Preparation Process Dossiers – a guide for processors of tissues and cells for patient treatment (human application)
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An introduction to the authorisation of preparation processes

1. The European Union Tissues and Cells Directives were transposed into UK law through the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Q&S Regs). The requirements for holding a licence for tissue and cell preparation processes are established in Schedule 2 paragraph 14 of the Q&S Regs, implementing Annex II part B of Directive 2006/86/EC (see paragraph 3 below).

2. The European Commission in 2010 adopted the recommendations of the EUSTITE (European Standards and Training in the Inspection of Tissue Establishments) project, in which EU Member States and the World Health Organisation recommended the authorisation of processing of tissues and cells using a Preparation Process Dossier (PPD). Competent Authorities, like the HTA, are expected to implement this recommendation.

3. The process validation requirements of Directive 2006/86/EC were implemented through Directions 003/2010 in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (the Q&S Guide). These requirements are reproduced below:

   - The critical processing steps must be identified and validated and must not render the tissues or cells clinically ineffective or harmful to the recipient. Validation may be based on studies performed by the establishment itself, or on data from published studies or, for well established processing methods, by retrospective evaluation of the clinical results for tissues supplied by the establishment.

   - It has to be demonstrated that the validated process can be carried out consistently and effectively in the tissue establishment environment by the staff.

   - Processing steps must be documented in SOPs which must conform to the validated method. The DI or LH must ensure that all processes are conducted in accordance with the approved SOPs. The processing steps must undergo regular critical evaluation to ensure that they continue to achieve the intended results.

   - Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.

4. Before implementing any significant change in processing, the modified process must be validated and documented. There should be regular review and evaluation of the cumulative effects of minor changes to the processing method. All licences are issued by the HTA with standard conditions, including:

   - Where the Licence Holder or the Designated Individual proposes a licence variation in any material respect, such as a major or a minor variation, this may not be undertaken until an application has been
made to the HTA for a licence variation and such a variation has been granted and any fee payable to the HTA has been paid.

- Where a new type of tissues and/or cells is to be procured, tested, processed, stored, distributed, imported or exported by the establishment, and where the processes required for this new type of tissues or cells differ substantially from those previously employed by the establishment, the Designated Individual must first notify the HTA and the new type of tissues and/or cells may not be procured, tested, processed, stored, distributed, imported or exported by the establishment until the HTA is satisfied that the establishment has suitable premises and employs suitable practices to carry out the proposed activity in respect of these tissues and/or cells.

5. These standard conditions necessitate that changes to preparation processes and the adoption of new preparation processes must be communicated to the HTA. These communications should include the submission of a PPD to the HTA.

**When Preparation Process Dossiers (PPDs) must be used**

**Before an inspection**

6. The HTA reviews preparation processes during site-visit inspections. You may be asked to complete a PPD so it can be reviewed in advance of an inspection. If necessary, the HTA will request more information to be made available during the inspection, when the HTA will normally complete the assessment. The outcome of the authorisation process will be recorded in the inspection report.

7. If your preparation processes have been authorised by the HTA following submission of a PPD, and you have not made any changes to them, then you will not be required to complete another PPD prior to an inspection.

8. You may not need to complete a PPD for preparation processes that are routine and well established, and which have been reviewed and authorised by the HTA during previous site-visit inspections. The HTA inspector will decide on the need for a PPD to assist in the process authorisation procedure.

**Before implementing changes to a process**

9. It is a requirement of the conditions of your licence (see paragraph 4 above) to inform the HTA if you make changes to the way you process tissues or cells for patient treatment; you may need to submit a PPD of the new process for review by the HTA prior to authorisation. If the changes are very minor then a change-of-process PPD might not be requested.

*For example, an establishment has been using a source of phosphate buffered saline in a process, but the supplier has withdrawn the product from sale, so the establishment sources an identical product (same*
10. If the HTA considers that the changes may have an impact on the quality or safety of the processed tissues and cells, then you will be asked to submit a PPD. You must not implement these changes before they have been authorised by the HTA. You must submit a PPD for revised processes whether or not the original process was authorised, because the HTA will not have reviewed process validation as part of either a site-visit or desk-based inspection.

