ToxBank

Deliverable D4.2

General Quality and Regulatory Criteria for Establishment and Dissemination of hPSCs

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1. Executive Summary

1.3 ToxBank overview

ToxBank is being developed to manage and provide access to all protocols and experimental data across SEURAT-1 to support an integrated data analysis. An additional key component is data on suppliers of biomaterials such that SEURAT-1scientists can select high quality materials for their research which can be translated to industry as part of the SEURAT-1 programme. Some means of evaluating the quality of data being entered on to ToxBank is essential and where relevant standards for quality issues exist ToxBank will utilise these and develop best practice approaches where standards are not available.

1.2 The ToxBank cell and tissue bank for *in vitro* toxicity testing

The ToxBank cell and tissue bank will provide an important service to European scientists through a coordination of a network of high quality delivering high quality cells and other relevant biomaterials to support the SEURAT-1 cluster by facilitating identification of, and access to, those research materials that provide best fit for purpose for SEURAT-1 scientists.

1.3 Collating and utilizing best practice standards for stem cell lines

Whilst this aspect of ToxBank will develop to include a range of biomaterials Deliverable 4.2 identified the need for a best practice standard for the scientific, ethical and commercial criteria for supply of one of the most critical biomaterials, pluripotent stem cell lines. This standard collates and utilizes standards recently developed as consensus amongst stem cell scientists and banks. The standard established will be used in ToxBank to develop evaluation criteria for suppliers of stem cell lines and use these to present data from these suppliers to demonstrate compliance with best practice. Thus, SEURAT-1 scientists will be able to identify suitable sources of cell lines that will meet scientific criteria, ensure compliance with EU and national regulation and provide assays which can be taken up by industry without delays or blocks due to adverse commercial constraints on commercial exploitation.

2. Introduction

The following report outlines the standards gathering process that was performed in order to develop SEURAT-1 quality and regulatory standards for the establishment and dissemination of human pluripotent stem cell lines.. This included identifying key and most recent standards established for human stem cell lines. These standards were than collated and gaps where a specific standards were needed for ToxBank were identified and appropriate standards established in close collaboration with other partners in the SEURAT-1 cluster.

3. Identification and Collation of Current Best Practice Standards

3.1. Design Process for a Quality and Regulatory Standard

Prior to designing and building the data warehouse, the ToxBank consortium initiated an extensive standards gathering exercise. This focused ion identification of standards for

pluripotnet stem cells established by consensus amongst a range of stem cell scientists and stem cell banks. The Process can be divided into 5 stages:

- Step 1. Identify scope of the standards framework required
- Step 2. Identify existing consensus standards and gaps where new ToxBank standards are needed
- Step 3. Generation of new standards in coordination with appropriate partners in ToxBank and other SEURAT-1 consortia
- Step 4. Collate relevant standards in a framework for use in ToxBank and SUERAT-1
- Step 5. Consider need for updating and developing the standards

Step 1. Identify scope of the standards framework required

The UK Stem Cell Bank partner (NIBSC-HPA) has played a key role n a number of international stem cell collaborations focused on standardisation, including the hESCreg project, the International Stem Cell Initiative and the International Stem Cell Banking Initiative. UKSCB experience in this are enabled it to identify the technical standards required were identified as follows:

- Nomenclature for pluripotent stem cell lines
- Minimal data to be published in original publications of PSC lines
- Procurement of cell lines (ethical, regulatory and commercial)
- Banking (culture, preservation and storage)
- Testing and characterization
- Shipment

Step 2. Identify existing consensus standards ad gaps where new ToxBank Standards are needed

Searches revealed a variety of publications dealing with standards (Appendix 1). From these those dealing with the appropriate level of technical detail and advice were selected and are given in the Table below.

