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PIC/S GUIDANCE DOCUMENT FOR INSPECTORS

PIC/S GUIDE TO INSPECTIONS OF SOURCE PLASMA ESTABLISHMENTS AND PLASMA WAREHOUSES (INSPECTION GUIDE)

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1. DOCUMENT HISTORY

Adoption by the PIC/S Committee	3 June 2003
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2. INTRODUCTION

2.1 The quality and safety of products derived from human plasma rely both on the source plasma material and the further manufacturing processes. Therefore the source plasma materials, that means the collecting, testing, storage and transportation of human plasma to the fractionation company are major factors in the quality assurance of the manufacture of biological medicinal products.

2.2 Source plasma material for further manufacturing is mainly collected in institutions which are managed solely for this purpose (source plasma establishments). Plasma testing is often performed in separate locations (laboratories). The storage of plasma, at least for an intermediate time period, is performed in the collection centre itself or in bigger (central) plasma warehouses, solely for the purpose of plasma storage or for the storage of various products which must be stored frozen.

Collecting of human plasma for further manufacturing as well as storing, testing and transportation must follow GMP criteria in order to ensure the expected product quality.

2.3 Basic GMP criteria for companies or institutions manufacturing and / or storing blood products are laid down in different documents, especially the "PIC/S Guide to Good Manufacturing Practice for Medicinal Products" (PH 1/97, rev. 3) and its Annex "Manufacture of Products derived from Human Blood and Human Plasma" as well as in the European Pharmacopoeia monograph "Plasma for fractionation". However, it was found that a summary of those criteria with specific regard to source plasma establishments or plasma warehouses would be helpful for inspectors as well as for companies. Insofar these GMP criteria are summarised in this document and should be used by the inspector as a source for his / her inspection.

3. PURPOSE

3.1 The purpose of this document is to provide guidance for GMP inspectors in preparation for inspections and conduct of inspections of source plasma establishments and / or plasma warehouses as well as for training purposes. For inspections of blood establishments, collecting and processing full blood donations by segregation into red blood cells, plasma and other components, reference is made to the PIC/S GMP Guide for Blood Establishments (PE 005).

3.2 This document is also made available for companies or institutions collecting and / or storing plasma for fractionation so that they may gather information about specific GMP requirements for these establishments.

4. SCOPE

- 4.1 This Guide to Inspections of Source Plasma Establishments and Plasma Warehouses (“Inspection Guide”) lays down principles for GMP inspections of source plasma establishments and of source plasma warehouses. Most of the plasma imported to the EU or PIC/S Member States, actually comes from the United States of America. Therefore, the Inspection Guide also takes into consideration the particular situation in U.S. facilities.
- 4.2 The Inspection Guide provides also basic information on GMP requirements, specific for source plasma establishments and for plasma warehouses. As in general the same GMP criteria are applicable for the storage of plasma in smaller facilities (e.g. a source plasma establishment with a freezer) and in bigger facilities (e.g. a central plasma warehouse with freezing rooms), the plasma storage requirements as defined in the Inspection Guide apply to both kind of facilities if not otherwise indicated. The document does not include plasma testing.
- 4.3 The Inspection Guide is supplemented by two additional PIC/S documents [Site Master File for Source Plasma Establishments (SMF-SPE in PI 019)) and Site Master File for Plasma Warehouses” (SMF-PW in PI 020)] defining a number of details for the routine running of source plasma establishments and of source plasma warehouses.
- 4.4 Both of the Site Master Files follow the PIC/S format (Site Master File, SMF, PE 008) in general. However, as the PIC/S SMF is valid for pharmaceutical companies, independent from the kind of the medicinal product and the scope of manufacturing, the PIC/S SMF format has been adapted to the special requirements of source plasma establishments and source plasma warehouses.
- 4.5 The SMF-SPE and the SMF-PW will be regularly adapted to current facts, if necessary.
- 4.6 At the time of issue, this document reflected the current state of the art. It is not intended to be a barrier to technical innovations or the pursuit of excellence. The advice in this document is not mandatory for industry. However, industry should consider this recommendation as appropriate.

5. PREPARATION OF INSPECTION

- 5.1 Each source plasma establishment or plasma warehouse should have available a detailed description of its activities, using the appropriate SMF form.
- 5.2 Inspectors should check the Site Master File (SMF-SPE or SMF-PW), completed by the company, in advance to the inspection. In case of a re-inspection the information given in the new SMF should be compared with the present knowledge of the facility

6. OPENING MEETING

Principle: *The inspector should normally meet the management and the key personnel of the facility (including the responsible QA person of the source plasma establishment / the central plasma warehouse). The opening meeting should be used for introduction and to become familiar with the establishment.*

- 6.1 The inspector should briefly explain the scope and the legal reason for the inspection and point out that the inspection is performed by order of a competent Health Authority.
- 6.2 The inspector should explain that the inspection is focusing on main and critical aspects, covering especially those areas, which might have relevance on the product (plasma) safety and / or quality. He / she should present an agenda to give an idea for the inspection course.
- 6.3 The inspector should point out that the documentation as well as observation of actual activities (e.g. for source plasma establishments: donor screening, donor interview, donor examination, plasma and plasma sample collection as well as plasma storage and for plasma warehouses: plasma storage and shipment) will be covered by the inspection. Besides this the suitability of rooms and equipment will be checked.
- 6.4 The inspector should ask the company to give a short overview on the overall organisation of the company and of the facility to be inspected in particular. In this regard the organisation charts of the facility and of the whole organisation should be discussed.
- 6.5 For re-inspections it is important that the company explains significant changes in facility, equipment, products and personnel since the last inspection as well as any (future) planned changes.
- 6.6 The inspector should check the SMF and its attachments (copies of documents as requested in the SMF) for completeness and plausibility and discuss relevant or questionable entries with the company.
- 6.7 In particular, the following items of the SMF and its attachments should be checked:
- **Manufacturing license(s) for the source plasma establishment by the national authority:** It should be checked whether the manufacturing activities of the source plasma establishment are covered by the manufacturing license(s) or its amendments.
 - **Annual Registration forms (U.S.A. only):** It should be checked, if the Annual Registration is actual.
 - **Specific products or special programs in source plasma establishments:**
These are in particular source plasma from immunised donors and the appropriate immunisation programs. There should be specific approvals by the competent national authority which include the facility. If source plasma is also collected from disease state donors this may require specific investigation with regard to the safety of the source plasma for manufacturing injectable products.

- **Last inspection result (report) by the national authority and / or an European / PIC/S Authority:**

The reports of the last inspection by the national competent authority should be available for the inspection. In the U.S.A. findings / objections by the FDA will be defined in a "Form 483" or a "Warning letter".

If the facility was already inspected by a European / PIC/S Authority, the inspection report should also be available.

If any objections were found during the previous inspections, the follow-up and the appropriate corrective actions should be checked.

- **Quality Assurance** in general, including the availability of at least one QA person in each facility, self inspections and proficiency testing.
- **Medical coverage** in the source plasma establishment

6.8 The inspector should compare the Look back information (as defined by the company in the SMF for the source plasma establishment) with other documents on site (e.g. donor record file, original test results, letter to the customer, destruction log book). Therefore the inspector should ask the management during the opening meeting and secure that at least the following documents are prepared and easily available during the inspection:

- **Donor record files** in question
- **Test results (originals)** for repeat tests and corresponding confirmatory tests
- **Information (letter)** to the customer (also listing the plasma units involved)
- **Documentation of destruction** of reactive, subsequent or otherwise involved plasma units (in special cases shipment under additional precautions).

7. PLANT TOUR

Principle: *The inspection should be continued with a plant tour. Special attention should be given to relevant deficiencies of the previous inspections (if applicable) and their rectification.*

7.1 In general a short plant tour should be used for familiarisation with the site and any major changes (some areas might already be checked completely during this short tour).

7.2 This is followed by a more detailed plant tour to determine whether the facility and equipment are of suitable layout, design and size and to ascertain the current GMP status. Normally the inspector should follow the flow of donors and the flow of donations in a source plasma establishment or the product flow in the plasma warehouse.

7.3 During the tour the inspector should normally discuss observations as they arise with the key personnel especially in order to establish facts and indicate areas of concern. Despite of that, observations should never be discussed in the presence of plasma donors in the source plasma establishment.

8. INSPECTION OF CRITICAL / MAIN AREAS IN SOURCE PLASMA ESTABLISHMENTS AND PLASMA WAREHOUSES

Principle: The inspection should cover thorough observation of acting staff and comparison with defined written procedures as well as a check of rooms and equipment. For plasma warehouses in principle the same requirements are valid as for source plasma establishments, as far as applicable.