**Before starting a new process**

11. If you intend to start processing a type of tissue or cell with which you have not previously worked, or if you intend to adopt a new process for tissues or cells you work with already, you must submit a PPD. You must not undertake this new process until it has been authorised by the HTA.

**As part of a licence application**

12. Preparation processes are authorised by the provision of a licence issued by the HTA through Schedule 1 and Regulation 7 of the Q&S Regs. Therefore, all applications for a licence to process human tissue intended for patient treatment (human application) must submit information to the HTA relating to the validation of processing methods. This information relating to the tissue preparation processes should be provided to the HTA by using a Preparation Process Dossier (PPD). Applicants will be prompted to complete a PPD during the preparation of their online licence application.

**Description of the Preparation Process Dossier (PPD)**

13. A fully completed PPD will contain all the information the HTA needs in order to determine the suitability of processes. In completing the PPD you will provide assurance that processes used to prepare tissues and/or cells are suitable for patient treatment. Establishments will also have confidence that their processes have been validated to the level required by the Regulations.

14. Only use the PPD to record information about preparation processes. Processes used to procure, distribute, store or engraft tissues or cells fall outside the scope of PPDs. Preparation processes include all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.

15. There are several sections, in which you are asked to describe the procedure, record the reagents and materials used, and provide a validation report.
16. The PPD can be downloaded from the HTA website by clicking here, or by typing this URL into your web-browser:

http://www.hta.gov.uk/_db/_downloads/Preparation_Process_Dossier.docx

17. This dossier must be completed for each whole process. If you use the same process for more than one tissue type, only one PPD should be submitted.

For example, an establishment may use a single PPD when the same process is used to cryopreserve peripheral blood stem cells, donor lymphocytes and bone marrow.

Completing the PPD

Section A – your details

18. Please ensure you complete Section A accurately, so that the HTA knows whom to address queries relating to the PPD, and so it can be recorded against the HTA’s records of your establishment.

19. Please ensure the Designated Individual (DI) is named in Section A, even if it is not this person completing the PPD. The DI is named on your licence, and he or she will have to make a declaration about the PPD in Section G later.

Section B – preparation process – general information

20. Provide here a descriptive name for the process to which the PPD refers. The HTA will use this process name in reference to the PPD and authorisation.

For example:

- cryopreservation of haematopoietic stem cells with DMSO
- freeze-drying and irradiation
- the excision and culture of corneas

21. Describe separately the tissues or cells to which the process applies, even if this is evident in the process name.

22. You will be asked in Section B to provide details of any tests or other donor selection requirements you use prior to accepting donation of tissues or cells for this process. Please do not list the mandatory serological testing in this section (HIV, HBV, HCV, and syphilis).
23. You will be able to record in this section the quality control requirements you have for the tissues or cells before accepting them for processing.

   *For example, you may ensure that stem cell mobilisation into peripheral blood has been successful as part of the procurement procedures with a CD34+ cell count, or that procurement must not have taken place more than 12 hours before initiating the process.*

24. The final part of Section B requires details of the process in a brief description or flowchart. Your SOP would be a suitable attachment to the PPD submission; in such a case please write ‘see attached SOP’ in Section B. Ensure you include the steps where quality controls samples are taken, and align these with the list of quality control tests in Section D later in the PPD.

**Section C – reagents and materials**

25. Record all details of reagents and materials in the table in Section C. Only list those reagents or materials that come into contact with the tissues or cells; you do not need to list the products that you use to decontaminate the packaging of plasticware.

