CELL HISTORY FILE TEMPLATE

Cell History File – Explanatory introduction

This template for a Cell History File (CHF) is a non-mandatory document intended for establishments and companies involved in the procurement, testing, processing, storage and distribution of human tissues and cells (including those derived from human blood) for human application or therapeutic use. These tissues and cells (or human donated materials) may be intended for either autologous or allogeneic use and may include a cell banking step. The CHF aims to gather the key quality and traceability information required by law in both the UK and the EU.

In the UK, tissues and cells are regulated under the following legislation: the Human Tissue (Quality and Safety for Human Application) Regulations (SI 1523/2007) (as amended), the Human Tissue Act 2004 and the Blood Safety and Quality Regulations 2005 (SI 2005/50) (as amended). Scotland also has their own national legislation, the Human Tissue Act 2006. Human tissues and cells that are used as starting materials for medicines manufacture will ultimately be regulated under the UK Human Medicines Regulations 2012 (SI 2012/1916). A complete list of the applicable UK regulatory texts can be found here.

In the EU, tissues and cells are regulated under the Tissues and Cells Directive (EUTCD) (2004/23/EC), the EU Blood Directive (EUBD) (2002/98/EC), and when used as starting materials for medicines manufacture, under the EC Regulation on Advanced Therapy Medicinal Products (ATMPs) (EC 1394/2007). However, it should be noted that on 27th May 2024, the European Council adopted the new Regulation on standards, of quality and safety for substances of human origin (SoHO) intended for human application (Regulation EU/2004/1938). The intention of this new regulation, which will replace the existing EUTCD and EUBD, is to further strengthen the quality and safety standards within the EU, but with an increased scope when compared to the existing requirements. This new Regulation will apply from mid-2027, 3 years after its publication and entry into force, with an extra year for certain provisions. A list of the currently applicable EU regulatory texts can be found here. Upon the implementation of the SoHO Regulation, this list and template will be updated accordingly.

This CHF is intended to be complementary to documentation required by the legislation in the UK and the EU, as described above. The choice of which legislation applies to the human donated material defined above will, as a minimum, default to that covering human tissues and cells e.g. 2004/23/EC in the EU and the Human Tissue Act 2004 in the UK (2006 Act in Scotland). For example, in the UK, donated blood used as a starting material for ATMP production can be managed under a licence for tissues and cells without a separate licence for the donation of blood. However, there may be cases in some EU member states whereby compliance with the blood legislation is required for all donated blood and clarity should be sought from the local regulatory authority in advance of initiating any activity.

This template should also satisfy the requirements for Human Cells, Tissues and Cell and Tissue-Based Products) HCT/P in the US listed under 21 CFR Part 1271 but this is not the focus of this document. A list of the key applicable US regulatory texts can be found here.

The intention is that this CHF could be a 'Cell Passport' which will accompany a tissue or cell derived product as it progresses through various processing stages. The non-mandatory template aims to provide a model document which developers can adapt to suit their individual requirements and provide a structure that ensures key traceability and manufacturing information is collected and contained in a single source document. It is hoped this document, while primarily providing a repository of information for various regulatory requirements, will also be useful in any due diligence evaluations.

The template comprises 2 sections:

The first section (A) covers the required information to be collected for all human tissues and cells procured for any future human application.

The second section (B) specifically covers the information required whereby human tissues and cells will be used as a starting materials intended for onward manufacture into a medicinal product.

Section A – Information Required for Tissues and Cells used for Human Application

Section A aims to capture all key information to ensure compliance with the quality and traceability requirements of tissues and cells legislation in the UK and EU i.e. information on the procurement, testing, storage and distribution of human donated material which can be further processed and used to treat a patient under the appropriate UK or EU legislation or processed further into a cell line, cell bank, intermediate or final medicinal product regulated under the appropriate medicinal product legislation, all of which will be referred to as a Product in Section B.

Section B – Information Required for Tissues and Cells used as Starting Materials for Medicines Manufacture

Section B aims to capture all traceability requirements required for human donated material from the point when it enters medicines legislation jurisdiction as a starting material that is manufactured into a medicinal product or ATMP. This section aims to capture an overview of the production process including information on the raw materials and reagents used in the manufacture of the product, the testing performed and the storage and distribution of the product.

Interaction of international regulatory documents required to comply with both sections A and B of the CHF template

The CHF should capture all relevant information for tissues and cells used for human application under UK and EU legislation or, in cases where a master cell bank/Line is produced as starting material for a human medicinal product, under UK and EU legislation (see reference section for applicable legislation and guidance). The following sections capture further helpful information related to the interaction between the international regulatory documents / procedures.