- 8.1 The inspector should observe the donor identification procedure (donor acceptance) when the donor signs in and his / her donor file is prepared.
- 8.2 The different procedures for applicant and for return donors in the U.S.A. should be checked.
- 8.3 In the U.S.A. (as well as in other states, if applicable) the inspector should ask for the listing of non acceptable addresses for donors (e.g. homeless shelters, brothels and "high risk areas") and check if it is dated and signed according to the company's own procedure.
- 8.4 The inspector should thoroughly check the donor identification prior to the donor screening procedure. Special attention should be taken if the screening process is divided into different steps and the single steps are performed by different employees on the same donor. In this case the donor has to be identified by each employee prior to each single step.
- 8.5 The inspector should observe the reading of test results (e.g. hematocrit, total protein) and check the related documentation (including log books).
- 8.6 The inspector should observe the verbal donor interview (under discretion as far as possible), especially with regard to the confidentiality of the booths and the manner of questioning / accepting donor answers. In case of a written donor interview the inspector should check the place where donors fill out the questionnaire with regard to sufficient confidentiality. The inspector should randomly check the entries into the donor file as well as its contents and the readability of any written information (e.g. Aids Bulletin, High risk behaviour poster) for the donors.
- 8.7 The physical examination should be explained to the inspector and be demonstrated by the appropriate staff, at least if it is not performed by a physician (e.g. by a physician substitute as it is usually the case in the U.S.A). However, any observance of a physical examination should be performed under sufficient discretion.
- 8.8 The inspector should observe the identification of the donor immediately prior to venipuncture as well as labelling of the unit and of any samples.
- 8.9 In case of manual plasmapheresis specific attention should be paid on the procedure to avoid mix-ups during re-infusion and during the pooling process of two donations coming from the same donor.

- 8.10 The inspector should check the softgood batches which are currently in use in the donor floor for any risk of mix up. If there is an interim storage of softgoods in the donor floor the inspector should check the suitability of this kind of storage.
- 8.11 As a pre-set of plasmapheresis machines might bear a risk of contamination, the inspector must investigate if such a pre-set could be definitively avoided.
- 8.12 Specific attention should be paid to general aspects of hygiene (e.g. possible risk of contamination with blood / plasma by biohazard containers intermediately stored in the donor floor).
- 8.13 The inspector should check the suitability of the processing area (especially the segregation to the donor floor).
- 8.14 Main focus in the processing area should be given to possible mix-ups of units and of samples as well as to any contamination (e.g. when cutting the tube segments) and that the samples are drawn from appropriately mixed plasma units.
- 8.15 Furthermore the inspector should randomly check the documentation in the processing area for correctness and completeness (e.g. entries, initials).
- 8.16 The inspector should check the actual temperature chart(s) of the plasma freezer(s) / freezing room(s).
- 8.17 The temperature of the back up thermometer inside the freezer(s) / freezing room(s) should be compared with the “manual temperature reading” as documented by the employees.
- 8.18 The inspector should additionally check the freezer / freezing room temperature charts and the manual recording for at least the last 12 months in order to get an impression about the functionality of the centre / warehouse in this respect.
- 8.19 Furthermore the inspector should check the performance and documentation of regular alarm checks and of unplanned alarms for the same time period (last 12 months). Special attention should be given to any unusual high number of freezer alarms.
- 8.20 The inspector should reensure that the freezer(s) / freezing room(s) are validated and suitable to freeze and / or store the plasma at suitable temperatures as defined by the European Pharmacopoeia. If different equipment is in use for freezing and for storage of plasma 8.16 and 8.20 is applicable to both (freezing and storage equipment).
- 8.21 Additionally the storage conditions should be checked for sufficient separation between released (tested) and unreleased plasma (untested, in quarantine, plasma from non qualified applicant donors) as well as for reactive units, ALT elevated units and Speciality Plasma or other products, if available. The single areas for the different plasma qualities should be adequately labelled.
- 8.22 The inspector should check if the storage conditions for softgoods / disposables in the storage area are appropriate and the rooms and equipment are suitable for

their use. This includes the minimum / maximum room temperature (defined and actual) and its documentation.

- 8.23 Special attention should be directed to sufficient and clear separation of released (ready for use) and unreleased softgoods (including appropriate labelling) as well as to the separation of different softgood batches.
- 8.24 The inspector should check if the biohazard waste from the daily production is stored in a place with limited and designated access and suitable air conditions.
- 8.25 The inspector should check the time period between collection of plasma units and the availability of non-reactive (negative) test results, (repeat) reactive test results and confirmatory test results. The time period should be defined and kept as short as possible (e. g. the repeat reactive test result should be available 7 days after drawing as maximum, the confirmatory test result 21 days after drawing).
In case of reactive test results the inspector should randomly check any further activities with the involved unit(s) and their documentation (e.g. destruction, special shipment).
- 8.26 The inspector should check if the donor deferral systems (national and / or company related) are followed by the centre personnel according to the company's written procedures.
- 8.27 The inspector should check the release performance for plasma units / intermediates from plasma especially with regard to personnel responsibilities and the safety of the system.
- 8.28 Particular notice should be given whether the company's procedure is safe enough to avoid inadvertent shipment of unreleased units.
- 8.29 The inspector should normally review 6-8 Look back cases within the last one to two years (if available). Specific attention should be given to the completeness of information, the date of information (straight after receipt of the laboratory test results, latest within two working days) the time period between the drawing date and the receipt of screening test results as well as the time period between the drawing date and the receipt of confirmatory test results, the confirmation of the customer upon receipt of Look back information, the documentation of destruction of the reactive unit and (if applicable) additional available donations.
- 8.30 The inspector should normally review 6-8 donor record files (preferably from the Look back cases mentioned above) with regard to Good Manufacturing Practice. Special attention should be given to unexplained and an unusual high number of missing or incorrect entries or other particularities (e.g. missing donor interview / answers, machine problems, donor health problems or general GMP failures as e.g. not signed or initialled corrections of entries). The donor files should be checked in connection with related documents (e.g. machine log books, softgoods log) for cross-references.
- 8.31 The inspector should check logbooks for correct entries (especially related to calibration, maintenance) and for general GMP aspects.

- 8.32 The inspector should randomly check the training documentation at least of persons in responsible positions (e.g. QA person, Supervisor) and if times allows, in addition randomly for staff members. Special attention should be given to the training of the Physician substitute (in which the physician should be adequately involved).
- 8.33 In addition, further aspects should be included into the inspection, e.g. hygiene program, documentation in general (archive, distribution, update).

9. FINAL MEETING

Principle: The inspector should normally discuss the outcome of the inspection with the management and the key personnel of the company (including the QA person of the source plasma establishment / the central plasma warehouse).

- 9.1 After the inspection has been completed the inspector should summarise the findings in a final meeting with representatives of the company, usually the key personnel from the source plasma establishment (including the QA specialist) or the central plasma warehouse and preferably personnel from the Corporate Office and / or the Regional Manager.
- 9.2 At least relevant deficiencies observed during the inspection should be explained. It should be pointed out if an observation seems to be critical. The inspector should mention that the final classification of deficiencies and the decision about the license or the "GMP certificate" (certificate confirming the actual GMP status) will be made in the office of the competent Health Authority.
- 9.3 The company should be encouraged to initiate any necessary corrective actions at the earliest date.
- 9.4 Finally further steps (concerning the inspection report, manufacturing license and / or the "GMP certificate") should be shortly explained.

10. INSPECTION REPORT

Principle: The inspection report should cover all relevant information of an inspection including any deficiencies, if applicable.

- 10.1 The inspection report should describe the reason for the inspection (e.g. routine / regular inspection, follow-up inspection, re-inspection), the participants, any major changes and cover the observations from the inspection.
- 10.2 Deficiencies will normally be specified and divided into categories (critical complaints / additional significant or major complaints / other complaints and recommendations, if applicable).
- 10.3 A list of Look back cases which were checked by the inspector during the inspection should be added to the report.

- 10.4 Furthermore the report should include the SMF (*completed by the company and provided with comments by the inspector, if applicable*) and copies of documents as far as requested or which are otherwise relevant for the inspection and its deficiencies reported.
- 10.5 The report should be available in the office of the competent Health Authority which has initiated the inspection as soon as possible [latest within 30 days after the inspection].
- 10.6 The written report will be sent to the inspected establishment and / or its Corporate Office.
If no legal aspects or mutual agreement speaks against it, the report may in addition also be sent to the (prospective) importer in the importing country.