Standards Applicable to Research Use of Human Stem Cell Lines

Activity	Relevant Standard/Qualification	Standard not available for ToxBank needs
Nomenclature for pluripotent stem cell lines	Luoung et al., 2011/Most recent proposal for a standard in cell line nomenclature that was passed for consultation with the International Stem Cell Initiative	_
Minimal data to be published in original publications of PSC lines	Luoung et al., 2011/Most recent proposal for minimal information to accompany the first publication of a PSC line. It was provided for consultation with the International Stem Cell Initiative	-
Procurement of cell lines (ethical, regualtory and commercial)	ISCBI 2009/consensus standard established by 106 representatives from the human ESC academia, stem cell banks, scientific societies and regulatory bodies	Detailed ethical and commercial review process for procurement of PSC lines
Banking (culture, preservationand storage)	ISCBI 2009/(as above)	
Testing and characterization	ISCBI 2009 for hESC and with broad application to human cel lines including iPSC lines. ESTools criteria for iPSC lines.	Supplementary requirements for iPSC lines
Shipment/Dissemination	ISCBI 2009	-
Publication of genetic data	EWP 2011 for hESC	Additional requirements for iPSC lines

Step 3. . Generation of new standards needed for ToxBank

The UKSCB partner in both ToxBank and ScrnTox had been considering the issues n relation to procurement of cell lines and quality control/characterisation of PSC lines with ScrnTox partners Cellartis (Goteborg, Sweden) and JRC (Ispra, Italy).This synergy with ToxBank requirements was used to develop two standards, one based on commercial and ethical (general European requirements) for evaluation of PSC lines to be used in ScrnTox and a second to identify common standards for QC and characterisation of PSC lines. The commercial and ethical standards are reported below as are the draft standards for QC/characterization. The latter are still under

consideration with a SEURAT-1 working group to produced concise guidance on quality control criteria for undifferentiated and differentiated PSC cultures.

Step 4. Collate relevant standards in a framework for use in ToxBank and SUERAT-1

In this step the various existing and new standards were combined into a single reference document (see section 4) to be used for further deliverables on standards expected of biomaterial suppliers and evaluation of these suppliers.

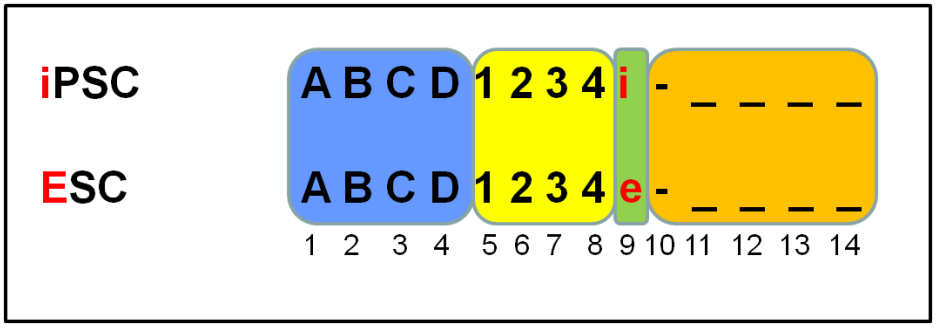
Step 5. Sustaining the relevance of the standard

Given the rapid rate of development ion the stem cell culture field it was important to consider need for updating and developing the established standards as reported in section 4.

3.2. Standard for PSC line nomenclature

The primary reference or key identifier for an individual cell line is the name commonly used for it in the published literature. Naming formats often vary somewhat between research groups and a search of the literature has shown that there are already numerous examples of name duplication in different centres which could cause significant confusion for researchers (Luong et al 2011). Whilst past efforts to standardise the structure of cell lines names for other cell types have failed to be adopted widely, the field of hPSC research is already generating large numbers of cell lines with plans for even larger collections of hPSCs and it will be particularly beneficial to establish a common nomenclature for the naming of hPSCs. Luong et al. (2011) proposed a naming convention which is designed to be simple, self explanatory and specific and which is not dissimilar to approaches adopted by a number of centres. The proposed convention captures the cell type and origin as follows:

Figure 1. **Proposed nomenclature for cell line names (after Luong et al., 2011)**



Legend: **Blue box:** sequence of letters to represent source reference e.g. laboratory, institution. **Yellow box:** a sequential numeric string to identify specific cell lines. **Green box:** "i" or "e" to represent "iPSC" or ESC", respectively. **Orange box:** a dash followed by letters and/or numbers (up to 12 in total). This box can be used to note or codify specific characteristics such as disease, reporter genes, patient number and clone number. The green and orange boxes were proposed as optional. Luong et al. Proposed the total number of characters (including dash) should be limited to 14.

It is proposed that any cell lines registered in the Toxbank database should be allocated a reference based on this naming standard in coordination with the group that derive the line. This will provide a common identifier that can provide unequivocal recognition of cell lines throughout the SEURAT programme and beyond.