26. All reagents and materials that come into contact with the tissues or cells must be of a standard that assures there is no additional risk to the quality or safety of the processed product. The simplest way to achieve this is through the use of CE-marked reagents and materials. However, the HTA will accept the use of reagents without CE-marks if there are no CE-marked alternative reagents or materials available, or if you determine that those with a CE-mark have a negative impact on the quality of the tissues or cells; the HTA may ask you to present documented reasons for not using CE-marked reagents. You may be able to raise the standard of ‘reagent grade’ products by using the analyses and tests required for a CE-marked product.

   *For example, a liquid reagent lacks CE-marking because it is not available in a sterile formulation, but you filter it prior to use using 0.2 micrometer pore-size equipment, followed by an integrity test applied to the filter after use.*

27. You may be asked by the HTA to supply a rationale for your choice of reagents and materials, including a documented risk assessment, and details of additional testing that you apply to them.

**Section D – quality control testing**

28. List all quality control tests applied to the processed tissues or cells, including characterisation and microbiology, providing details of the test supplier where applicable.
29. List in Section D only the tests that are undertaken routinely during the processing of tissues or cells.

The following are examples:

- sterility testing of in-process samples and the end product
- quantity and viability of cells
- residual water in freeze-dried tissues
- purity of CD34⁺ cells

30. You may have undertaken a number of other assays during process validation, but these do not need to be listed in this section if they are not to be used during quality control of the process.

31. All tests used to ensure the quality or safety of tissues or cells must be validated by you or CE-marked; please indicate which applies to each test in the table in Section D. Describe the test article (analyte) that is used for each assay, and the criteria for release (i.e. pass or fail criteria).

Section E – process validation

32. This is the most important section of the PPD where you demonstrate that tissue and cell processing procedures have been validated, and do not render the tissues or cells clinically ineffective or harmful to the recipient. There is no requirement for studies demonstrating clinical effectiveness, though such validation is acceptable for process authorisation.

33. Validation reports may be based on your own studies, data from studies published by others, or through a retrospective analysis of clinical outcomes.

Studies performed by your establishment
You may conduct your own studies to validate your preparation processes. You may also use the validation reports conducted by another establishment, provided that you demonstrate that you can effectively reproduce their process with the same results in your facility (treat this kind of validation report as a ‘published’ study).

If you perform your own process validation you must first decide the Critical Quality Attributes (CQAs) necessary for you to be satisfied the tissues or cells are not rendered clinically ineffective or harmful, then you will be able to demonstrate that the process is reproducing these attributes consistently. You may need validated assays to measure CQAs. Where there has been open processing or decontamination-process steps, the HTA expects to see a CQA based on microbiology testing or media-simulation in the validation plan.
The CQAs for solid tissues may be those that make them suitable for engraftment.

*For example, the CQAs for a cornea may be the density of viable cells per surface area, freedom from microbiological contamination, and transparency.*

For cell preparations, the HTA expects as a minimum that the CQAs include:

- the minimum number of cells per unit;
- a minimum acceptable viability; and
- a minimum purity of the cells, based on an analysis of the phenotypes in the cell population.

You must also identify the Critical Process Parameters (CPPs), which are conditions that will bring about or preserve these CQAs.

*For example, when freeze-drying acellular pericardium the CPPs of temperature and duration of the process have a critical impact on the CQAs of residual water and stability of the resulting collagen matrix.*

Validation reports should include at least:

- a process optimisation report specifying the CPPs, how they were optimised and, where necessary, how their tolerance levels have been set;
- a description of the CQAs, how they are to be assessed, and the acceptable result thresholds;
- a validation plan with documented methodology;
- all results obtained, in a clear form with relevant interpretation showing how at least three independent runs have produced tissues or cells within predetermined criteria for CQAs.

*Data from published studies*

The publications upon which you base your validation should be appended to the PPD for review. In this case, you should demonstrate that you can effectively reproduce the published process with the same results in your facility (operational validation). Copies of the relevant SOPs and the results of
the operational validation should be provided to demonstrate that the process is equivalent to that applied in the published study. Where specific steps have been changed or adapted, separate validation should confirm that these changes have not invalidated the method.