11. FOLLOW-UP

Principle: *When deficiencies were found during the inspection, the companies are required to remedy them as soon as possible.*

- 11.1 The inspected companies are requested to notify the competent Health Authority (which has initiated the inspection) normally within 30 days of receipt of the inspection report about the specific steps which were taken to correct the failures and to prevent their recurrence.
- 11.2 If corrective actions cannot be completed within the regular time of 30 days, the company should state the reason for the delay and the time within which the corrections will be completed. After completion of corrective actions the company should immediately notify the competent Health Authority of the importing country.
- 11.3 The report and the company's response (follow up) should be available in the (inspected) source plasma establishment / plasma warehouse to be used during the following (next) inspection and handed out to the inspector on site at the beginning of this inspection.

12. INFORMATION BETWEEN TWO INSPECTIONS

Principle: *As each inspection can only give information about the actual situation it is of great importance that the responsible Health Authority which has issued a license or a GMP certificate (valid for a given time period) will be informed about relevant later changes.*

- 12.1 Companies (e.g. importers, inspected source plasma establishments or plasma warehouses) should announce important changes concerning source plasma establishments or plasma warehouses routinely at least 6 months in advance to its occurrence (only in cases which could not be foreseen immediately afterwards).
- 12.2 The inspector should draw the company's attention to the fact of these notification requirements. Especially the following changes require such a notification, because they might influence the existing license or GMP certificate:

- **New owner / sale of establishment** (as far as relevant changes, e.g. new SOP Manual, new name of the facility are concerned)
- **Personnel changes** (personnel in responsible positions, e.g. manager, head of production, QA person) or loss of responsible persons (including the QA person)
- **Relocation**, major remodelling
- **Use of another test laboratory** (for screening / repeat tests, for confirmatory tests)
- **Changes of important equipment** (e.g. additional / loss of freezer, installation of a new type of plasmapheresis machine, installation of plasmapheresis machines from another manufacturer, new software or updated software for plasmapheresis machines)
- **Major changes of the company's SOP Manual**
- **Changes of programs** (e.g. collecting reactive units)
- **Implementation / change of a computer system**
- **Changes of national licenses issued by other authorities** (e.g. withdrawal, suspension, restriction).

13. BASIC GMP CRITERIA FOR SOURCE PLASMA ESTABLISHMENTS AND PLASMA WAREHOUSES

Basic GMP criteria can be found in different documents, some of them define these criteria in general, some are more specific to plasma. Under this chapter GMP criteria which are found to be of importance for a source plasma establishment or a plasma warehouse are listed and references are made to the original documents. As far as references are made to the PIC/S Guide to Good Manufacturing Practice, these general GMP criteria are adapted to the specific conditions in a source plasma establishment or a plasma warehouse. The abbreviations which are used and the documents which are referred to, are:

- **GMP:** PIC/S Guide to Good Manufacturing Practice (PH 1/97, rev. 3, January 2002)
- **GMP-b:** Annex 14 to the PIC/S Guide to Good Manufacturing Practice: Manufacture of Products derived from Human blood or plasma
- **GMP-s:** Annex 1 to the PIC/S Guide to Good Manufacturing Practice: Manufacture of sterile medicinal products
- **GMP-c:** Annex 11 to the PIC/S Guide to Good Manufacturing Practice: Computerised Systems
- **CPMP:** Note for Guidance on Plasma-derived Medicinal Products (Committee for Proprietary Medicinal Products, CPMP, January 25, 2001)
- **PhEur:** European Pharmacopoeia, Monograph Plasma for fractionation in the current version.
- **Council:** Council of Europe: "Guide to the preparation, use and quality assurance of blood components", 4th edition

13.1 QUALITY ASSURANCE (QA)

Principle: *Quality Assurance is a long-range concept which covers all aspects influencing the quality of the product.*

- 13.1.1 Source plasma establishments should be inspected and approved by the competent national authority (*CPMP 2.3.3.*), the same is valid for plasma warehouses. In general, a manufacturing license should be available for the source plasma establishment and any other kind of license for the source plasma warehouse.
- 13.1.2 The manufacturer shall establish and implement an effective pharmaceutical Quality Assurance System (QAS). The QAS should be fully documented and its effectiveness monitored (*GMP 1, principle*).
- 13.1.3 All parts of the QAS should be adequately resourced with competent personnel (*GMP 1, principle*). A source plasma establishment as well as a plasma warehouse is regarded to be adequately resourced with competent QA personnel, if at least one QA person and a “back-up” QA person is available per establishment as a rule.
- 13.1.4 Sufficient competency should be acquired by corresponding training in all relevant areas and certified according to the company’s own procedure. The certification criteria (including the responsibilities) as well as the contents for the QA training and the requirements for the QA trainer should be defined in writing (*GMP 4, principle*).
- 13.1.5 The QA person / QA specialist should not routinely be involved in manufacturing activities and must be independent from production. Therefore e.g. the Manager, the Assistant Manager, the head of production, the head of a plasma warehouse or their substitutes will not be acceptable as QA person of the same establishment. The independence of the QA specialist should be demonstrated and defined, e.g. by the reporting line in the organisation chart and the job description.
- 13.1.6 The QA person should have sufficient time during the working day to perform the required QA activities. Therefore the QA person should normally have no additional responsibilities.
- 13.1.7 The necessity and frequency of regular QA checks should be defined in writing and its performance documented (*GMP 1, principle*).
- 13.1.8 Self-inspections (audits) are relevant aspects of QA. Repeated self-inspections should be conducted as part of the QA System in order to monitor the implementation of Good Manufacturing Practice and its maintenance and to propose necessary corrective measures (*GMP 9, principle*).
- 13.1.9 Self-inspections should be performed according to a pre-arranged program (defining frequency and areas which should be covered) and by auditors especially trained for this purpose (*GMP 9.1, 9.2*).
- 13.1.10 Records of such self-inspections and any subsequent corrective action should be maintained (*GMP 9.3.*). Documentation for official purposes (e.g. external inspections) should be available. This requires at least the date of performance,

the area inspected, the personnel involved and the letter of closure (date and acceptance of corrective measures).

- 13.1.11 Proficiency testing is an aspect of Quality Assurance which monitors the ability to perform laboratory procedures within acceptable limits of accuracy through the analysis of unknown specimens distributed by an external source. Therefore the facility should take part in proficiency testing on a regular basis and with sufficient success, as far as testing is performed there (e.g. total protein testing in the source plasma establishment). Any result less than the expected percentage should be subject to an investigation.

13.2 PREMISES AND HYGIENE

Principle: All rooms and work areas where manufacturing operations are performed (e.g. donor screening area, donor floor, processing area) must meet current GMP requirements. The same is valid for storage areas, e.g. for plasma and for softgoods.

Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the product, the starting material (incl. softgoods) or the accurate functioning of equipment (GMP 3.3).

The premises should include separate areas for donor selection (screening, interview, physician's room), plasma collection, processing, storage (materials, plasma, biohazard, documents) and auxiliary facilities (GMP-b 6). Special requirements for single areas are defined under 13.4. ff. of this Inspection Guide (e.g. donor interview rooms, processing area).

- 13.2.1 An actual floor plan (signed and dated) should be available with specification of the single rooms / areas and their function. These are for source plasma establishments at least the donor waiting area, donor interview, screening, processing, storage of active donor files, storage of inactive donor files and from rejected donors, biohazard room, storage area for softgoods and plasma as well as the flow of donors and the flow of donations. The floor plan for plasma warehouses should show at least the plasma receiving and loading area, storage area for plasma, differentiated according to the plasma status, storage area for look back units and other rejected material and the storage area for other material.
- 13.2.2 The facility must be designed and of sufficient size in order to minimise the risk of errors and to avoid crossing lines (GMP 3, principle).
- 13.2.3 Premises should be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations (GMP 3.7.).
- 13.2.4 The premises should include separate areas for donor selection (screening, interview, physician's room), plasma collection, processing, storage (materials, plasma, biohazard, documents) and auxiliary facilities (GMP-b 6).
- 13.2.5 Production areas (as well as storage areas) should not be used as a right of way by personnel who do not work in these areas (GMP 3.5.). Therefore such areas

(e.g. storage area for sterile softgoods) should not be used as pass through areas.