For human application under the UK Human Tissue Act 2004 (2006 in Scotland) and EU Tissues and Cells Directive (Section A)

In the UK, a HTA Preparation Process Dossier (PPD) was developed to meet UK regulatory expectations for the inspection of tissue establishments and to capture processing, testing and labelling of tissues and cells; however, it does not include procurement, distribution, storage or engraftment information. The CHF dovetails with the PPD by capturing all necessary information required for the production of human tissues or cells for direct clinical application (Figure 1).

As the UK now operates outside the EU regulatory framework and there is no mutual recognition agreement in place, EU authorities are not obligated to consider UK systems aligned with EU standards. Consequently, while the UK approach remains broadly consistent with former EU requirements, compliance with EU legislation should not be assumed and may require additional verification for activities involving the EU.

For use under the UK Human Medicines Regulations 2012 (SI 2012/1916) and EU Medicines Directive (2001/83/EC) (Section B)

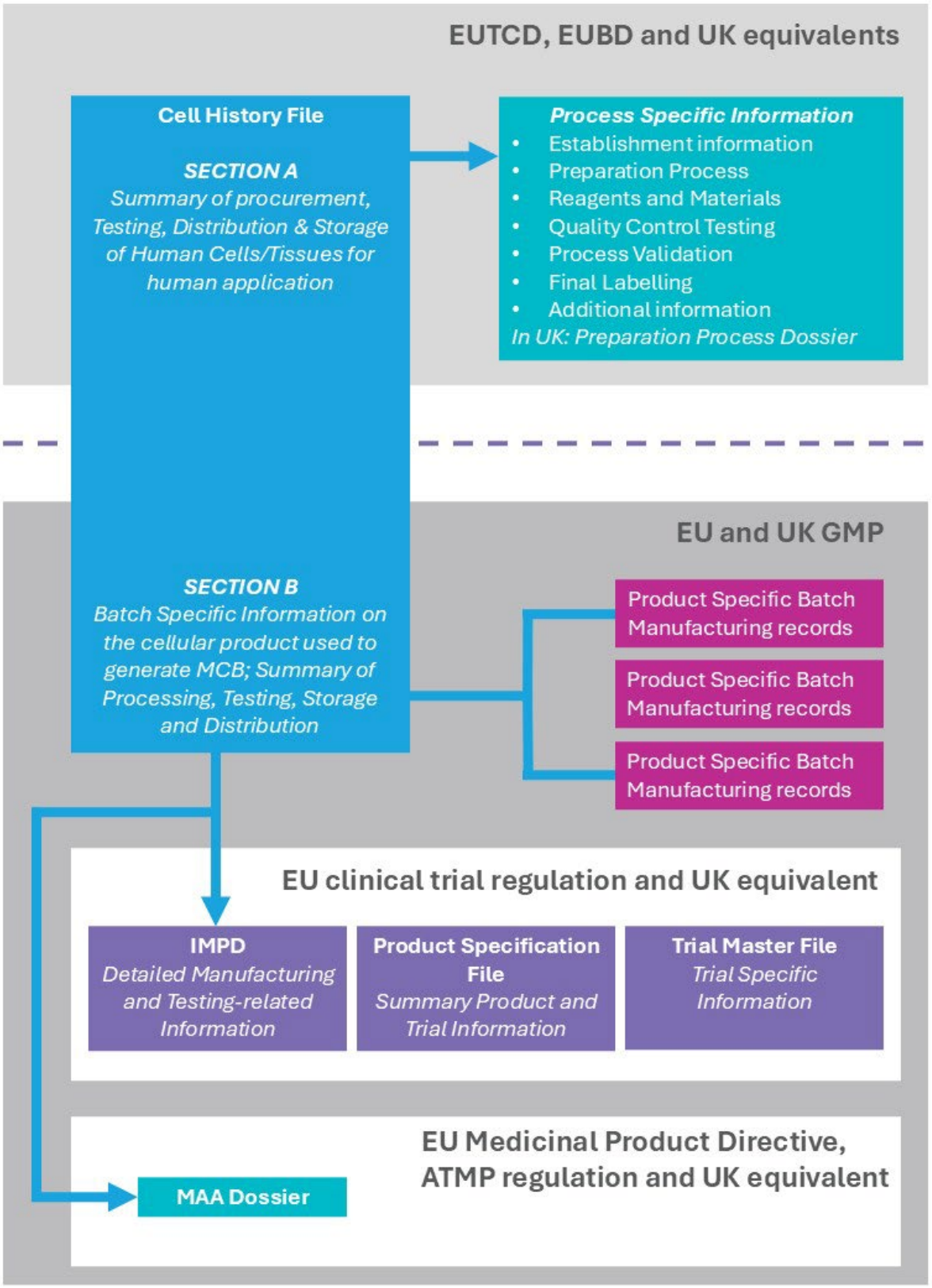
In the UK and EU, there are currently a number of regulatory 'compendium' documents which capture some of the downstream processing of human tissues and cells such as the Investigational Medicinal Product Dossier (IMPD), Marketing Authorisation Application (MAA) and the Product Specification File (PSF) (Figure 1). These documents provide an overview of the production processes which the cell/tissues may have been exposed to. They do not however capture lot/batch specific information. As such, they do not preserve the record of the history of the tissue/cells started by the CHF.

