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Legal basis for requiring the authorisation of preparation processes

1. The requirements for holding a licence for tissue and cell preparation processes are established in Schedule 2 paragraph 14 of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) (Q&S Regs).

2. The HTA's Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (the Q&S Guide) sets out the requirements for process validation, as follows:

    a. 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.

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

    c. 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.

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

    e. 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.

When PPDs must be used

Before implementing changes to a process

3. You are required to inform the HTA if you make significant changes to the way you process tissues or cells for patient treatment. The HTA defines a significant change as any change that may impact the quality and safety of the tissues / cells. You may need to submit a PPD of the new process for review by the HTA prior to authorisation. If the changes are unlikely to impact significantly on quality and safety then a new PPD might not be required.

   For example, an establishment has been using a source of phosphate buffered saline in a process, but the supplier has withdrawn the product from sale, so the establishment sources an equivalent product (same formulation and quality) from another supplier. The establishment informs the HTA of this change. The PPD Working Group is able to update the PPD and submission of a PPD is not required.

4. 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 will be required to submit a PPD to revise a process whether or not the original process was authorised using a PPD.

Before starting a new process

5. 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

6. All applications for a licence to process human tissue or cells intended for human application must include a PPD that demonstrates that the preparation process has been validated.

If requested by HTA

7. Submission of a PPD may be requested by the HTA if critical evaluation of a particular preparation process is required.

   For example, if during a HTA inspection shortfalls are noted against HTA standards relating to preparation processes, then submission of a PPD may be required as part of the Corrective and Preventative Action Plan.

Description of the PPD

8. A completed PPD should contain all the information the HTA needs to assess the suitability of the preparation process. The PPD form can be downloaded from the HTA website.

9. There are several sections in which you are asked to describe the procedure, record the reagents and materials used and provide a validation report.

10. In completing the PPD you should provide an assurance that the process used to prepare tissues and cells does not render them clinically ineffective or harmful to the recipient.

Completing the PPD

Section A – Establishment information

11. Please ensure you complete Section A accurately, so that the HTA knows to whom queries relating to the PPD should be addressed.

12. 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 H later.

Section B – Preparation process – general information

13. Provide 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

14. Describe separately the tissues or cells to which the process applies, even if this is evident in the process name. The HTA will use the tissue and cells described in this section as a record on the HTA's database of which tissue and cells are authorised for the process. If you intend to apply the process in the future to tissue and cell type not described here, you must inform the HTA and submit an amended PPD.

15. Describe the intended purpose(s) of the processed tissues and cells, even if this is evident in the process name. The intended use of the processed tissues and cells will be taken into account as part of the HTA's review of your PPD. When the PPD is authorised, it is the HTA's expectation that the tissues and cells are not used for any other indication or medical claim, other than the one described in this section. If you intend to use the processed tissues and cells for another purpose, you must inform the HTA and submit an amended PPD.

16. You will be asked in Section B to provide details of any tests or other donor selection requirements. Please do not list the mandatory serological testing in this section (HIV, HBV, HCV, and syphilis), but please include virology testing over and above the mandatory requirements. For example, if you routinely test all donor samples for HTLV- I/II. If there are any wider donor selection requirements (e.g. donor age range) please include these here.

17. 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.

18. The final part of Section B requires a brief description and/or flowchart of the preparation process. Critical process parameters should be identified and ranges included; these should be justified by validation or operational qualification (see section E). Include any steps where quality control samples are taken and align these steps with the list of quality control tests from Section D later in the PPD.

19. You must include the standard operation procedure for the process.

Section C – Reagents and materials

20. 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 plastic ware.

21. All reagents and materials that come into contact with the tissues or cells must be of a standard that minimises risk to the quality or safety of the processed product.

22. Wherever possible, in Great Britain, UK Conformity Assessed (UKCA) medical devices should be used, although CE marked medical devices may continue to be used until 1 July 2023. In relation to Northern Ireland, medical devices should be CE marked if certified by a notified body in the European Union, or CE and UK(NI) marked if certified for Northern Ireland.

23. You may be asked by the HTA to supply additional information about your choices of reagents and materials. Information requested may include, but is not limited to: rationale, risk assessments and evidence of validation.

Section D – Quality control testing

24. Acceptance criteria should be included here. They should be specific and reflect the criteria that area required to ensure that the processed tissues and cells are not rendered clinically ineffective or harmful.

25. You should list all quality control tests applied to the processed tissues or cells, including characterisation and microbiology, providing details of the test supplier where applicable.

26. In Section D, you should only list the tests that are undertaken routinely during the processing of tissues or cells.

    For example:

    - sterility testing of in-process samples and the end product
    - quantity and viability of cells
    - residual water in freeze-dried tissues
    - purity of a cell population sorted for a phenotypic marker, such as CD34

27. 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.

28. All tests used to ensure the quality or safety of tissues or cells must be validated by you or be UKCA/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

29. This is the most important section of the PPD. A validation report should be presented which demonstrates that tissue and cell processing procedures have been validated and do not render the tissues or cells clinically ineffective or harmful to the recipient. If this information is not provided, this may delay the authorisation of the PPD.