- 13.2.6 Steps should be taken in order to prevent entry of unauthorised people (*GMP 3.5*). Therefore back doors should be arranged in such a way that they may not be opened from outside without a key and unauthorised persons (including plasma donors) should be forbidden and prevented to enter production areas.
- 13.2.7 Premises to which donors have access should be separate from other working areas. In production areas where donors are available (e.g. donor floor), suitable measures should be taken in order to avoid the possibility that donors may have access to production material (e.g. softgoods) or manufacturing documents (e.g. donor record files).
- 13.2.8 The layout of premises and equipment must permit effective cleaning and maintenance in order to avoid cross contamination and build up of dust and dirt (*GMP 3, principle*). Therefore the walls, floors and ceilings should be smooth, free from cracks and open joints and should permit easy and effective cleaning and if necessary disinfection (*GMP 3.9*). *It is reminded that the current plasma collection is not performed in a "closed system", as the disposables for the plasmapheresis machines have to be connected prior to the collection process and the plasma bottles must be sealed in the donor floor after finishing the collection process.*
- 13.2.9 Out of hygienic reasons carpets should be avoided in source plasma establishments, e.g. in the physician's room or the donor floor and living plants cannot be accepted in production or storage areas.
- 13.2.10 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures (*GMP 3.2*). The performance of cleaning and disinfection should be recorded, also in the case when cleaning is conducted by an external company (*GMP 4.2.6*).
- 13.2.11 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals (*GMP 3.4*). Therefore doors to the building should be held closed and doors and walls should not leave a gap.
- 13.2.12 Pest control procedure should be defined in writing (*GMP 4.26*) and cover at least the frequency of performance, the areas, the method of application and the pesticides in use. Only approved pesticides should be used. The documentation of performance should give the information as defined in the procedure (*GMP 4.26*). *-Contracts and invoices are normally no sufficient documents with regard to the required GMP criteria.-*
- 13.2.13 Biohazard waste from the daily production should be stored at the end of a day in a place with limited and designated access. Out of hygienic reasons a separate room (not only a cage or an area within a room) should be designated for the storage of biohazard waste until it will be destroyed or shipped to a destruction company. The air condition of this room should not be in connection with other rooms of the source plasma establishment or the plasma warehouse. Frequency

of biohazard waste pick-ups should be adequate to the amount of biohazard per day.

13.3 EQUIPMENT

***Principle:** Manufacturing equipment should be designed and maintained to suit its intended purpose (GMP 3.34.). The same is valid for equipment for storing purposes. Regular maintenance of equipment forms an essential part of QA and should be performed according to a proper schedule.*

- 13.3.1 Manufacturing equipment (as well as storing equipment) should be designed so that it can be easily and thoroughly cleaned (GMP 3.36.). It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition (GMP 3.36.).
- 13.3.2 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination (GMP 3.37). Therefore cleaning equipment should be stored separately and not within production or product storage areas.
- 13.3.3 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods, adequate records of such tests should be maintained (GMP 3.41.). Therefore calibration and routine maintenance should be regularly performed (e.g. for balances, plasmapheresis machines, centrifuges, thermometers). Their return to use after repairs and routine maintenance should be approved (GMP-s 36).
- 13.3.4 All calibrations should be traceable to an official references standard (e.g. National Institute of Standards and Technology, (NIST) in the U.S.A.). The accuracy of the instrument to be calibrated and of the reference standard should be adequate for the intended use. Action limits should be defined taking into account the specification for the intended use and the accuracy of the measuring device.
- 13.3.5 Defective equipment should be removed from production or at least be clearly labelled as defective (GMP 3.44.). Previously defective equipment may only be returned to use after their suitability has been approved by a responsible person.
- 13.3.6 SOP's should be available regarding the prior usage of equipment after the detection that an instrument was not properly working. The results which were obtained with such equipment should be thoroughly investigated and appropriate measures taken if necessary.

13.4 DONOR SUITABILITY AND ACCEPTANCE

***Principle:** Donors should be carefully selected according to national regulations. Only persons in normal health should be accepted as plasma donors (PhEur). Criteria for a permanent or temporary deferral have to be observed. Donors should not be unobserved (e.g. while changing from one floor to the other in a two-storied building) after they have started the process.*

- 13.4.1 All donor identification procedures should be clearly defined in writing (*GMP 4, principle*).
- 13.4.2 Adequate identification of a donor is important, especially in order to prevent acceptance of rejected donors or cross donation. Therefore each donor must be positively identified during the process, if necessary more than once. The *first identification* should be performed at the reception (*GMP-b 10*).
- 13.4.3 First time / prospective donors must offer acceptable (not expired) documents for identification purposes and proof the current address as well as (in U.S.A) the Social Security Number (SSN). Any official document, as far as also the donor's photograph is included (e.g. passport, driver's license or military ID) may normally be regarded as acceptable.
- 13.4.4 Repeat donor must be verbally asked to give the required identification information (e.g. donor number, donor name etc.) which can be checked in the donor record file (as far as there is also the donor's photograph available) or provide the same official information as required for first time / prospective donors prior to each acceptance.
(*Exclusively the comparison of the donor's appearance with the photograph in the donor's record file is not regarded to be sufficient to "positively " identify the donor.*)
- 13.4.5 Only persons with a permanent place of residence should be accepted as plasma donors. The donor's local address should be checked by adequate means *prior* to the acceptance of a donor, especially of a new donor.
- 13.4.6 In the U.S.A. and also in other states, if applicable, an actual list of any non-acceptable address (dated and signed by a responsible person of the facility according to the company's own procedure) should be easily available for the staff in the front area where potential donors sign in. Such non-acceptable addresses are e.g. homeless shelters, missions or comparable locations. The list should be regularly updated as soon as new information becomes available.
- 13.4.7 Previously rejected donors [who are e.g. listed in a national / industry deferral list (in the U.S.A. the NDDR) or in a company / source plasma establishment own deferral list] must not be accepted as donors. Therefore a careful and unmistakable check must be performed in this respect. Details for the deferral lists should be defined in writing.
- 13.4.8 Careful check must be made on the identity of the donor for a *second time* during the process, this is prior to donor screening. In such cases where the donor is processed during the same session in different steps (e.g. weighing, taking blood pressure and pulse, finger stick for a blood sample), performed by different employees, the donor identification must be repeated prior to each step of the process and by each of the employees. The identity checks should be documented.
- 13.4.9 The determination of donor suitability should include the check of temperature, blood pressure and pulse rate as well as the total serum protein and the haemoglobin / hematocrit, if not otherwise defined by national regulations.

- 13.4.10 Special note should be taken of under-nutrition and reasonable suspicion of intoxication from alcohol or narcotic drugs. Additionally the donor's appearance should be carefully taken into account, as well as a remarkable weight loss within a defined time period.
- 13.4.11 The skin at the venipuncture site should be free from lesions including local eczema, and therefore should be checked as an acceptance criterion.
- 13.4.12 The check of blood pressure and pulse rate may be performed by trained personnel if an automated method is in use, the manual method should be restricted to the physician, the physician substitute or a nurse.
- 13.4.13 Retaken of blood pressure or pulse rate which is initially out of range is acceptable by using an automated instrument if this is clearly defined in a written procedure.
- 13.4.14 Abnormal conditions (e.g. irregular pulse) should be referred to the physician in charge who should have the final decision on whether the donor is acceptable.
- 13.4.15 Special attention should be paid to possible mix-ups of blood tubes during the process of donor suitability (sample testing for hematocrit / protein).
- 13.4.16 For the donor interview a pre-printed and approved questionnaire should be used. Immediately after completion, the questionnaire should be signed by the donor and in addition by the person who carried out the verbal interview or who checked the interview answers if it is the company's policy that the donor answers the questions in writing.
- 13.4.17 Careful check must be made on the identity of the donor for a *third time*, prior to the donor interview if this is verbally performed.
- 13.4.18 There should be suitable donor interview facilities so that these verbal interviews are carried out in private (*GMP-b 6*).
- 13.4.19 *Separate rooms* for the verbal donor interviews will be normally regarded as sufficient confidential. If the donor interviews are not performed in separate rooms but in *booths*, these booths must be sufficiently separated from each other in order to prevent that a donor / prospective donor might listen to or observe another donor's interview. The height of the separation walls should be up to the ceiling and may only in exceptional cases (e.g. by ventilation problems) be reduced to some few centimetres under the ceiling. Any donor waiting area or hallway should be sufficiently separated from the interview area.
- 13.4.20 "White noise" (e.g. music in the background in order to make listening to the donor interview by unauthorised persons more difficult) as substitute to a sufficient segregation of donor booths will not be acceptable.
- 13.4.21 For donor interviews which are performed in writing by the donors, adequate space should be provided for the single donors so that they can make their entries in private. Sufficient separation to other donors (e.g. also writing their answers onto the questionnaire or waiting or passing through) should be available in order to secure that no other person may read the entries. Any possibility that donors can discuss their entries of the questionnaire among each other before handing the questionnaire over to the medical staff should be avoided.