Section B of the CHF aims to capture the key quality and traceability requirements for a master cell bank/cell line which will be further processed into medicinal products for human use.

All similar information for processes downstream of the master cell bank (line) should be captured in the individual processing batch records.

It should be permissible for the CHF, if used, to be referenced in IMPD and MAA dossier without the need for duplication.

Figure 1: Visual Representation of the Interaction of the CHF with EU and UK Regulatory Documents



References

UK and EU Legislation

- The Human Tissue (Quality and Safety for Human Application) Regulations (SI 1523/2007) (as amended). https://www.legislation.gov.uk/uksi/2007/1523/contents/made
- The Human Tissue Act 2004. https://www.legislation.gov.uk/ukpga/2004/30/contents
- The Blood Safety and Quality Regulations 2005 (SI 2005/50) (as amended). https://www.legislation.gov.uk/uksi/2005/50/contents/made
- The Human Tissue (Scotland) Act 2006. https://www.legislation.gov.uk/asp/2006/4/contents
- Directive 2004/23/EC setting standards of quality and safety for the donation, p rocurement, testing, processing, preservation, storage and distribution of human tissues and cells http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32004L0023
- Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1423750875527&uri=CELEX:32012L0039
- Directive 2012/39/EU amending Directive 2006/17/EC of 26 November 2012 as regards certain technical requirements for the testing of human tissues and cells. https://eur-lex.europa.eu/eli/dir/2012/39/oj/eng
- Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1423750646005&uri=CELEX:32006L0086
- Directive (EU) 2015/565 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells. https://eur-lex.europa.eu/eli/dir/2015/565/oj/eng
- Directive (EU) 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. https://eur-lex.europa.eu/eli/dir/2015/566/oj/eng
- Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:c11565
- Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical for blood and blood components. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004L0033
- Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notifications of serious adverse reactions and events. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32005L0061
- Directive 2005/62/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and

specifications relating to a quality system for blood establishment. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32005L0062

- Directive 2001/83/EC on the Community code relating to medicinal products for human use. http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32001L0083
- Regulation (EC) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex:32007R1394

Helpful Guidance and US Regulatory Documents (non-exhaustive list)

- ICH Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin https://database.ich.org/sites/default/files/ICH_Q5A%28R2%29_Guideline_2023_1101.pdf
- ICH Q5B Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products https://database.ich.org/sites/default/files/Q5B%20Guideline.pdf
- ICH Q5C Stability Testing of Biotechnological/Biological Products https://database.ich.org/sites/default/files/Q5C%20Guideline.pdf
- ICH Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products https://database.ich.org/sites/default/files/Q5D%20Guideline.pdf
- ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf
- Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
- EMEA/CHMP/410869/2006 Guideline on human cell-based medicinal products https://www.ema.europa.eu/en/human-cell-based-medicinal-products-scientific-guideline
- 21 CFR Part 1271 Human Cells, Tissues and Cellular and Tissue-based Products https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Points to Consider in the Characterization of Cell Lines used to Produce Biologicals (1993). https://www.fda.gov/media/70868/download
- FDA Guidance for industry: characterization and qualification of cell substrates and other biological starting materials used in the production of viral vaccines for the prevention and treatment of infectious diseases: February, 2010. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/characterization-and-qualification-cell-substrates-and-other-biological-materials-used-production

Use of the Cell History File template

The following template was agreed by a group of stakeholders in the UK. It aims to provide a flexible format for use by developers and manufacturers of tissue and cell-based therapy

products that will ensure necessary traceability and provenance information is captured in a common source document(s) which can accompany the cellular product at each stage of manufacture. The use of the template is voluntary and is supported by the UK competent authorities responsible for human tissues and cells, and blood, and medicinal products, the Human Tissue Authority and Medicines and Healthcare products Regulatory Agency, respectively.