3.3 Minimal data to be published in original publications of PSC lines

It s important that researchers can identify the origin and characteristics of the somatic cells used to isolate and the features they exhibit. The EC funded project ESTools (www.estools.eu) established key scientific criteria to demonstrate that a purported iPSC line does in fact have the correct features to justify this description. More recently, Luong et al. (2011) identified key features that should be reported in first publications of hPSCs (Table 2). Here we have used these published consensus criteria to establish the features that SEURAT scientists should expect to see reported for a hPSC intended for use in the SEURAT cluster workprogrammes. Table 2 shows these key criteria.

Table 2. Recommended minimal set of information for publishing new lines (Luong et al., 2011)

SOURCE	DERIVATION METHOD	CHARACTERIZATION	GENETIC IDENTITY AND STERILITY	PROVENANCE
Patient-derived or cell bank *Cell type, tissue source and passage number *Age (a range, if specific age cannot be disclosed) Ethnicity (self-reported and/or determined by analysis)	hESC (e.g. zona pellucida removal, cell isolation and seeding, culture conditions) *Reprogramming method (e.g. vector system, small molecules, protein, mRNA, or miRNA transduction/transfection)	Undifferentiated state (e.g. immuno-cytochemistry, FACS, molecular profiling) Pluripotency (e.g. in vitro differentiation, teratoma assay, molecular profiling) Genetic characterization (e.g. karyotype, SNP genotype) Disease history, if applicable.	Identity profile (e.g. STR, SNP) Not necessarily published fully, but held for matching. Mycoplasma (recommended routine practice, include specific test used)	Consent (statement about consenting process and evidence of human subjects oversight) Conflict of interest disclosure

3.4 Ethical and Commercial Review Process

In order to ensure that all laboratory work performed meets relevant criteria to ensure ethical acceptability and compliance with commercial demands researchers need to be aware of appropriate procedures, regulations and laws and take personal responsibility for these important aspects of their research. The following sections of guidance have been developed by collaboration between ToxBank and ScrnTox for the evaluation of cell lines being brought into the ScrnTox project.

3.4.1 Ethics Criteria for Cell Lines Selection (hiPSCs and hESCs):

In order to establish that all cell lines were obtained from tissue that has been ethically sourced the researchers must be able to provide evidence for the following:

- That fully informed consent was obtained and recorded for the donor tissue
- That consent permits the intended uses of the hPSC lines derived fro the donor's tissue
- That the donor's identity was anonymised
- A validated copy of the original consent form (with donor details redacted) is available and/or a statement is available from a person authorised by the owner or derivation centre on the ethical provenance of the cell line including a contact that would facilitate confirmation of the original consent without breaking donor anonymity.
- There should be a clear statement on any constraints applied by the donor on the use of derivatives from their cells/tissues.

Supplementary information:

- All cell lines are registered within the hESCreg database
- Copies of blank consent form (or an English translation) and any information provided to the donor are available.
- Evidence from the donation process that the donor was aware that:
  - Derived lines may be exploited commercially but that donors would not receive personal financial benefit.
  - The donors decision to donate tissue would not influence their personal treatment an there would be no feedback on data from the cell line derived from their tissue.
  - Derived hPSCs could be used for a wide range of purposes in different laboratories and may be tested for genetic characteristics, microbiological contamination and other features of the cells.

3.4.2 Commercial Criteria

Failure to address key commercial issues relating to the use of any research materials for use in SEURAT-1 projects could invalidate delay or otherwise compromise their ultimate use to deliver the required outputs from SEURAT-1 for use in industry. It is therefore important that researchers understand the kind of issues that could lead to difficulties for delivery of commercial product safety testing , and apply suitable vigilance when obtaining hPSCs and other research materials that may be critical at a later stage. Key criteria for selection of hPSCs should therefore include:

- The owner of the cell line is clearly identifiable (NB numerous cell lines have shared ownership)
- Permission has been granted by the owner/s or their agents for the intended use or is the line released for general research without constraint (see also ethics criteria re: donor constraints).
- Intellectual property rights relating to the cell line or any components used to derive the cell line (e.g. DNA constructs) are clear and would not influence their use for commercial application. If there is a potential affect on ultimate use of research materials for commercial purposes this should be discussed with the consortium coordinator and any limitations on the use of the materials agreed.