- 13.4.22 The donor's medical history shall be evaluated by a suitable qualified person trained to use accepted guidelines. This person should work under the supervision of a physician. Abnormal conditions should be referred to the physician in charge who should have the final decision on whether the plasma may be collected from the donor.
- 13.4.23 Only persons in normal health with a good medical history should be accepted as plasma donors (*PhEur*). Criteria for a permanent or temporary deferral have to be observed.
- 13.4.24 Physical examinations should be carefully performed, at least prior to the first donation and at regular intervals. Its performance should be documented. Abnormal conditions should be referred to the physician in charge who should have the final decision on whether the plasma may be collected from the donor.
- 13.4.25 Any piercing of the body or tattoos should be clearly documented in the donor record file (including kind and location on the body and date of receiving).
- 13.4.26 If no proof can be brought that acupuncture, tattoos, or body piercing were performed under sterile conditions, donors have to be temporary rejected. A confirmation, issued by the studios / establishments themselves cannot be regarded as acceptable proof for sterile handling.
- 13.4.27 Medication might indicate an underlying disease, which may disqualify the donor. Therefore an approved list of commonly used drugs, which regulates the acceptability of donors, should be available and up to date.

13.5 PLASMA COLLECTION (DONOR FLOOR)

Principle: *The donor floor should be separated from other working areas, e.g. the donor selection area, and should provide adequate space to allow free access to the single donor beds.*

All handling of materials and products should be done in accordance with written procedures or instructions and should be recorded (GMP 5.2.).

- 13.5.1 Eating, drinking and chewing is normally not allowed in any of the production areas, including the donor floor (GMP 2.17) - except of drinking in case of a reaction -. Therefore a juice machine or a drinking water fountain / container should not be available in the donor floor.
- 13.5.2 Donors should not have access to production material (GMP 3.5.). Therefore they should not be allowed to carry their record files (which are manufacturing documents), the empty plasma containers as bottles or bags (which is packaging material) or any other sterile material (e.g. Sodium citrate, Sodium chloride, needles) or the containers filled with plasma (product in the final container) on their own.
- 13.5.3 At every stage of production products and materials should be protected from microbial and other contamination (*GMP 5.10.*).
- 13.5.4 Therefore any pre-set of plasmapheresis machines with sterile softgoods should be avoided as far as no donor is available to be processed (ready for plasmapheresis).

- 13.5.5 Removal of solutions from protective over pouch as well as spiking of solutions must not be performed in advance.
- 13.5.6 The plasma container (bottle or bag) and apheresis systems should be inspected for damage or contamination before being used to collect the plasma (*GMP-b 13*). Plastic containers should also be checked after donation for any defect.
- 13.5.7 Damage to containers and any other problem or deviations from normal procedures which might adversely affect the quality of the plasma should be noted and reported (*GMP 5.4, 5.15*).
- 13.5.8 During the whole process all plasma containers should be clearly labelled (*GMP 5.12*) with the labels sufficiently fixed on the containers. There should be instructions available concerning the type of labels and the method of labelling.
- 13.5.9 The labels on the single plasma units must enable to trace back to the individual origin of the plasma (*PhEur*). They must bear at least the identification number of the donation, the name and address of the collection establishment (source plasma establishment), the batch number of the container, the storage temperature, the total volume or weight of plasma, the type of anticoagulant used and the date of collection (*GMP-b 21*).
- 13.5.10 In order to ensure traceability, the batch number of the bags or bottles and apheresis system (as well as other sterile softgoods) should be recorded (*GMP-b 13*).
- 13.5.11 Procedures should be installed and thoroughly followed in order to avoid any mix-up of softgood batches (*GMP 5.44, GMP-b 13*).
- 13.5.12 Donors should not have access to softgoods. Therefore softgoods should normally not be stored (also not intermediately) in the donor floor or at least stored in a secure area.
- 13.5.13 Each donor must *again be positively identified* before venepuncture (*GMP-b 10*). Therefore the donor must be verbally asked to give the required identification information (e.g. donor number, donor name etc. as defined in the company's own procedure) which should be rechecked in the donor record file. Exclusively the comparison of the donor's appearance with the photograph in the donor's record file is not sufficient to "positively" identify the donor.
- 13.5.14 It is required that the donor identification and the venipuncture are performed by the same employee. The identification procedure must be defined in writing and thoroughly followed.
- 13.5.15 A strict, standardised procedure for the preparation of the phlebotomy area must be observed and clearly defined in writing (*GMP-b 11*). Of particular importance is that the antiseptic solution be allowed to dry completely before venepuncture. The time taken will vary with the product used but should be subject to a minimum of 30 seconds prior to venepuncture. The prepared area must not be touched with fingers before the needle has been inserted.

- 13.5.16 Collection of plasma by cell-separators (plasmapheresis machines) requires adequately trained personnel for operating such machines.
- 13.5.17 The collection procedure should be clearly defined in writing and carefully controlled (*GMP 5, principle*).
- 13.5.18 In order to decrease any risk of contamination, biohazard waste containers in production areas should have a cover or at least the opening as small as possible. These biohazard waste containers should be emptied frequently, at least once per day.

13.6 PROCESSING AND SAMPLING

Principle: The processing area (which is a working area) must be sufficiently separated from other areas to which donors have access and exclusively be used for this purpose. Entry to this area should be restricted to authorised personnel. The processing and sampling procedure must be clearly defined in writing (GMP 5, principle). Any mix-ups of units and of samples as well as any contamination (e.g. when cutting the tube segments) must be avoided.

- 13.6.1 The processing area should be as enclosed as possible, preferably it should be a separate room.
- 13.6.2 If there is no separate room for the processing area, there should be at least a floor-to-ceiling wall, separating the processing area from the donor floor, with a closable window as a hatch for plasma bottles and donor files and a door to the donor floor, if applicable. In exceptional cases, depending on the actual layout of the source plasma establishment, the height of the separation walls may be reduced to some few centimetres under the ceiling. This would be an isolated case decision.
- 13.6.3 Out of hygienic reasons the processing areas should not be equipped with a carpet or with mats which cannot be disinfected (*GMP 3, principle*).
- 13.6.4 Donation number labels must be re-checked independently to ensure that those on plasma containers, sample tubes and donation records are identical (*GMP-b 12*). This might be performed by a two (2)-person check or an additional check by electronically measures.
- 13.6.5 The processing and sampling procedure should be clearly defined in writing and carefully controlled (*GMP 5, principle*). This includes specification for the maximum time period between end of collection and start of processing and sampling.
- 13.6.6 A completely efficient method of sealing the tubes is obligatory.
- 13.6.7 Samples should be representative of the unit from which they are taken (*GMP 6.12.*). Therefore the contents of the part of the tube which still communicate with the container should be completely discharged into the container by stripping and the tube allowed to refill.

- 13.6.8 Any mix-ups of units and of samples as well as any contamination (e.g. when cutting the tube segments) must be avoided.

13.7 SAMPLE STORAGE, TRANSPORTATION AND SHIPMENT TO THE TEST LABORATORY

Principle: Samples should be tested as soon as possible after they are drawn. Storage and transportation / shipment to the test lab should be performed under defined conditions which secure the sample integrity.

- 13.7.1 For the single types of samples (back up samples, PCR samples, samples for virus marker testing) specific storage conditions (including the freezing conditions, if applicable) must be clearly specified.
- 13.7.2 If the test laboratory is not in the same building / city as the source plasma establishment, samples should be packed according to a defined procedure (at least specifying the kind, number and arrangement of cooling / ice packs, pre-treatment of cooling / ice packs etc.).
- 13.7.3 The samples should be transported / shipped to the test laboratory under defined conditions as specified by the test kit manufacturer. The sample shipment should be validated as to guarantee stable conditions and finally correct test results.
- 13.7.4 Samples should be tested as soon as possible after they are drawn in order to have the results at the earliest convenience, especially for the background of Look back information.

13.8 PLASMA FREEZING

Principle: Freezing is a critical step for the recovery of proteins that are labile in plasma (e. g. clotting factors). Plasma which is intended to be used for manufacturing of clotting factors and other labile plasma proteins should be frozen shortly after collection and by cooling rapidly at a temperature of -30°C or below (PhEur).

- 13.8.1 Freezing of plasma should be defined in a written procedure (GMP 5, principle).
- 13.8.2 As freezing of plasma should be performed shortly after collection (PhEur), the maximum time period between end of collection and start of freezing should be specified, documented and carefully controlled.
- 13.8.3 If freezing is performed by using a flash freezer, this equipment should be used according to the manufacturers specification. The temperature should be monitored on a regular basis (at least daily and prior to the first run per day). The single freezing processes should be documented and related to the units which were treated in the same run.
- 13.8.4 If freezing is performed in a freezer, the daily production should be located in an area which meets the temperature requirements (at least -30°C or colder) as shown by validation. This area should be clearly indicated.

