ARTHIQS

Assisted Reproductive Technologies & Haematopoietic stem cells
Improvements for Quality & Safety throughout Europe

Inspection guidance

Cord Blood Banks

ARTHIQS – Deliverable 10
Work Package 5

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1. INTRODUCTION

This *Inspection Guidance – Cord Blood Banks (CBB)* has been developed as a result of an European Joint Action project entitled Assisted Reproductive Technologies and Haematopoietic stem cells Improvements for Quality and Safety throughout Europe -ARTHIQS (www.arthiqs.eu).

ARTHIQS is a European Joint Action funded by the European Commission under the 2008-2013 Health Programme. It has lasted four years, from May 1st 2014 till April 31st 2018. This project has focused on Assisted Reproductive Technologies and Haematopoietic Stem cells for transplantations. In the ARTHIQS consortium 16 partners and 9 collaborators from 18 different Member States have participated. ARTHIQS has been organised in five Work Packages (WP) each led by a Member State, as follows: WP1 Coordination (France), WP2 Dissemination (Czech Republic), WP3 Evaluation (Sweden), WP4 Assisted Reproductive Technologies (France), WP5 Haematopoietic Stem cells for Transplantation. WP5 was co-led by Ministry of Health (Croatia) and Centro Nazionale de Trapianti – Instituto Superiore di Sanita (Italy).

Specific objectives of WP5 were to

1. set up the model for Haematopoietic Stem Cells donors' follow-up registry (Italy),
2. define minimal standards for safety and quality for Cord Blood Banks according to the EU tissues and cells Directives and compatible with other standards (Croatia)
3. provide the basic guidance and training for cord blood banking inspectors (Croatia).

Aiming to reach objectives 2 and 3 WP5 has produced two guiding documents, *Guide of Recommendations for Cord Blood Banking* and this *Guide for Inspection of Cord Blood Banks* which are complementary.

1.1 Aim and scope

The purpose of this *Guidance* is to provide assistance and support to Competent Authorities responsible for inspections in preparing and conducting on-site inspections of Cord Blood Banks. It is targeting especially inspection bodies and inspectors that are not participating in international CBB inspection schemes such as NetCord, or do not have substantial experience in CBB inspection.

Furthermore, *Guidance* can aid CBB personnel in pre-inspection self –assessment.

It could be used regardless of the type of inspected Cord Blood Bank, respecting specificities of each. In addition, this *Guidance* can be useful for all types of on-site inspection: authorisation, regular, general or a specific inspection.

The scope of this Guide extends within the frame of EU Tissues and Cells Directives covering issues that are specific to Cord Blood Banking or more general but of utmost importance. This *Guidance* provides the minimum requirements for maintaining Quality and Safety and is not a substitute for established accreditation standards.

This *Guidance* summarises the steps in the processes for Cord Blood Banking presented as control points for the inspector during inspection but also during self-assessment. Control points subchapters comprise examples of evidence for the requirements that are, to a certain extent, specific for Cord

Blood (CB) in comparison to other tissues and cells. Other earlier projects like EQSTB and EUSTITE cover the general requirements.

This Guide is designed as a basic and non-exhaustive handbook that can be useful as a checklist for trainees during inspection. Inspectors will have to continuously develop it and adapt the inspections and protocol according to national legislation or obligations.

2. INSPECTON PREPARATION

In order to fully understand the task of inspecting a Cord Blood Bank (CBB) the inspectors should have basic knowledge in the area of hematopoietic progenitor cells (HPC) and their clinical use. As described in the *Guidance for Cord Blood Banks* (Deliverable 9) the organisation and purpose of the CBB can vary. There may be several procurement sites and the purpose of the CBB may be for allogeneic use or for family use.

Irrespectively, the minimal requirements for quality and safety should be fulfilled in order to authorise or licence the CBB.

2.1 Qualification of inspectors

In addition to general inspection knowledge and knowledge in quality management, inspectors should have a basic knowledge in the laboratory and clinical processes in the field of hematopoietic progenitor cells and CB in particular. It should also be pointed out that in order to obtain accreditation / authorisation for CBB from other accreditation bodies (NetCord, AABB) a certain activity in number of collections and stored CB have to be reached. Until that requirement is fulfilled the authorization / licencing and inspections by the CA may be the only external guarantee for quality and safety.

