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Commission Directive 2015/566 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells

Sinead Masterson

Tissue Establishment Update

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Overview of Presentation

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Relevant Timelines

- Transposition required by 29th October 2016;
- Application required from 29th April 2017.

Background

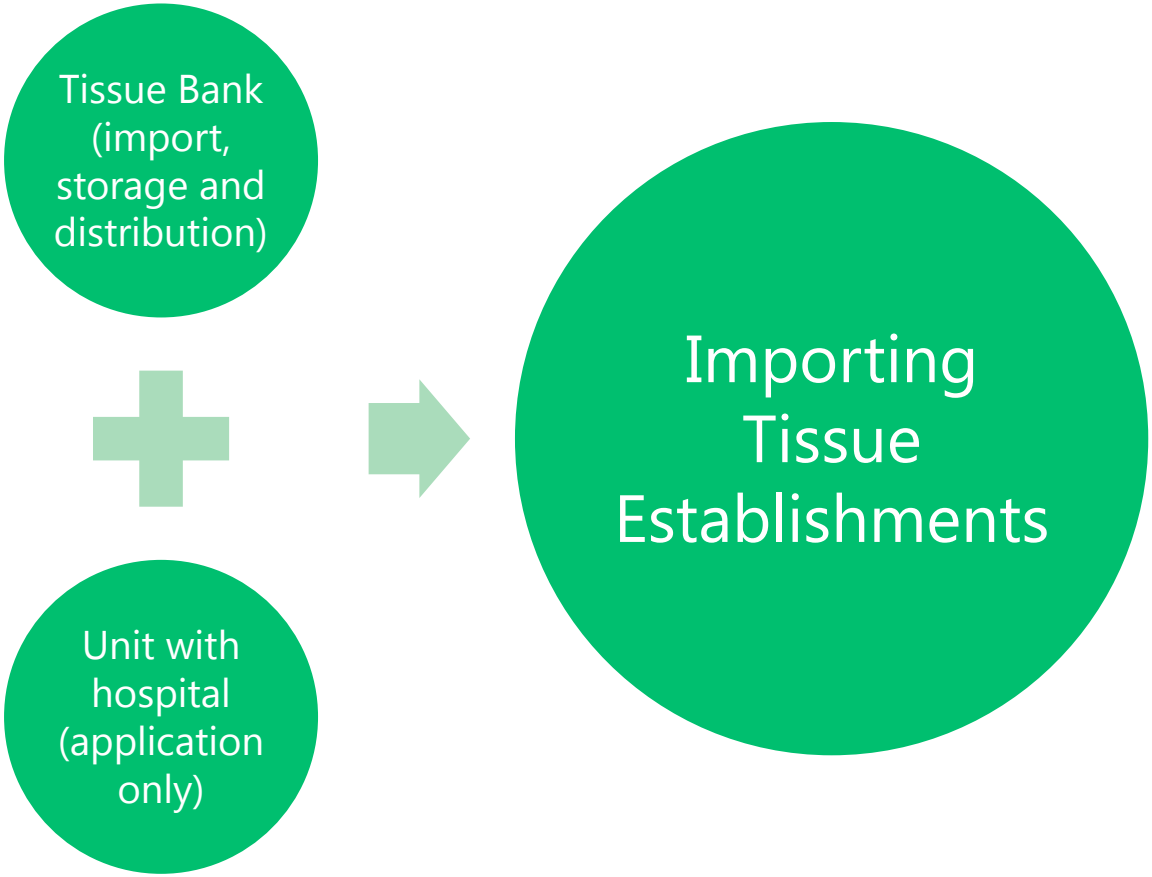
Directive 2004/23/EC requires that imports of tissues and cells are undertaken by authorised TEs.

Directive 2004/23/EC requires that MS and TEs ensure that imports of T&C meet the standards of quality and safety laid down in 2004/23/EC.

And calls for the establishment of procedures to verify the equivalency of the quality and safety standards of imported tissues and cells.

Directive 2015/566 lays down these procedures.

Importing Tissue Establishments (ITEs)



Background

Aims:

To establish authorisation and inspection schemes for ITEs mirroring the process in place for tissues and cells within the EU;

To establish procedures to be followed by importing TEs (ITEs) in their relations with third country suppliers (TCSs).

Scope of Directive 2015/566/EC

- Applies to import of all human tissues and cells for human application in the EU;
- Applies to manufactured products derived from human T&C intended for human application – where these products are not covered by other EU Legislation;
- ATMPs – applies to the donation, procurement & testing of human T&C which takes place outside the of the EU.