13.9 PLASMA STORAGE, RELEASE AND TRANSPORTATION

Principle: Correct and GMP conform storing of plasma is an important part in a source plasma establishment as well as in a plasma warehouse. Therefore freezers / freezing rooms) must secure the required storage temperature (defined by validation) and freezing temperature, if applicable. Furthermore they should be of sufficient capacity to allow an orderly storage of plasma and samples (GMP 3.18). Access of unauthorised persons should be prevented (GMP 3.5.). Written release and rejection procedures for plasma should be available (GMP 4.24.). Transportation should be performed at the same temperature conditions which are defined for plasma storage and should also be validated (GMP-b 17).

- 13.9.1 Freezers / freezing rooms should be protected from access by unauthorised persons (GMP 3.5.). Therefore they should be locked up during the closing hours of the source plasma establishment if external personnel may be present [e.g. cleaning personnel outside opening hours, donors during opening hours (depending on the location of the freezer)]. They should also be locked up during nighttime in plasma warehouses if external personnel may be present.
- 13.9.2 Out of hygienic reasons wooden pallets should be avoided in freezers / freezing rooms because they might have to undergo wet cleaning or disinfection (GMP 3 principle) in order to prevent any risk of contamination (GMP 3.38.).
- 13.9.3 Freezers with automated defrosting must at least guarantee that the defined low temperature is maintained during defrosting cycles.
- 13.9.4 Freezers / freezing rooms -at least in plasma warehouses- should be connected to a reserve power source ("back up power supply") as well as to the main supply.

- 13.9.5 The maintenance of the reserve power supply (e.g. back up generator) should be tested at defined intervals.
- 13.9.6 The freezers / freezing rooms should be equipped with an appropriate temperature recording and alarm device. The alarm system should have both acoustic and optical signals.
- 13.9.7 The sensor (probe) of the thermograph should be placed in a container of equivalent kind and size to the plasma containers, filled with an appropriate solution. The solution should be changed on defined intervals. The container should be located in the “warmest” part of the freezer, defined by validation.
- 13.9.8 The temperature within the freezer / freezing room should be recorded continuously. Special attention should be given to the correct installation of the temperature charts. Additionally a daily manual reading should be performed and documented.
- 13.9.9 The maximum allowable difference between the automatic temperature recording and the manual reading should be defined. The temperature charts as well as the manual records should be regularly controlled.
- 13.9.10 Any deviation (e.g. gaps or overlaps / overwriting) should be avoided as far as possible (*GMP 5.15.*). If a deviation occurs it should be commented and approved in writing by a competent person (*GMP 5.15.*).
- 13.9.11 The freezer alarm device should be tested regularly, independently from any “real” alarms. The tests should include the complete line from the probe / sensor to the alarm company (if applicable) and should be documented.
- 13.9.12 The test documentation should cover at least the alarm start temperature and time as well as the time for the response from the alarm company (if applicable). The alarm company should not be informed in advance about the performance of the alarm test.
- 13.9.13 The alarm start temperature (alarm set) should be defined in writing as at least two (2) degrees Celsius colder than the warmest (maximum) storage temperature. The maximum acceptable response time should be defined.
- 13.9.14 Any real (unexpected) alarm which occurs should be investigated and documented (*GMP 5.15.*). The need of any consequences should be taken into account.
- 13.9.15 Products others than plasma, intermediate products from plasma or plasma samples should normally not be stored in the same freezer / freezing room. In case of a central plasma warehouse which is also in use for other frozen products (e.g. food), at least sufficient separation should be secured to avoid any risk of contamination.
- 13.9.16 Separate (and sufficient) space should be allocated for the different types of plasma products and clearly marked as such. This labelling should be performed outside the freezer / freezing room (preferably at or beside the door) and inside the freezer / freezing room.

- 13.9.17 Where plasma quarantine status is ensured by storage in separate areas, these areas must be clearly marked (*GMP 3.21.*). Any system replacing the physical quarantine should give equivalent security (*GMP 3.21.*).
- 13.9.18 Plasma should be stored at -20°C or colder (*PhEur*). The specific storage temperature of plasma in the freezer(s) should be checked and validated ("freezer mapping") so that the required storage temperature will be sufficiently met (*GMP-s 36, GMP-b 17*).
- 13.9.19 If the required storage temperature (-20°C or colder) is inadvertently exceeded for only one event and for not longer than 72 hours and the temperature was at least -5°C , the plasma may still be used for further fractionation (*PhEur*). In any case (even if no reclassification is necessary) the customer should be notified about this event so that he will be able to assess the plasma quality in case of more than one similar notification (e.g. warming up in the source plasma establishment, in a central warehouse or during transportation).
- 13.9.20 The maximum storage times for plasma / intermediates from plasma should be defined in writing (*CPMP 2.3.8.*).
- 13.9.21 Written release and rejection procedures should be available for materials and products and in particular for the release for sale (*GMP 4.24.*).
- 13.9.22 Release of plasma or intermediate products from plasma should only be performed by designated personal. Procedures should be in place to avoid any mix-ups between unreleased and released donations.
- 13.9.23 Transportation should be performed at the same temperature conditions which are defined for plasma storage or the storage of intermediates from plasma. Information should be provided to the manufacturer on how storage conditions are maintained from the collection centre to the plasma warehouse and further to the manufacturer. Confirmation of compliance with the requirements of the European Pharmacopoeia should be given (*CPMP 2.3.8.*).
- 13.9.24 Plasma or intermediates from plasma should be transported by a system which has been validated to maintain the required storage temperature over the proposed maximum transportation time.
- 13.9.25 The temperature during transport should be continuously recorded (*GMP-b 17*). In case of any malfunction of the recorder, a back-up system should be in place, at least guaranteeing a discontinuous temperature control (e.g. every 15 minutes).
- 13.9.26 Trailers for plasma transportation should be suitable for their use at specified temperature and their qualification completed before they are taken into use.
- 13.9.27 The responsibilities for the transportation (e.g. by the source plasma establishment / plasma collection company, plasma warehouse) should be clearly defined.

13.10 STORAGE OF REACTIVE / POSITIVE UNITS AND OF ALT ELEVATED UNITS

Principle: Plasma units tested reactive for any of the viral markers or positive by PCR test must be stored in a secure way while awaiting a decision on their fate (GMP 8.13.). Any further handling of reactive units (e.g. special shipment, destruction) should be documented; the documentation should clearly refer to the single units in question. ALT elevated units should be stored separately from other plasma units.

- 13.10.1 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products (GMP 3.23, GMP 5.61, GMP 3.24.), potential highly active material should be stored in safe and secure areas until they are destroyed or otherwise handled (GMP 3.24.). Therefore reactive units should be stored separately and under lock and key.
- 13.10.2 Any further handling of such units (destruction or shipment under defined conditions to special consignees) must be clearly documented.
- 13.10.3 ALT elevated plasma units should be separated (e.g. by a physical barrier) from other plasma units.

13.11 RELEASE AND STORAGE OF SOFTGOODS

Principle: Storage areas (as well as production areas) must meet current GMP requirements with regard to their construction and design (GMP 3.19). Storage areas should be clean and dry and maintained within acceptable temperature limits. Storage areas should be of sufficient capacity to allow an orderly storage of materials and products (GMP 3.18.). Storage areas (as well as production areas) should not be used as a right of way by personnel who do not work in these areas (GMP 3.5.).

- 13.11.1 Incoming softgoods should be physically or administratively quarantined immediately after receipt. (GMP 5.5.).
- 13.11.2 Where the quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel (GMP 3.21.). Any system replacing the physical quarantine (e.g. by a computerised system) should give equivalent security (GMP 3.21).
- 13.11.3 Damaged cartons should be carefully checked to detect possibly affected softgoods (GMP 5.4.). Such cartons should be clearly labelled; the check should be documented (GMP 5.4.).
- 13.11.4 Manufacturers of sterile softgoods (such as plasma container, sterile solutions as Sodium Chloride or Sodium Citrate etc.) should provide a certificate of quality compliance.
- 13.11.5 The source plasma establishment should define acceptance criteria for such certificates in writing. These are at least the name of the material and its manufacturer, confirmation of compliance with European Pharmacopoeia (in the U.S.A. at least with the USP) requirements and the CE marking (CPMP 2.3.7.). If

there is no CE marking available, further information is required, including the composition of the plasma container and its specification, a description of the sterilisation procedure and the site where sterilisation is performed, information on the production and quality control of anticoagulant solution (CPMP 2.3.7.). Furthermore it should be confirmed that the materials are sterile and pyrogen free.