The following two sections describe a few of the specific and important steps to know about in order to maintain good quality of HPC in CB.

2.2 Procurement of CB

Procurement (collection) of CB is a process that takes place directly after delivery and should be performed, after consent, by midwives or other hospital personnel after relevant training. It is the responsibility of the CBB to ensure that personnel collecting CB have received the proper training. Special care should be taken not to draw blood with too much pressure from the blood vessel in the cord since this may increase contamination with maternal blood. On the other hand, the collection should contain as large a volume as possible in order to have sufficient number of nucleated cells and in particular, hematopoietic stem- and progenitor cells.

2.3 Quality parameters of CB

Cord blood contains a portion of immature cells, leucocytes as well as nucleated red blood cells as well as more differentiated leukocytes and red cells and several laboratory assays can be used to establish the quality of the CB unit collected.

Volume and number of nucleated cells are not sufficient laboratory measurements to establish the number and functionality of HPC.

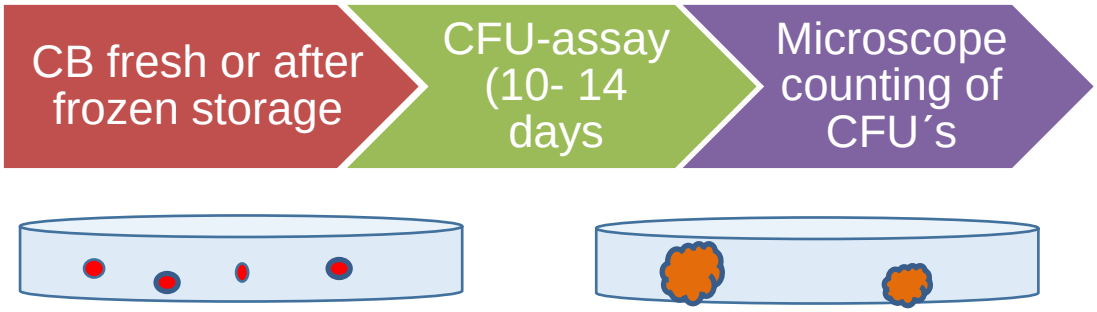
HPC may express different surface markers depending on their level of differentiation and destined lineage, but up until now, a common marker for all of them is the expression of CD34+.

Hence, this phenotype should constitute a minimal quality parameter for the number of immature hematopoietic cells. In addition, the functionality of the CD34+, that is ability to divide and

differentiate, is of importance for the ability to reconstitute haematopoiesis in a patient. For this, some functional colony assays should also be included in the panel of assays before a CB unit is released for human use. These assays may be performed on fresh CB or on a test sample after frozen storage.

For initial validation of the freezing-thawing process, in addition to the viability measurement, the colony- assays are highly recommended since they require functional HPC.

By seeding a fixed number of CB cells with relevant growth factors, the number of immature cells, able to proliferate and differentiate into granulocytes, macrophages or erythroid cells can be determined by their ability to form colonies in a semi-solid media. The number of Colony Forming Units (CFU) thus represents the ability of the CD34+ cells to function.



2.4 Before the inspection

As a part of the preparation before an on-site inspection, it is advisable to ask for certain documentation to be sent to the inspectorate. The actual inspection can thus focus on follow up questions when needed and the inspector will have time to read and understand, thus be more prepared. It also gives the inspector time to consult external experts if needed. Such external experts may be from another CA or from another body but independent from the CBB to be inspected. The Basic Inspection Form below indicates which documents can be asked for ahead of the on-site inspection. It is an attempt to cover the general quality management requirements (with reference to the EU Directives for Tissues and cells) and the more CB specific quality parameters. It should be pointed out, as described in the Guidance for CB Banking (deliverable 10) that other standards and recommendations are available (NetCord, AABB, EDQM guide to the quality and safety of Tissues and cells). The control points in this Basic Inspection Form are to be used as minimum requirements for any CBB.