It is recommended that, wherever possible, the CHF accompanies the distribution of a tissue or cell-based product thereby ensuring the provenance of the product is known to all parties involved in its use or distribution. It may not be appropriate for an establishment to complete both sections of the template, in such cases the relevant section should be marked as not applicable with a brief explanation where necessary. For some products, for example where a master cell bank is used in the manufacture of multiple final products, it is anticipated that there may be multiple Section B documents. Where a section is applicable to the product, but the information is not available then it is recommended that a risk assessment is performed and documented as appendices to this CHF.

Cell History File – Template

1. EXECUTIVE SUMMARY

Insert a summary of relevant details of procurement and processing for the various stages of the process:

1. A description of the nature of the tissues or cells, the intended purpose and other key information.
2. Tissue / cell history including procurement, testing, storage and distribution (if relevant).
3. Processing to an intermediate, progenitor, master cell line, or master cell bank including a summary of process, testing, storage and distribution (if relevant).
4. Storage (short or long term) and the transport system to another organisation (e.g. for later development of a master cell bank or therapeutic product etc).

Illustrations/appropriate flow diagrams can be used as an aid in this summary. Supplementary information e.g. Risk assessment should be appended in the relevant annex.

1. VERSION CONTROL

VERSION	CHANGES	DATE
1.0	N/A, first version of template	29 September 2015
2.0	Updates to the explanatory introduction, regulatory references, and document format	19 February 2026

Section A: INFORMATION ON DONATION/PROCUREMENT OF TISSUES/CELLS

A.1 RELEVANT LEGISLATION

Include details of regulation cells/tissues procured against e.g. *The Human Tissue (Quality and Safety for Human Application) Regulations (SI 1523/2007); Tissues and Cell Directive (2004/23/EC)*

A.2 DETAILS OF PROCUREMENT ORGANISATION

Information on centres or establishments in which procurement/collection of tissues and / or cells is performed. For each site, please include the following general information:

- Name of Contact Person
- Address
- Licence/Authorisation number and any relevant accreditations
- Details of organisation(s) responsible for obtaining consent and where record is held
- Details of organisation(s) responsible for assessing donor suitability and where details of medical screening and medical history are held (if different from consenting organisation)

A.3 DONOR CONSENT

Insert:

- A copy of a blank Patient Information and Consent protocol.
- A confirmatory statement that the donor consent has been signed and that consent is in compliance with relevant legislation.

A.4 DONOR SUITABILITY

Insert a copy of a blank donor assessment (donor screening and medical history) record including agreed deferral criteria.

A.5 DETAILS OF DONOR TESTING ORGANISATION(S)

Information on centres or establishments in which testing of donor samples is carried out. For each test, please include the following general information:

- Testing performed including details of mandatory and additional testing performed
- Name of Contact Person
- Name and address of testing organisation
- Licence/Authorisation number (if relevant) and any relevant accreditations
- Copy of Specification (if relevant)

A.6 DETAILS OF PROCUREMENT

A.6.1 Donation details

- Quantity and type of cells/tissue
- Donation number (ISBT compatible if available)
- Date of collection/procurement
- Details of collection/procurement

A.6.2 Testing

- Details of testing performed on donor material including methods
- Test results

A.6.3 Details of any processing and/or cell selection (if appropriate)

- Selection procedures
- Any processing performed including information on materials and reagents which have been in contact with the cells
- Procedures of quarantine for testing purposes

A.6.4 Storage

- Place of storage (Name and address of storage facility if different from collection centre)
- Cryopreservation medium (where applicable)
- Storage container materials
- Temperature specification for storage
- Shelf-life (may change as more data gathered)
- An inventory should be established and maintained. The fates of the unit should be detailed (this may be separate from this CHF)

A.7 CONTRACTS/AGREEMENTS

Include a list of relevant contracts and service level agreements

A.8 SUMMARY

Include a summary of information outlining any omissions or issues and any mitigation actions (all risk assessments should be contained in Section A Annex 1).

Section A, Annex 1

List all risk assessments performed for the cell/tissues.

Append a copy or reference the appropriate file/location.