- 13.11.6 Responsible personnel of the source plasma establishment should release these sterile materials for use in the source plasma establishment (GMP 5.5, 5.31). The availability of certificates with sufficient information should be the minimum criteria for the release.
- 13.11.7 Softgoods should be stored in designated areas which are not adjacent to a pass through (GMP 3.5.), e.g. to a personnel entry or to an exit for biohazard waste material.
- 13.11.8 Out of hygienic reasons wooden pallets should be avoided for the storage of sterile softgoods (GMP 3 principle).
- 13.11.9 Softgoods should be stored in an orderly fashion to permit batch segregation and stock rotation (GMP 5.7.).
- 13.11.10 Storage and use of softgoods should follow the first in / first out procedure, the use of the expiry dates as an alternative inventory management technique is also acceptable.
- 13.11.11 It is important to ensure traceability between the plasma units and the sterile softgoods which were used in order to collect the units (GMP-b 13). Therefore softgoods not yet in use (for the daily production) should be clearly labelled as such in order to avoid mix-ups with the current lots in use; alternatively the current lots in use may be clearly labelled.
- 13.11.12 Softgoods should be stored under appropriate conditions established by the manufacturer (GMP 5.7.).
- 13.11.13 Where special storage temperature conditions are required (e.g. "room temperature") these should be provided, checked and regularly monitored (GMP 3.19). The acceptable temperature range should be specified in a written procedure. Monitoring of room temperature should be performed at least on a daily basis using a calibrated thermometer (GMP 3.41.).

13.12 COMPLAINTS AND LOOK BACK INFORMATION

Principle: Complaints must be handled according to written procedures and should be part of statistical evaluation.

There must be a system in place which enables the path taken by each donation to be traced, both forward from the donor and back from the finished medicinal product (GMP-b 14). Look back should consist of tracing back of previous donations for at least six months prior to the last negative donation (GMP-b 15, CPMP 2.3.6.).

- 13.12.1 All complaints must be carefully investigated and part of statistical evaluation.
- 13.12.2 Written procedures must exist for recalling defective plasma units or units suspected of being defective. These written procedures must encompass any look back procedures which may be necessary.
- 13.12.3 All complaints should be dealt with and investigated as quickly as possible.
- 13.12.4 Look back information must be forwarded to the customer if a subsequent donation from a donor previously found negative for viral markers, is found reactive for any of the viral markers. These are actually HIV 1 / 2, (p24-HIV-1 Antigen, as far as performed), HBsAg, HCV, including PCR test results.
- 13.12.5 Look back information must also be given if the donor develops CJD or did not meet the relevant health criteria or if it is discovered that testing for viral markers has not been carried out according to agreed procedures (*GMP-b 15, CPMP 2.3.6.*).
- 13.12.6 The mutual information system should also include information about any donor who is subsequently found to have a risk factor for CJD, e.g. family history or treatment with substances of pituitary origin or recipients of dura mater grafts (*CPMP 2.3.6.*).
- 13.12.7 The Look back period should include all previous donations for at least 6 months prior to the last negative donation (*GMP-b 15, CPMP 2.3.6.*).
- 13.12.8 The search for the last negative unit should go back for 5 years prior to the sample / unit tested reactive or caused the look back information.
- 13.12.9 Look back information should be sent to the customer (importer / fractionation facility) as soon as possible (without culpable delay). The information should be given straight after receipt of the laboratory test results, latest within two working days.
- 13.12.10 Results of confirmatory / supplementary test results should additionally be forwarded to the fractionating facility as soon as possible (without culpable delay).

13.13 DOCUMENTATION

Principle: Good documentation constitutes an essential part of the quality assurance system (GMP 4, principle). SOP's and other procedures, records, donor record files, description of computer hardware and software, protocols (e.g. concerning audits, complaints, incidents, accidents), log books and training records are an important part of the documentation system.

The documentation system must permit tracing in either direction of a unit or procedure from the first step to final disposition. The company's own documentation system should be described in writing. A minimum storage period must be observed.

- 13.13.1 Documents should be approved, dated and signed by appropriate and authorised persons (GMP 4.3.).
- 13.13.2 Documents should have unambiguous contents; title, nature and purpose should be clearly stated (GMP 4.4.).
- 13.13.3 They should be laid out in an orderly fashion and be easy to check (GMP 4.4.).
- 13.13.4 Reproduced documents should be clear and legible (GMP 4.4.).
- 13.13.5 Documents should be regularly reviewed and kept up-to-date (GMP 4.5.).
- 13.13.6 When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents (GMP 4.5.).
- 13.13.7 Where documents (e.g. donor record files) require the entry of data, these entries should be made in clear, legible, indelible handwriting (GMP 4.6.). Sufficient space should be provided for such entries (GMP 4.6.).
- 13.13.8 The records should be made or completed at the time each action is taken (GMP 4.8.).
- 13.13.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information (GMP 4.7.). The reason for the alteration should be recorded (GMP 4.7.) if this is appropriate for understanding the alteration.
- 13.13.10 Any deviation from instructions or procedures should be avoided as far as possible (GMP 5.15.). If a deviation occurs, it should be approved in writing by a competent person (GMP 5.15.).
- 13.13.11 Records should include notes on special problems including details with signed authorisation for any deviation (GMP 4.17 i).
- 13.13.12 Donor record files are an important part of manufacturing documents, therefore unauthorised persons (including the donors) should not have access to them (GMP 3.5.).

- 13.13.13 Files of rejected donors should be stored under lock and key (e.g. in locked cabinets or in locked rooms), also during working hours and limited access by authorised persons should be secured.
- 13.13.14 Donor record files should be laid out in an orderly fashion and be easy to check (*GMP 4.4.*). Therefore file folders should not contain loose pages which also might be a risk for loss or mix up of information.
- 13.13.15 If a donor evaluation or the donation process was started but could not be finished, the reason for this incomplete process should be explained in the donor file. There should be no unexplained gaps or missing entries in the donor files.
- 13.13.16 Donor record files should contain a clear and up-to date donor photo (photos should be taken in front of a suitable background) in order to assure sufficient identification. Changing / renewing of donor photos in the donor record files should be performed according to a written procedure and should be documented. If the donor photo is combined with the donor's signature a new (dated) signature will be necessary in case of renewing the photo.
- 13.13.17 The donor record file should indicate each single donation and related measures. The documentation must enable the path of each donation and indicate at least the donor name and number, the donation number as well as the results of the medical examinations, screening and interview results and any other relevant information concerning the donor's health. Also unsuccessful donations should be recorded in the donor record file.
- 13.13.18 Log books should be kept for major or critical equipment recording (*GMP 4.28*), e.g. plasmapheresis machines, microhematocrit centrifuges, scales etc. and contain information about any validation, calibration, maintenance, cleaning or repair operations, including the dates and identity of people who carried out these operations (*GMP 4.28.*). They should also contain the approval of return to use after validation and planned maintenance (*GMP-s 36*) as well after major repairs.
- 13.13.19 Logbooks should record in chronological order the use of major or critical equipment and the areas where the products have been processed (*GMP 4.29*).
- 13.13.20 Documents related to the selection of donors and the preparation and quality control of plasma should be retained according to the legal regulations. For exported plasma the minimum storage time should also comply with the legal requirements of the importing country. Different storage times may be defined in case of donations from immunised donors.
- 13.13.21 The document storage time (specified for the storage in the source plasma establishment and in an external warehouse, if applicable) should be defined in writing.
- 13.13.22 If an off site document storage is used, actual documents (e.g. donor record files, test results, shipment documents, documents needed for customer Look back information) should be stored in the source plasma establishment or the plasma warehouse for a suitable time period (e.g. two years corresponding to a two year's inspection frequency).
- 13.13.23 The external warehouse for documents should be defined in writing (kind, address) and approved by the company's own procedure. A responsible person

for the external warehouse should be determined within the company and defined in writing.

- 13.13.24 Archiving conditions must be suitable to permit the storage of documents during the complete storage time period as defined; any damage or loss of documents should be avoided.
- 13.13.25 The basic archiving requirements should be defined in writing (especially with regard to waterproof, fireproof, theft or other loss). The access to archived documents (in the source plasma establishment or the plasma warehouse as well as in an external warehouse) should be restricted and defined in writing.

13.14 DATA PROCESSING SYSTEMS

Principle: Data processing systems are sensitive systems and require careful implementation and inspection.