3. BASIC INSPECTION FORM

Scope:	**1. Authorisation/Licensing requirements of CBB**				
Control point	Requirement from EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
1.1 Authorisation / Licensing	2004/23 Art 6.2, 6.3.	CBB should be accredited/ designated/ authorized or licensed by CA for all activities they perform (collection, testing, processing, preservation, storage, and distribution). All substantial changes from original authorisation notified to CA are also authorised. Strategy for take-over of the stored CB units and documentation and in case of bankruptcy (private CBB) or closure for other reasons.	Check authorisation document issued by CA and compare with activities performed	Authorisation document List of activities	
1.2 Accreditation		In the cases of legal requirement for accreditation according to national or international standards (*e.g.* Net-Cord, AABB…).	Check accreditation Advisable to ask even if is not legal requirement	Accreditation document	

Scope	**2. Quality System**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
2.1 **Organisation**	2006/86 Art 3 Annex I 2., 4.,5.	CBB have quality system in place, organisational structure, quality management appropriate for the activities, insuring minimal risk for product and personnel and maximal quality of the product.	Quality manual, policies, procedures (SOPs), work instructions and forms regarding organisational issues Organisational chart with clearly stated (written) hierarchy of duties and responsibilities	Quality manual List of relevant (organisational) SOPs Organisational chart	
2.2 **Personnel including responsible person**	2004/23 Art 17. Art 18. 2006/86 Art 3. Annex I A.1., A.3. B.	- designation, education and responsibilities of responsible person - competent personnel	Responsible person (RP): - Responsible person designation (written, signed) - RP diploma in the field of biomedical science on university level - Certificates on education and trainings, evidence of experience in the field of CBB (min 2 years) - Specification of responsibilities (written and signed) - Specification of RP's responsibilities delegated to other employees Personnel education and training records Job descriptions Education plans Staff appraisal including competency assessment	RP diploma Evidence of experience for RP RP job description	

Scope	2 Quality System (cont)				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
2.3. Documentation	2004/23 Art 10.1. Art 14. Art.15.3. Art.16.3, 16.4. 2006/17 Art.2.12. Annex IV 1.4. 2006/86 Art 3. Annex I E.	- reporting obligations - data protection and confidentiality - documentation on donor evaluation and testing - general donor documentation - documentation of QS - documentation available to inspection	Report templates Data protection policies Donor evaluation forms (signed) Test results and interpretation (signed) Documents presented to inspection in reasonable time Documentation should contain: consent, health declaration, Quality Manual with written processes (SOPs) for procurement, assays performed on the donor, assays performed on the CB, processing and storage. Also drafts of agreements with third parties, plan for education of midwifes/personnel responsible for the procurement. Transportation guidelines and agreement (consent) of parents should also be included Check Quality Report	Master list of processes (SOPs)	
2.4 Quality assurance	2006/86 Art 3. Annex I A.7., C., F.	- verification of fulfilment of specification for product's quality and safety - verification of equipment and material's appropriate performance - audit system	Validation master plan (DQ, IQ, OQ, PQ) Audit reports Nonconformity records and analysis CAPA Written procedures for quality assessment of the CB Plan for units that do not fulfil the specification requirements (*e.g.* if stored anyway)	Specification of the product The latest audit report (external and internal)	

Scope	**2 Quality System (cont)**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
2.5 **Infection disease testing**	2006/17 Art 4. Annex II 2012/39 (1)	- requirements for testing donors for infection diseases	Test shall be performed from mother's blood Type of testing: serology or NAT (repeated serology if not NAT) Check whether the testing is carried out by a laboratory authorised for screening testing Check stored samples for future screening Check the records of test results Dedicated appropriately educated person for test results interpretation SOPs in case of transmissible disease for autologous/family use units	List of markers tested List of manufacturers and tests used	
2.6 **Quality control**		Quality / release criteria; minimum cells	Release criteria can vary among the banks Documentation of QC should contain data on at least: Visual inspection of unit Volume Assays on the CB: TNC, viable nucleated cells, viable CD34+ cells Identity testing Sterility tests	List of parameters monitored under QC	