3.5 Quality Control and Characterisation

Whilst substantial published guidance on hESC charaerisation and quality control had been identified (Table 1) wich was aso considered to be broadly genric for iPSC lines. However, there are are clearly additional requirements to establish the verascity of an iPSC line, which whilst identified had not been published. This standard had been developed within the FP6 ES Tools consortium and was kindly provided by Prof Peter Andrews (University of Sheffield and ES Tools coordinator) and is reproduced in Table 3. The key additional characterisation requirements beyond those identified in the hESC guidance document were the determination of downregualtion of transgenes to which could be added determination of copy number of transgenes with evidence of silencing; or evidence of transgene deletion or non-incorporation for more advanced characterisation.

It was noted that given the rapid developments in stem cell research it would be appropriate to review the requirements for characterisation of PSC lines and coordination with ScrnTox partners (JRC) on development of quality control standards

for PSC lines has been intitiated. This has now developed as a central SEURAT-1 workprogramme which will be used to update the ToxBank requirements.

Table 3. Minimal Criteria for the classification of putative iPS cells for further study *

- Stable ES cell like morphology and growth pattern
- Expanded in culture as established line for > 10 passages
- Viable frozen stocks
- Human ES cell surface antigen profile: Expression of SSEA3, SSEA4, TRA-1-60/TRA-1-81, L-ALP (TRA-2-54 or TRA-2-49) – quantitated by flow cytometry
- Express key endogenous pluripotency-associated genes: Oct4, Nanog, Sox2, Rex, TDGF, assessed by:
  - qRT.PCR
  - immunostaining/western blot
- Neural differentiation in vitro – immunostaining for TuJ1 and GFAP
- Primary evidence of pluripotency in embryoid body or other in vitro differentiation assays by qRT-PCR for lineage markers
- Transgenes down-regulated
- Diploid karyotype

Advanced characteristics that should be assessed for putative iPS cells

- Array CGH or SNP analysis of genetic integrity
- DNA fingerprint confirming identity with somatic cell of origin
- Teratoma formation
- Detailed evidence of differentiation in vitro to three germ layers with functional markers
- Copy number of transgenes with evidence of silencing; or evidence of transgene deletion or non-incorporation
- Gene expression profile – quantitative assessment by TLDA
- Methylation status of Oct4 and Nanog promoters
- X chromosome activation/inactivation status for female cells
- Comprehensive transcriptomic analysis by microarray or high throughput cDNA sequencing (for selected lines)

***Note:** These minimal criteria should be met before putative iPS cells are entered into further study, unless a strong case can be made that one or other criterion should not exclude the cells from specific experiments. For example, it should be noted that, although no SSEA3(-) or SSEA4(-) human ES cells have yet been identified, rare polymorphisms in the human population indicate that SSEA3(-) or SSEA4(-) human ES or iPS cells might be encountered.*

(Courtescy of Prof P Andrews, ES Tools and University of Sheffield)

3.6 Publication of Genetic Data

PSC lines have all been relatively recently isolated from donated cells and tissues and as a generic principle it is important to protect the identity of the donors. Publication of detailed genetic data inadvertently could lead to identitification of the donor or their family.

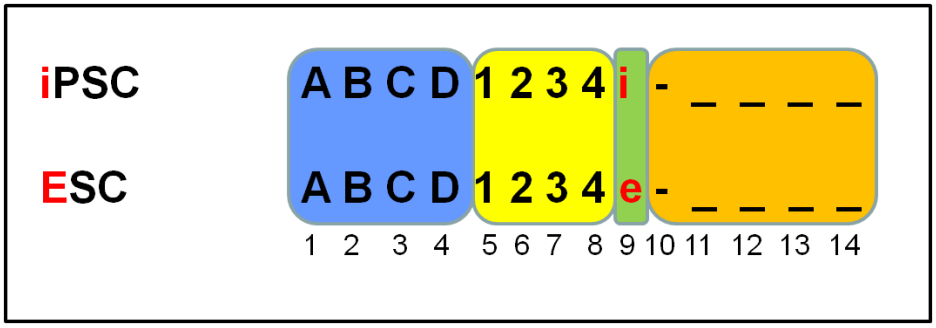
4. Current Best Practice for Regulatory and Quality Standards for PSC Lines

The following sections provide current best practice in quality and regulatory issues and dissemination of PSC lines. It is specifically written for the needs of ToxBank and other partners in the SEURAT-1 cluster and was prepared in close collaboration with other partners (JRC and Cellartis) from ScrnTox.