- 13.14.1 Data processing systems might be critical to the product and its quality and must be fully validated to ensure that they meet predetermined specifications for their functions, that they correctly preserve data integrity, and that their use is properly integrated into the source plasma establishment operating procedures.
- 13.14.2 If the software is designed and validated by an external company, additional validation in the source plasma establishment should be performed at a minimum, e.g. on-line performance testing of the system under at least limiting and boundary conditions.
- 13.14.3 Testing should be part of the system installation. Testing should also be performed after any system modification to ensure that the changes did not cause any unintended results. Testing should follow a written plan. A record should be kept of the validation testing.
- 13.14.4 A written description of the system elements and their functions that it is designed to perform and all human interactions should be available. The documentation should include at least a detailed specification of the hardware, software and peripheral devices, including the environmental requirements and limitations, diagrams or flow charts of the system's operation describing all component interfaces and all database structures (e.g. file sizes and output formats), SOP's defining when and how the system is used. Such SOP's should address all manual and automated interactions with the system including routine, maintenance and diagnostic procedures and procedures for handling errors and disasters.
- 13.14.5 International rules and national laws on data protection have to be taken into consideration. Security of the database should be maintained especially by periodically re-arranging electronic passwords (without reuse) and by removing unnecessary and outdated access.
- 13.14.6 Only authorised persons should be able to enter or modify data in the computer, the result of entry of critical data should be independently checked (GMP 4.9.). There should be a record of changes and deletions (GMP 4.9.).

- 13.14.7 Data stored by these systems shall be made readily available in legible form. Data should be archived periodically using a long-term stable medium and placed “off-site”.

13.15 TRENDING

***Principle:** Trend evaluation is an important tool to detect developments and deviations from procedures before they might become a problem.*

- 13.15.1 The facility should evaluate statistical variations from the usual pattern or from given normal values. Evaluation should take place on a regular basis. Examples for the statistical evaluations are:
- Rejection or deferral (numbers, reasons)
 - Donor reactions (number, sex, age, reaction, category)
 - Unsatisfactory donations (numbers, category)
 - Reactive / positive tests for infectious markers (numbers, specific, false)
 - Discarded units (numbers, categories, reasons)
 - Freezer failures
 - External complaints (number, origin, category)
 - Clerical errors (numbers, category)
 - Incidents, accidents.

13.16 PERSONNEL AND ORGANISATION

***Principle:** An adequate number of suitable qualified personnel should be available in the source plasma establishment as well as in the plasma warehouse (GMP 2.2.). There should be an actual (dated) and approved organisation chart (GMP 2.2.) showing the hierarchical structure (reporting lines) of the establishment and of the company. Organisation charts and job descriptions shall be approved in accordance with the company's internal procedures. Job descriptions should be signed by the jobholder and a person from the corresponding superior position.*

- 13.16.1 In general at least one physician should be available in a source plasma establishment during the normal opening hours, when donors might be present (medical coverage).
- 13.16.2 However, currently a physician who is at least “constructively” on the premises but easily within reach (within max. 15 minutes after being contacted) is still acceptable for source plasma establishments as it is the rule in the U.S.A. In this case at least a well-trained Physician Substitute must be on site during the whole hours of operation, taking over the duties of the physician.
- 13.16.3 The Physician Substitute must be sufficiently trained in all relevant areas. The physician in charge must be sufficiently involved in the training of the Physician Substitute as well as in his / her evaluation.

- 13.16.4 There must be a strong supervision of the Physician Substitute by a licensed Physician.
In any case a formalised interaction between the physician and the Physician Substitute must be secured by a written procedure. This should include documentation of meetings, discussion of problems / special questions, training, donor complaints, donor treatment etc.
- 13.16.5 Sufficient training should be provided for all the personnel whose duties take them into production areas or storage areas (*GMP 2.8.*).
- 13.16.6 Besides the basis training on theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them (*GMP 2.9.*).
- 13.16.7 Continuing training should also be given, and its practical effectiveness should be periodically assessed (*GMP 2.9.*).
- 13.16.8 Approved training programs should be available and training records should be kept (*GMP 2.9.*).
- 13.16.9 Detailed hygiene programs should be established and adapted to the different needs within the facility (*GMP 2.13.*).
- 13.16.10 All personnel in the production area should receive medical examination upon recruitment (*GMP 2.14.*). After the first examination, re-examinations should be carried out when necessary for the work and personnel health (*GMP 2.14.*), e.g. after travelling into specific risk areas. Instead of medical examinations, alternatives leading to the same results may be regarded as acceptable at present.
- 13.16.11 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of human plasma (*GMP 2.15.*).
- 13.16.12 Eating, drinking, chewing or smoking or the storage of food, drinks, smoking materials or personal medication should be prohibited in the production and storage areas (*GMP 2.17.*). No juice machines or automates for soft drinks or water containers should be available in the donor floors.
- 13.16.13 Personnel should be instructed to use the hand-washing facilities (*GMP 2.19.*). Such instructions should be posted in the specific areas.

13.17 AUXILIARY FACILITIES

Principle: Auxiliary facilities should be arranged in such a way that they do not bear a risk for the plasma product.

- 13.17.1 Rest and refreshment rooms (e.g. staff rooms, canteens) should be separate from other areas (GMP 3.30.). Cabinets for the staff should not be located in the softgood area and changing processes for clothes should not be performed there.
- 13.17.2 Facilities for washing and toilet purposes should be appropriate for the number of users (GMP 3.31.) and be clean and well maintained. They should offer clear instructions for hand washing and hand disinfecting (posted in these areas).
- 13.17.3 Lavatories should not directly communicate with production or storage areas (GMP 3.31.). They should be designated for donors and personnel from the source plasma establishment (preferably separated), excluding public access.

14. RELEVANT TERMINOLOGY

Active donor files	Record file of donors which donate frequently and actually
Annual Registration	In the U.S.A. in addition to the Biologics License available for source plasma establishments and for plasma warehouses; Annual Registration forms are filled in by the companies and confirmed by the FDA only.
Applicant donor	Non qualified donor, first time donor; U.S. companies normally follow an industry standard defining that source plasma may only be used for further manufacturing into injectable products (from a previously so called "applicant" or "non qualified applicant" donor) after virus marker test results of a second sample from the same donor is available (the donor becomes now a "return" / "repeat" donor).
Biohazard	(Biological) Material from donors or contaminated material which might be infectious or is definitely infectious
Closed system	Softgoods combined to a system for the aseptic collection and collection of plasma and sterilised by an approved method, which can be used for plasmapheresis without a breach in the system
Disease state donors	Donors which are tested reactive / positive for viral markers; their plasma may be collected for in vitro diagnostics
Donor booth	Non completely separated area for donor interviews
Form 483	Deficiency report, issued by the FDA (after an inspection has been performed during which relevant deficiencies were detected)

Inactive donor files	Record files from donors who have not donated for a longer time period
Look back information	Post collection information, given from the collection centre to the plasma manufacturers / fractionators if it is found subsequent to the donation that the donor did not meet the current donor health criteria, the donor seroconverts or develops an infectious disease
Manufacturing License	License issued by the competent authority for manufacturers. In the U.S.A. this is the Biologic license and its amendments, if applicable, which are issued by the FDA / CBER.
Medical Coverage	Availability of a physician; Medical coverage should be secured in the source plasma establishment during the whole opening hours, when donors might be present on site. In the U.S.A. a physician substitute may fulfil the duties under the strong supervision of a licensed physician.
NDDR	National Donor Deferral System; in the U.S.A used by industry to exclude donors from further donations; at least first time donors must be checked against this system and the check must be documented
Non-qualified donor	see applicant donor
Plasmapheresis	Process to which plasma is selectively obtained from a donor by withdrawing whole blood, separating it in a plasmapheresis machine by centrifugation / filtration into plasma and cellular components and returning the cellular components to the donor
Plasma warehouse	Establishment for the storage of frozen source plasma
Pre-set of plasmapheresis machines	Installation of softgoods on the plasmapheresis machine before a donor is on the donor bed
Processing area	Area in which the filled plasma bottles are handled (e.g. weighed, sealed) and samples are drawn from the plasma bottle
Prospective donors	Persons who appear for the first time in the collection centre with the goal to donate
Reactive / positive units	Plasma donations which have been tested reactive for virus markers (tested in duplicate) or positive by PCR testing
Rejected donors	Donors who are rejected (not allowed to donate) out of different reasons, either temporarily or permanently
Return / repeat donor	See explanation under applicant donor
Softgoods	Disposables; material for single use which is needed for the plasmapheresis, sterilised by an approved method (e.g. plasma bag / bottle, bowl, anticoagulant solution, needles)

Source plasma establishment	Plasmapheresis centre that collects and stores only or mainly source plasma
Source plasma	Human plasma for further manufacturing (fractionation)
Specialty plasma	Plasma from previously immunised (e.g. tetanus, hepatitis B) donors
Spiking of solutions	Preparation of sterile solutions (e.g. anticoagulant, sodium chloride) for immediate plasmapheresis by inserting the needle / connecting the tubes
Warning letter	Deficiency report, issued by the FDA (after an inspection has been performed during which critical deficiencies were detected)

15. REVISION HISTORY

Date	Version Number	Reasons for revision
1 July 2004	PI 008-2	Change in the Editor's co-ordinates
25 September 2007	PI 008-3	Change in the Editor's co-ordinates
