. The documentation of used instruments, medical devices etc. is mandatory.

4.3 Storage (complete or in separately packed pieces).
Generally accepted storage methods are:

- At room temperature:
  - Dehydrated in 70% ethanol or higher, glycerine

- Aqueous solution after denaturation with ethanol
- Fixed in formalin
- Freeze dried or frozen

- In the refrigerator (+2°C - +8°C) in hypothermic storage solution (e.g. Optisol-GS, Eusol, Corneal Chamber), 70% ethanol or dehydrated in saline supplemented with antibiotics.

4.4 Decontamination and Microbiological control:

Decontamination in an antibiotic bath for 20 minutes before storage in glycerine, or a quarantine period in ethanol 70% for 14 days before renewal of the ethanol 70%, is recommended in addition to the performance of microbiological tests of storage solution and/or piece of tissue before final storage and release for surgery. The efficacy of the microbiological testing method should be evaluated and validated.

4.5 Clinical use:

An expiry date for scleral tissue must be indicated. A suitable reconstitution protocol for further surgical use must be documented and made available to the surgeon or surgical centre. Microbiological testing of storage medium and/or scleral tissue remaining after surgery is recommended but is at the discretion of the surgeon. Follow-up-forms for surgical outcome must be included with the tissue to document any SAREs.

5 AMNIOTIC TISSUE.

5.1 Tissue selection:

Amniotic membrane is typically procured under strict aseptic conditions from living donors undergoing elective caesarean section and involves a different procurement process, including written informed consent to retrieve amniotic membrane for human application and the carrying out of an exhaustive pre-natal screening of the donor's medical history for malignancies and genetic or transmissible diseases. A second set of serology tests on the donor is required after six months of quarantine unless NAT testing was performed along with the initial serological tests.

5.2 Processing:

The amniotic membrane must be processed in an aseptic manner in a controlled environment with appropriate air quality (similar to processing of ocular tissue). The required air quality standard of the environment (air particle/CFU-count) in which the amniotic tissue will be processed should be defined and monitored routinely (usually class A equivalent [JA6]in a laminar flow cabinet with a minimum of class D background).

The whole placenta is rinsed several times with suitable sterile solution (to rinse off all remaining blood particles) and the amnion and chorion are separated according to a standard operating procedure. The amnion is then placed on a carrier (e.g. Merocel®) and divided in smaller pieces.

5.3 Storage:

Generally accepted storage methods are cryopreservation, in glycerol, or without any storage media for an approved storage time (mainly up to 12months)

- In a freezer at - 80º C
- In liquid nitrogen, vapour phase
- Freeze dried
- On a carrier in humid environment (< -20°C)

Microbiological testing:
During the entire procedure samples of the different rinsing solutions and finally also pieces of tissue are taken for microbiological testing. The efficacy of the microbiological testing method should be evaluated and validated.

5.4 Clinical use:
A preservation and/or expiry date for amniotic tissue must be indicated (according to national legal requirements). A suitable reconstitution protocol for further surgical use must be documented and made available to the surgeon or surgical centre including recommendation of microbiological testing of storage medium and/or remaining tissue postoperatively but this is at the discretion of the surgeon.
Follow-up-forms for surgical outcome must be included to report any SARs/SERs (e.g. graft-failure) as quality control.

NOTE: All tissues will remain under QUARANTINE until all donor selection, testing and processing steps are fulfilled for final release of tissue. There may be circumstances where exceptional release is permissible and, especially for cornea, microbiological tests may not have been completed and the tissue is distributed 'negative-to-date'. Exceptional release is at the discretion of the Responsible Person/ her/his designee and the transplanting surgeon.

6 TISSUE DISTRIBUTION AND FOLLOW-UP

Written agreements with all parties (e.g. transport company, receiving surgeon/surgery centre) should be available for clear differentiation of every party's responsibilities.

6.1 Data concerning the donor and in case of the cornea the microscopic evaluation should be annexed to the documentation accompanying the donor tissue (tissue information sheet). Minimum information should include:
donor age, gender, date/time of death, post-mortem-time interval, date/time of any media change (e.g. into deswelling/transport media), date/time of any later 'manipulation' on donor tissue (e.g. lamella preparation), results of lab-testing (including microbiological testing) and tissue itself (e.g. cell-count).
Transport of the tissue to the transplanting facility should be regularly revised in accordance with a validated procedure (e.g. validated transport box etc.) to make sure that tissue specification will be preserved.

6.2 Shipping containers for transport of tissues need to be labelled according to national legal requirements and for EU Member States, the EU Tissue and Cell Directives with at least the following information:

- name, address and telephone of sender
- name, address and telephone of receiving hospital/surgeon
- precise contents (type of tissue)

- unique EU-tissue code (SEC-code)
- date and time of transport
- storage information (e.g. ‘do not freeze’)
- transport information (e.g. ‘keep upright’)

6.3 Surgeons should fill in the appropriate form (e.g. recipient form) accompanying the graft with the name of the recipient and all other requested data and send it back to the providing tissue facility in order to ensure full donor tissue traceability.

6.4 Surgeons should report to the eye bank all serious adverse reactions and/or events (SAR/SAE), such as a primary graft failure, post-operative endophthalmitis or disease transmission, as these may be related to the quality of the transplanted tissue (Follow-up-form).

All reported serious adverse reactions and/or events must be investigated by the Responsible Person / her/his designee and, where necessary, appropriate corrective and preventive actions must be taken. If other tissue(s)/organ(s) from the same donor has/have been transplanted, the affected transplantation centre(s) must be informed. Eye banks are required to seek this information from their surgeons on a regular basis. Notification of confirmed serious adverse reactions and/or events must be communicated without delay to the appropriate regulatory authority (Competent Authority in the EU) as required by national legislation and regulations.