4.1 Nomenclature for Pluripotent Stem Cell Lines

It is proposed that any cell lines registered in the Toxbank database should be allocated a reference, based on the naming standard proposed by Luong et al., 2011) (Figure 1), in coordination with the group that derive the line. This will provide a common identifier that can provide unequivocal recognition of cell lines throughout the SEURAT programme and beyond. This standard is also recommended to partners within the SEURAT-1 cluster who are engaged in the derivation of PSC lines.

Figure 1. **Proposed nomenclature for cell line names (after Luong et al., 2011)**



Legend: **Blue box:** sequence of letters to represent source reference e.g. laboratory, institution. **Yellow box:** a sequential numeric string to identify specific cell lines. **Green box:** "i" or "e" to represent "iPSC" or ESC", respectively. **Orange box:** a dash followed by letters and/or numbers (up to 12 in total). This box can be used to note or codify specific characteristics such as disease, reporter genes, patient number and clone number. The green and orange boxes were proposed as optional. Luong et al. Proposed the total number of characters (including dash) should be limited to 14.

4.2 Minimal Data to be Published in Original Publications of PSC Lines

It is recommended that researchers publishing or making data available on new PSC lines should make available or publish the following information modified from Luong et al., (2011):

4.2.1 Cell Source

If the parental cells were obtained from a cell bank or culture collection the Accession number from the supplier should be reported. Authors should also report:

- the cell type believed to have been reprogrammed, its tissue source and passage number
- the "age" of donor e.g. foetal, young adult, senior adult (NB a specific age should not be disclosed to avoid the possibility of facilitating identification of the donor)
- Ethnicity given by the donor or identified by genetic analysis.

4.2.2 Method Used to Derive the Cell Line.

For hESC lines a description should be given of the process by which the embryonic stem cells were isolated *in vitro* and cultured, including, culture conditions, passage procedure, feeder cell preparation and seeding. For iPSCs additional information should be reported on the reprogramming technique used and the specific protocol used to generate the iPSC line.

4.2.3 Characterisation

Characterisation of new cell lines should include:

- Phenotype of the undifferentiated state using classical markers (e.g. immuno-cytochemistry, FACS, molecular profiling)
- Potential for pluripotency (e.g. *in vitro* differentiation, teratoma assay, molecular profiling)
- Genetic characterization (e.g. karyotype, aCGH, SNP genotype)
- Disease state or genetic lesion in donor, if applicable.

4.2.4 Identity

An identity profile (typically by an STR (short tandem repeat) method) should be produced for each cell line but should not be published at least in its complete form as this could threaten the anonymity of the donor. These profiles should be held for internal quality control and for resolution of cell authenticity issues with other researchers or cell banks on a case by case basis.

4.2.5 Mycoplasma Testing

Mycoplasma can be passed readily between cell lines in a cell culture lab and can have dramatic and potentially irreversible effects on cell characteristics and function. Researchers should be able to demonstrate that their published PSC lines are not infected with these organisms by reporting mycoplasma test results and the specific method used so that others can consider the sensitivity and reliability of the testing performed.

4.2.6 Provenance

Publications should include a statement about the consenting process, any donor constraints on research with their tissue and a conflict of interest disclosure

4.3 Procurement of Cell Lines (ethical, regulatory and commercial)

The guidance found in the ISCBI (2009) publication provides key factors to take into account regarding appropriate management of ethical consent and governance.

In order to establish that all cell lines used have been obtained from tissue that has been ethically sourced the researchers must be able to provide evidence for the following:

- That fully informed consent was obtained and recorded for the donor tissue
- That consent permits the intended uses of the hPSC lines derived fro the donor's tissue
- That the donor's identity was anonymised
- A validated copy of the original consent form (with donor details redacted) is available and/or a statement is available from a person authorised by the owner or derivation centre on the ethical provenance of the cell line including a contact that would facilitate confirmation of the original consent without breaking donor anonymity.
- There should be a clear statement on any constraints applied by the donor on the use of derivatives from their cells/tissues.