Scope of Directive 2015/566/EC

Exemptions:

- The import of tissues and cells as referred to in Article 9(3) of Directive 2004/23/EC as regards authorisation of 'direct distribution' and 'in the case of emergencies'.
- Brokerage Services – organisation party to a contract with a TCS to facilitate the import of T&C but not the import itself – the receiving organisation (hospital, TE etc) is considered to be the importing TE.

New Definitions

- 'Emergency'
- 'Importing Tissue Establishment' (ITE)
- 'Third Country Supplier' (TCS)
- 'One – Off Import'
  - The import of any specific tissue or cell which is for the personal use of an intended recipient(s) known to the importing TE and the TCS before the importation occurs.
  - Shall not (normally) occur more that once. If it occurs on a regular or repeated basis shall not be considered 'one-off'.
- (Currently captured by HPRA using 'Non-Routine Import Procedure)

Obligations on Competent Authorities

Authorisation of ITEs:

- Ensure that imports of T&C are only undertaken by authorised TEs;
- Obtain the information from ITEs set out in Annex 1 of this Directive;
- Issue to the ITE a certificate as set out in Annex II to this Directive;
- Establish a system for approval of changes to import activities undertaken by ITEs.

Obligations on Competent Authorities

Inspections and other Control Measures:

- Organise inspections and other control measures of ITEs and *where appropriate their 'third country suppliers;*
- Evaluate and verify the procedures and activities carried out…..to ensuring the equivalency of the quality and safety standards of the tissues and cells to be imported….
- Provide information when requested on such inspection and control measures to the Commission and other MS;
- Co-operate with the Competent Authorities in other MS to which the imported T&C are likely to be distributed.

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Obligations on Importing Tissue Establishments

- Verify that the standards of quality and safety of the tissues and cells they import into the EU are equivalent to the standards laid down in Directive 2004/23/EC;
- Provide certain information and documentation when requested to the CAs;
- Establish written agreements with TCS;
- Audit TCS – strongly encouraged as part of verification process.

Obligations on Importing Tissue Establishments

- Provide to the CA the information and requested documentation set out in Annex 1 to this Directive;
- Make available to the CA when requested, the information set out in Annex III to this Directive;
- Seek the approval of the CA for any planned substantial changes to import activities;
- Notify the CA of SAREs reported to them by the TCS which may influence the quality and safety of the T&C imported.
- Notify the CA of any suspension or revocation of a TCS authorisation to export T&C and any other decision relating to non-compliance taken by a CA where the TCS is based which may influence the quality and safety of the imported T&C.

Obligations on Importing Tissue Establishments

Written Agreements:

- Must be in place with TCS;
- Must specify the quality and safety requirements to be met to ensure the equivalency of the T&C imported with the requirements of Directive 2004/23/EC;
- Shall include as a minimum the contents listed in Annex IV to this Directive;
- Shall establish the right of the CA to inspect the activities and facilities of the TCS during the duration of the agreement and for 2 years following its termination;
- Shall provide copies of the agreements with TCS to the CA.

Obligations on Importing Tissue Establishments

Registers:

- ITEs shall keep a record of their activities including the types and quantities of T&C imported and on their origin and destination;
- This information shall be contained with TE Annual Report.

Single European Code:

- Must be applied to imported T&C by either the ITE or by the TCS (as part of terms of written agreement).

Annex I

- Minimum requirements concerning the information and documentation to be provided by importing tissue establishment applicants when applying to be accredited, designated, authorised or licensed for the purpose of import activities.
- Part A – General Information on the Importing TE
- Part B – Contact Details of the ITE
- Part C – Details of the Tissues and Cells to be Imported
- Part D – Location of Activities
- Part E – Details of Third Party Suppliers
- Part F – Documentation to accompany application

Annex I

F. Documentation to Accompany the Application

1. A copy of the written agreement with the third country supplier(s).

2. A detailed description of the flow of imported tissues and cells from their procurement to their reception at the importing tissue establishment.

3. A copy of the third country supplier's export authorisation certificate or, where a specific export authorisation certificate is not issued, certification from the relevant third country competent authority or authorities authorising the third country supplier's activities in the tissue and cells sector including exports. This documentation shall also include the contact details of the third country competent authority or authorities. In third countries where such documentation is not available, alternative forms of documentation shall be provided such as reports of audits of the third country supplier.