Scope	**2 Quality System (cont)**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
2.4. Third party agreements	2004/23 Art 24. 2006/86 Art 3.6. Annex I.6.	Circumstances in which third party agreement is mandatory	Text of the agreement contains: Responsibilities Requirement for designation of persons responsible for agreement's activities Provisions for regular review, revision and renewal of the agreement	List of agreements with specification of activities preformed under each agreement	
2.5. Agreement with the collection facility (CF)	2004/23 Art 24. 2006/86 Art 3.6. Annex I.6.	CBB should have written agreement with collection facility/collection site in every country of procurement	List of collection facility personnel trained for collection, training records Means of training Person responsible for training Contacts Responsibilities of collection facility and TE (including critical materials, equipment, premises) Policy for informing relevant authority in MS of collection facility	List of collection sites Results of the latest audits of collection sites Results of quality parameters monitoring for collection sites	

Scope	**3 Procurement / Collection**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
3.1. General	2004/23 Art 13.	Consent	Written consent of one or both parents, depending on MS legislation Dated and signed Written agreement with mother/parents for family use units (contains also fate of the CB in case donor/parents decide not to continue storage)	Template of consent	
	2004/23 Art 13.2. Annex A.	Information to the donor (in this case to the mother or both parents depending on national legislation/requirements)	Written procedures for donor informing – (list) adverse reactions during donation Donor info brochure Check if info given by trained person Clear information to the parents on the possible use of autologous vs allogeneic HPC transplantation (check EDQM A guide for parents umbilical cord blood banking - https://www.edqm.eu/sites/default/files/umbilical_cord_blood_banking_2nd_edition_2016_0.pdf for a reference)	Donor info brochure	

Scope	**3 Procurement / Collection (cont)**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
3.1. General (cont)	2004/23 Art 15.1.-15.3. 2006/17 Art 2.1.-2.11. Art 3. (a) Annex I.2. Art 5. Annex IV 1.1.-1.4	Collection procedure - requirements for the collection - selection criteria for donors - donor identification - donor evaluation - donor documentation	Collection sets stored in appropriate conditions close to delivery box. Written SOP for collection and working instruction at working place. Check, if possible performance of collection and compare with working instructions. Written procedures for donor (mother) identification / check performance of identification if possible - identification should be by asking patient at least name, surname and year of birth. Check working instructions and practice for cord disinfection. Check critical materials (CE marked medical devices). Check facilities/premises (to minimise the risk of CB contamination)	SOP for collection procedure (check if collection procedure intervenes with regular birth procedure)	
3.2. Transport conditions		Transport from collection site	SOPs for transport Validation of transport (should prove holding required temperature (18-22°C) in worst case scenario: longest transport, temperature extremes) Check log book of shipping temperature Check transport containers cleaning records Check integrity of product container	Final transport validation report	

Scope	**3 Procurement / Collection (cont)**				
Control point	Reference in EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
3.3. Unit reception at the bank	2004/23 Art 19. 2006/17 Art 5. Annex IV 2.1.-2.4. 2006/86 Art 4. Annex II A.	- data, info, documents to be checked at the reception	Visual inspection of the collection set (integrity) Report on collection Presence of samples Labelling	List of parameters checked at reception	

Scope	**4. Processing**				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
4.1 Processing	2004/23 Art 20 2006/86 Art 3. Annex I D. Art 4. Annex II B.	For each processing activity written procedures are in place Minimised risk of cross contamination	SOPs for: processing cryopreservation release procedure process validation records, at least freezing process -Air class A/D environment for open process - validation report according to ISO 14644-1 to 10 -Check if overwrap is used -Check if closed system is used -Environment monitoring records -Check microbiology testing results	The latest air quality report Report of occurred non-conformities in microbiological tests results since last inspection	
4.2 Equipment	2006/86 Art 3. Annex I C.	Equipment suitable for intended use and qualified Critical equipment identified	Calibration records Containers qualification for capacity to maintain temperature below -150°C uniformly in whole volume. List of critical equipment must contain: freezing device, cell separator, laminar flow cabinet (if open system used)	List of critical equipment	
4.3 Maintenance		Regularly maintained and cleaned Used by trained personnel	Record of cleaning and maintenance. Use of non-cytotoxic disinfectants (check product info). Requalification after repairs or translocation.	Qualification Master Plan	