Retrospective evaluation
In the case of well established processing procedures, retrospective evaluation of the clinical results for tissues and cells supplied by your establishment can be used.

Evidence should be provided of the number of tissue or cell grafts implanted following processing by the method under consideration, and the period during which these implantations occurred. You should demonstrate how clinical users were informed of the procedure for reporting adverse reactions.

The context of the data should be provided if available, with reference to national or worldwide success rates for clinical use of such tissues or cells.

34. Some processes will be covered by patent. If this applies to the process in your PPD please provide the patent number so that the HTA may review the supporting data.

35. If a process includes steps that inactivate viruses or sterilise the tissues or cells, please append a copy of the validation report for each of these steps.

Section F – final labelling and accompanying documentation

36. This section must be completed if you are distributing or exporting the cells for patient treatment. You must provide a copy of the primary container label and append any accompanying documents included in the packaging.

37. The requirements for labelling and accompanying documentation are provided in the Guide to Quality and Safety at paragraphs 159 to 161 (p.36).

159. Primary tissue or cell containers must contain:
   a. type of tissues and cells, identification number or code of the tissue or cells, lot or batch number;
   b. expiry date;
   c. identification of the tissue establishment or distributor in the UK;
   d. in the case of autologous donation: labelled as such and the donor/recipient has to be identified;
   e. in the case of directed donations – the label must identify the intended
recipient;

f. when tissues and cells are known to be positive for a relevant infectious
disease marker, it must be marked as: BIOLOGICAL HAZARD.

160. If any of the information under points (c) to (e) above cannot be included
on the primary container label, it must be provided on a separate sheet
accompanying the primary container. This sheet must be packaged with the
primary container in a manner that ensures that they remain together.

161. The following information must be provided either on the label or in
accompanying documentation:

a. description (definition) and, if relevant, dimensions of the tissue or cell
product;

b. morphology and functional data where relevant;

c. date of distribution of the tissue or cells;

d. biological determinations carried out on the donor and results;

e. storage recommendations;

f. instructions for opening the container, package, and any required
manipulation/reconstitution;

g. expiry dates after opening/manipulation;

h. instructions for reporting serious adverse reactions and/or events;

i. presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc.).

Section G – declaration by the DI

38. Finally, the PPD must be signed by the Designated Individual (DI) for the
licence as a declaration that the information included in the PPD is
accepted by him or her as evidence that the preparation processes
described are validated. The DI must print his or her name, sign and date
the PPD. The HTA recommends electronic submission of PPDs through
email, and prefers these are made by the DI, so the DI may make this
declaration in writing; in such circumstances, there is no requirement to
scan the DI’s signature.

Submission

39. A Completed PPD may be submitted to the HTA by email to the
Regulation Manager that requested it or to enquiries@hta.gov.uk or by
mailing to HTA, 151 Buckingham Palace Road, London, SW1W 9SZ;
please mark your submission ‘PPD’ in the subject heading or on the
envelope. Those PPDs that for part of a licence application must be submitted with the rest of the application details. If you have any questions please call a member of the Regulation Team on 020 7269 1900.

40. Please ensure all necessary documents accompany the submission. You may find this checklist helpful:

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**PPD review by the HTA – the outcome**

41. Once your PPD is received, it will be reviewed by a Regulation Manager at the HTA.

42. If the HTA considers that preparation processes are not suitable for authorisation, then the reasons for this will be given. The HTA may request further information, or that you conduct additional validation work prior to submission of a revised PPD.

43. If you have submitted your PPD ahead of a site-visit inspection, the HTA will continue its review of the PPD during the inspection, and will provide feedback then; the inspection report will record the outcome of the authorisation process.

44. If your PPD was submitted independently of an inspection because of changes to the processing you undertake, then the HTA intends to provide the outcome of the authorisation in writing within four weeks. Processes that have been authorised will be recorded in your next inspection report.

45. If your PPD was submitted as part of a licence application, your processes will be authorised at the time the licence is granted.