Annex II

- Certificate of Accreditation, Designation, Authorisation or Licence to be issued by the competent authority or authorities to importing tissue establishments.
- This will be added as an appendix to the current TEA for those TEs undertaking the import of T&C from third countries.

Annex III

- Minimum requirements concerning the documentation to be made available to the competent authority or authorities by tissue establishments intending to import tissues and cells from third countries – when requested

Annex III

A. Documentation relating to the importing tissue establishment

1. A job description of the Responsible Person and details of his/her relevant qualifications and training record as laid down in Directive 2004/23/EC;
2. A copy of the primary label, repackage label, external package and transport container;
3. A list of relevant and up-to-date versions of standard operating procedures (SOPs) relating to the establishment's import activities including SOPs on applying the Single European Code, reception and storage of imported tissues and cells at the importing tissue establishment, management of adverse events and reactions, management of recalls and traceability from donor to recipient.

Annex III

B. **Documentation relating to the third country supplier or suppliers**

1. A detailed description of the criteria used for donor identification and evaluation, information provided to the donor or donor family, how consent is obtained from the donor or donor family and whether the donation was voluntary and unpaid or not;
2. Detailed information on the testing centre(s) used by third country suppliers and the tests performed by such centres;
3. Detailed information on the methods used during the processing of the tissues and cells including details of the validation for the critical processing procedure;
4. A detailed description of the facilities, critical equipment and materials and criteria used for quality control and control of the environment for each activity carried out by the third country supplier;
5. Detailed information on the conditions for release of tissues and cells by the third country supplier or suppliers;
6. Details of any sub-contractors used by the third country suppliers including the name, location and activity undertaken;
7. A summary of the most recent inspection of the third country supplier by the third country competent authority or authorities including the date of the inspection, type of inspection and main conclusions;
8. A summary of the most recent audit of the third country supplier carried out by, or on behalf of, the importing tissue establishment;
9. Any relevant national or international accreditation.

Annex IV

- Minimum requirements concerning the contents of written agreements between importing tissue establishments and their third country suppliers.

Annex IV

1. Detailed information on the specifications of the importing tissue establishment aimed at ensuring that the quality and safety standards laid down in Directive 2004/23/EC are met and the mutually agreed roles and responsibilities of both parties in ensuring that imported tissues and cells are of equivalent standards of quality and safety;
2. A clause ensuring that the third country supplier provides the information set out in Annex III B to this Directive to the importing tissue establishment;
3. A clause ensuring that the third country supplier informs the importing tissue establishment of any suspected or actual serious adverse events or reactions which may influence the quality and safety of tissues and cells imported or to be imported by the importing tissue establishment;
4. A clause ensuring that the third country supplier informs the importing tissue establishment of any substantial changes to its activities, including any revocation or suspension, in part or in full, of its authorisation to export tissue and cells or other such decisions of non-compliance by the third country competent authority or authorities, which may influence the quality and safety of tissues and cells imported or to be imported by the importing tissue establishment:

Annex IV

5. A clause guaranteeing the competent authority or authorities the right to inspect the activities of the third country supplier, including on-site inspections, should it wish to do so as part of its inspection of the importing tissue establishment. The clause should also guarantee the importing tissue establishment the right to regularly audit its third country supplier;
6. The agreed conditions to be met for the transport of tissues and cells between the third country supplier and importing tissue establishment;
7. A clause ensuring that donor records relating to imported tissues and cells are kept by the third country supplier or its sub-contractor, in line with EU data protection rules, for 30 years following procurement and that suitable provision is made for their retention should the third country supplier cease to operate;
8. Provisions for the regular review and, where necessary, revision of the written agreement including in order to reflect any changes in the requirements of the EU quality and safety standards laid out in Directive 2004/23/EC;
9. A list of all standard operating procedures of the third country supplier relating to the quality and safety of imported tissues and cells and a commitment to provide these on request.

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Next Steps for TEs

- Don't panic – Review the Directive in detail especially the Annexes
- It is likely that a lot of this information is already available to you.
- Discuss additional requirements with your third country supplier.
- Review SOPs, Quality Manual, written agreements etc.
- Revisit your external audit plans and work together in this regard.

Next Steps for HPRA

- Consult with DoH regarding the transposition;
- Review and update our Application for TEA, Variation Application and the format of our TEA;
- Review any changes that are required to current non-routine import process;
- Review the information requested in the Annexes and identify the information that will need to be updated from ITEs and the documentation that will need to be submitted and retained on file;
- Review with other MS a risk based approach to inspections of TCS.