Scope	**5. Labelling and coding**				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
5. Labelling	2004/23 Art 8.3 Art 22. 2006/17 Art 5. Annex IV 1.5., 1.6. , 1.7. 2006/86 Art 4. Annex II E., F. 2015/565	Packaging and labelling after collection Information on the label Single European coding system (SEC)	Check if package label contains donation identification, “cord blood”, date of collection, hazard warning: “human blood”, additives (CPD or lyophilised heparin), if for family use “for autologous use”. Check if shipping container label contains inscriptions: “human cord blood, “biological material”; “handle with care”; information for contact (name, address and phone number) at maternity hospital; and information for contact person of CBB; date and time of start of transportation; When shipped from collection site to CBB: temp 18-22°C, protect from heat source, do not irradiate; When shipped for distribution: frozen human cells for transplantation, do not open, handle with care, do not irradiate, sign for package orientation. Check if the CB is labelled with SEC. Check if label and ink are validated for storage temperature and nitrogen phase used (manufacturer validation can be accepted; inspector should assess reliability of manufacturer	Label templates Final validation report of labelling (freezing resistant)	

Scope	**6. Storage**				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
6. Storage conditions	2004/23 Art 21. 1.-4. 2006/86 Art 4. Annex I D.9. Annex II C.	Controlled storage conditions Max storage time Assurance of unit identification	Environment (storage room) monitoring records: temperature and humidity according the equipment manufacturer's specifications, pest control, cleaning. Controlled entrance in storage room (electronic card or key). Alarm for low oxygen level. Validation of process of CB units' insertion in the container (should not raise temperature). Monitoring records of liquid nitrogen tanks levels and temperature (log book). Alarm system for temperature and nitrogen levels changes (with specified liquid warning and action of the responsible person in charge of the action)	Short description of monitoring system- if automated; manufacturer and model	

Scope	7. Traceability /coding				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
7.1 Traceability	2004/23 Art 8.4.-8.6. Art 16.5. Art 21.5. 2006/86 Art 3 Annex I 8., 9. Art 9. Annex VI A., B., Art 10. Annex VII	Assurance of CB traceability from donor to recipient and vice versa Assurance of materials traceability Length of data keeping Agreement in the case of activity termination	Register for traceability Min 30 years of keeping records regarding traceability. Check if data on materials and reagents (*e.g*. name of product and producer, lot, expiry date, results of incoming quality controls) can be linked with the product. Policy and procedures for documentation maintenance in the cases of activity termination	Summary of the contingency plan	
7.2 Coding	2006/86 Art 10. Annex VII 2015/565	Single European Coding system (SEC)	Donation identification sequence and traceability to donor ID. Product Identification sequence. Label on the CB bag or attached documentation.		

Scope	8. Notification of SAR and SAE				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
8.1 Reporting	2004/23 Art 10, 11.2.- 11.5. 2006/86 Art 4 Annex II 4.- 6. Annex III Annex IV	Obligation of reporting relevant information Notification SAR and SAE to CA Annual reports to the CA	Check if an internal SAE reporting system exists Written procedures for SARE reporting Reporting forms/templates including minimum data available Designated person for rapid notification and investigation of SARE – contact data of that person must be available to the personnel Training of personnel in SARE and education records Contact data of CA's SARE dedicated person Written procedures for informing parents/donor in case of SAE regarding units for autologous/family use	Designation of person for rapid notification and investigation of SARE Summary of procedures for informing parents/donor in case of SAE regarding units for autologous/family use	
8.2 Recall	2004/23 Art 11.5.	Product recall	Written procedures for product recall - including communication with CA Designated person for product recall	Designation of person for product recall	

Scope	**9. Import and Export**				
Control point	Criterion by EU Directive	Requirement description	Example evidence	Minimum of documents recommended to ask prior to inspection	Remarks
9.1 Authorisation 9.2 Traceability 9.3 Quality	2004/23 Art 9. 2015/566	Import/export activities authorised/licenced Traceability of imported/exported CB ensured Quality and safety requirements of imported	Check the authorisation/licence of CBB for import/export Written agreement with third country CBB or CB collection site Check the documents of third country's CBB/ collection site: CA licence, accreditations (*e.g.* NetCord) Check the info of third country's CBB activities: infectious diseases testing, closed/open system, type of storage, quality control parameters and benchmarks	List of third country CBB or CB collection site Authorisation/accreditation certificates of third country CBB or CB collection site	