30. The validation report should define and provide evidence to support the Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs). See the next section for information on CQAs and CPPs.

Critical Quality Attributes (CQAs)

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

The validation report should specify the CQA necessary for you to be satisfied the tissues or cells are not rendered clinically ineffective or harmful by the preparation process. The validation report should precisely define the CQAs and provide information on the tests performed to determine whether the CQAs have been achieved. You must also demonstrate that the process is reproducing the CQAs consistently. You may need validated assays to measure CQAs.

CQA example 1: The CQAs for a cornea may be the density of viable cells per surface area, evidence of freedom from microbiological contamination, and transparency.

CQA example 2: For cell preparations, CQAs may include: the minimum number of cells per unit; minimum acceptable viability; and a minimum purity of the cells, based on an analysis of the phenotypes in the cell population.

CQA example 3: Where there has been open processing or a decontamination step, include a CQA based on microbiology testing or media simulation.

Critical Process Parameters (CPPs)

A CPP is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality.

The validation report should identify the CPPs that will bring about or preserve the CQAs. The validation report should specify how the CPPs have been optimised and, where necessary, how their tolerance levels have been set. The rationale for the specified CPPs should be clearly explained.

CPP example 1: For freeze-drying acellular pericardium, residual water and stability of the resulting collagen matrix are defined as CQAs. The temperature and duration of the process are CPPs because they critically impact the CQAs.

Further examples of CPPs: transport times, temperature in transit or volume/size of starting material.

31. A 'Validation Report Template' has been prepared by the HTA's Preparation Process Dossier Working Group to help establishments produce validation reports to fulfil this section of the PPD. Whilst the use of this template is not required, it is highly recommended and will facilitate the efficiency of the PPD review process. A sample template can be found at the end of this guidance document. The template for use can be downloaded from the HTA website.

32. You may conduct your own studies to validate your preparation processes. You may also use the validation experiments conducted by another establishment or data from published studies, provided that you demonstrate that you can effectively reproduce their processes with the same results in your facility (operational validation).

- The publications upon which you base your validation should be appended to the PPD for review.
- 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 preparation process.

33. There is no requirement for you to perform studies demonstrating clinical effectiveness; although where a preparation process is well-established a retrospective evaluation of the clinical results for tissues and cells supplied by your establishment may be used to validate your preparation process.

- 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. In exceptional cases, we may issue 'conditional authorisation' of a PPD pending clinical data. If this applies to your PPD, then please use the points in paragraph 33 to guide your submission of clinical data to the HTA.

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

36. 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

37. 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.

38. The requirements for labelling and accompanying documentation are provided in the Guide to Quality and Safety paragraphs 167 to 170.

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; and

g. in Northern Ireland only, the SEC as applicable to tissues and cells being distributed for human application.

If any of the information under points (d) (e) and (g) 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.

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 (for example. antibiotics, ethylene oxide, etc.); and

j. for imported tissues and cells, the country of procurement and the exporting country (if different from the procurement country

Section G – Additional information

39. Any additional information that is pertinent to the review and authorisation of the PPD should be included here. This could include for example, if there is a patient awaiting treatment and an urgent review is required.

Section H – Declaration by the DI

40. 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.

Section I – Checklist of documents

41. Your submission must include a completed PPD, the SOP for the preparation process, a flowchart or description of the process, a validation report and an example final label. The checklist can be used to ensure your submission is complete. If any of the required documentation is not submitted, this may delay the authorisation of the PPD.

Submission

42. PPDs that form part of a licence application must be submitted with the rest of the application details.

43. For all other PPDs, the completed PPD and accompanying documentation may be submitted to the HTA by any of the methods listed below. Please mark your submission 'PPD' in the subject heading or on the envelope.

    - Email to the relevant Regulation Manager
    - Email to: enquiries@hta.gov.uk
    - By post to HTA, 2nd floor, 2 Redman Place, London E20 1JQ

44. If you have any questions please call 020 7269 1900 and ask to speak with a member of the Regulation Team.

PPD review by the HTA

45. Once your PPD is received, it will be assessed independently by two Regulation Managers who are members of the PPD Working Group.

46. The PPD will be discussed by the PPD Working Group at the next available fortnightly meeting where a decision will be made on how to proceed with your PPD. All PPD meetings and decisions require a quorum of at least three members.

47. You will receive a response informing you of the meeting's outcome within 20 working days of receipt of your PPD by the HTA. The PPD may be authorised as presented, or the HTA may request further information or that you conduct additional validation work.

48. If the HTA considers that preparation processes are not suitable for authorisation, then the reasons for this decision will be given.

Validation report template

This template has been prepared by the HTA's Preparation Process Dossier Working Group (PPDWG) to help establishments produce validation reports to fulfil Section E of the Preparation Process Dossier (PPD). Whilst use of this template is not required, it is highly recommended and will facilitate the efficiency of the PPD review process.

You can find the PPD validation report template on the HTA website.