It is also helpful to have access to other supplementary information as follows:

- All cell lines are registered within the hESCreg database
- Copies of blank consent form (or an English translation) and any information provided to the donor are available.
- Evidence from the donation process that the donor was aware that:
  - Derived lines may be exploited commercially but that donors would not receive personal financial benefit.
  - The donors decision to donate tissue would not influence their personal treatment an there would be no feedback on data from the cell line derived from their tissue.
  - Derived hPSCs could be used for a wide range of purposes in different laboratories and may be tested for genetic characteristics, microbiological contamination and other features of the cells.

It is important to note that laws relating to the use of human tissues and embryos will vary from one country to another and the researcher should understand their responsibilities under national law when using cells tissues and cell lines derived from human tissues.

Failure to address key commercial issues relating to the use of any research materials for use in SEURAT-1 projects could invalidate delay or otherwise compromise their ultimate use to deliver the required outputs from SEURAT-1 for use in industry. It is therefore important that researchers understand the kind of issues that could lead to difficulties for delivery of commercial product safety testing , and apply suitable vigilance when obtaining hPSCs and other research materials that may be critical at a later stage. Key criteria for selection of hPSCs should therefore include:

- The owner of the cell line is clearly identifiable (NB numerous cell lines have shared ownership)
- Permission has been granted by the owner/s or their agents for the intended use or is the line released for general research without constraint (see also ethics criteria re: donor constraints).
- Intellectual property rights relating to the cell line or any components used to derive the cell line (e.g. DNA constructs) are clear and would not influence their use for commercial application. If there is a potential affect on ultimate use of research materials for

commercial purposes this should be discussed with the consortium coordinator and any limitations on the use of the materials agreed.

4.4 Banking (culture, preservation and storage)

The ISCBI (2009) guidance gives a description of the best practice for the banking process which covers:

- Procurement of Cell Lines
- Cell Banking Procedures and Documentation
- Cell Bank Quality Control
- The Process of Releasing Cell Banks

These sections include key issues for preservation and storage of stem cell lines.

4.5 Testing and characterization

Drawing on the ISCBI (2009) guidance for hESC lines and ES Tools criteria for hiPSC characterisation a summary on appropriate characterisation can be summarized as outlined in the following table.

Criteria for hPSC Line Characterisation

Analytical Technique	Required Characteristic Reported for Each Cell Line
Identity e.g. DNA profile	Matches parent cell line
Karyotype	Report karyotype from a specified number of metaphase analyses (see Methods and Measurements in ISCBI (2009))
Post-Thaw Recovery	Viable colonies recovered (quantified efficiency of recovery of each bank/lot should be given) NB viable colonies should also be predominantly free of differentiated cells.
Pluripotency	Report data available or traceable to stocks tested for pluripotency*
Growth Characteristics	Report value
Cell antigen expression	High proportion of cells (approx. 70%) positive for each marker*
Cell gene expression	Report data available*
Genetic stability	Report data available*

* Precise requirements for hESC lines are discussed in ISCBI (2009) and are under development for hESC and hiPSC lines in Scr&Tox.

4.6 Shipment/Dissemination

For general recommendations on shipment the reader is referred to section XX of the International Stem Cell Banking Initiative (ISCBI, 2009). In particular, researchers and suppliers of cells should consider the following recommendations from that guidance:

- "Vials and straws shipped should be from a homogenous distribution bank of cells and contain sufficient cells to readily recover a culture"
- "The method of transport should be consistent with the method of preservation and validated "
- "Preservation methods are developing and improved methods are needed to assist in stable storage and shipment and it is important that banks maintain awareness of current developments in preservation science and technology."

4.7 Publication of Genetic Data

Little guidance specific to the publication of genetic data from PSC lines exist in the literature. However, the 'Ethics Working Party' of the International Stem Cell Forum (http://www.stem-cell-forum.net/ISCF/) has produced a policy statement on the publication of genetic data from hESC lines and the UK Stem Cell Bank also

5. Review and Update Procedure

It is anticipated that in a rapidly moving field such as stem cell research, it will be appropriate and necessary to review and update this guidance (section 4) at least every two years.

6. Acknowledgements

All SEURAT-1 cluster PIs and stem cell researchers who gave up their time and knowledge to assist the authors in preparing the documents necessary for this recommendation.

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Professor Peter Andrews University of Sheffield and ES Tools.

7. Appendices

7.1. Standardisation References

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