Section B: DETAILS OF TISSUE OR CELL-BASED PRODUCT

A tissue or cell-based product refers to any intermediate of final product e.g. progenitor cell line, master cell bank, intermediate product, final medicinal product. As such it will be necessary to complete separate Section B file for each processing event for the cellular product.

B.1 INFORMATION ON THE TISSUE OR CELL-BASED PRODUCT

Insert summary details of the cells used to generate the tissue or cell-based product (if SECTION A not completed/available).

B.1.1 Details of organisation(s) supplying the material for tissue or cell-based product

Information on centres or establishments in which procurement/collection of cells and/or tissues is performed. For each site, please include the following general information:

- Name of Organisation
- Name of Contact Person
- Address

B.1.2 Transfer details

Provide details on the following:

- Purpose of transfer
- Name and address of Establishment/Company where the cells/tissues were obtained from
- Number of units transferred
- Date of transfer
- Date of receipt
- Vessels used in transfer
- Temperature specification for transfer
- Copy of temperature logger printouts
- A statement/information from the users of this document about their systems and practice for maintaining traceability and anonymity requirements throughout.

B.1.3 Information on storage of tissues or cells prior to processing

Include information on storage, the date of entry into storage, date of retrieval from storage, storage conditions and verification that correct storage conditions have been maintained during storage period.

B.2 DETAILS OF SUBSEQUENT PROCESSING

B.2.1 Details of processing site

Information on processing centre, include the following general information:

- Name of Contact Person
- Address
- Licence/Authorisation number and any relevant accreditations
- Summary of licensed activities
- Summary of other activities performed

B.2.2 Summary of processing

B.2.2.1 Description of processing

Include a flow diagram and summary narrative including details of passage numbers, derivation and expansion steps and critical controls.

B.2.2.2 Raw Materials used in the production of the tissue or cell-based product

Provide the following details:

- Identification code, manufacturer name and address
- Source and traceability details
- Specification
- Batch numbers and expiry dates
- Compliance with national and/or European specifications *e.g. EDQM Certificate of Suitability or Pharmacopoeia*

B.2.2.3 Details of other key materials used in the production of tissue or cell-based product

Provide the following details:

- Storage Container product code, manufacturer name and address
- Batch numbers and expiry dates
- Compliance with national and/or European specifications of all materials *e.g., CE marked*

B.2.3 Details of product generated

- Provide the following information on each tissue or cell-based product generated.
- Lot number
- Passage number
- Dates of manufacture
- Quantity and product type (include total amount/volume collected, amount/volume entered into storage, the amount/volume used for testing purposes and the amount/volume discarded)
- Storage details

- Storage materials and conditions
- Preservatives used
- Place of storage (name and address of storage facility if different from collection centre)
- Storage temperature specification
- Number of units placed into storage (unless recorded elsewhere, Section B Annex 1 should be used as a record of withdrawal of units, this should include date of withdrawal, proposed use of cells and name and address of company/person cell supplied to)

- Date lodged with Stem Cell bank *(if relevant)*
- Stability protocol summary
- A statement/information from the users of this document about their systems and practice for maintaining traceability and anonymity requirements throughout
- An inventory should be established and maintained *(this may be separate from this CHF)*

B.2.4 Analysis of tissue or cell-based product

B.2.4.1 Testing performed on cellular product

Include a description of the methods employed for all analytical testing performed on the cellular product

B.2.4.2 Specification

Include a copy of the approved Specification for the cellular product

B.2.4.3 Batch analysis

Include a copy of results of batch analysis and/or copy of the Certificate of Analysis

B.2.4.4 Details of testing organisation(s)

Information on centres or establishments in which testing of the processed cells and / or tissues is carried out. For each site, please include the following general information. In addition, please include the following specific information for any testing performed on processed cells/tissues.

- Testing performed
- Name of Contact Person
- Address
- Summary of licensed activities
- Authorisation number and any relevant accreditations
- Copy of Specification

B.2.5 Statement of manufacture

Include a statement on whether the cellular product was generated under GMP or Good Tissue Practice, this should be provided by EU Qualified Person wherever possible.

B.2.6 Contracts/agreements

Include list of all relevant contracts/agreements.

B.2.7 Summary

Include a summary of information outlining any omissions or issues and any mitigation actions (all risk assessments should be contained in Section B Annex 2)

Section B, Annex 1

List all risk assessments performed for the tissue or cell-based product.

Append a copy or reference the appropriate file/location