

**RECOMMENDATION ON**  
**SUPERVISION OF THE USE OF CONVALESCENT PLASMA**  
**AND IMMUNOGLOBULIN CONCENTRATES IN COVID-19 THERAPY**  
**AND**  
**QUALITY ASSURANCE TECHNICAL GUIDANCE OF**  
**COVID-19 CONVALESCENT PLASMA PROCESSING**

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Published by:  
NATIONAL AGENCY OF DRUG AND FOOD CONTROL  
Jalan Percetakan Negara No. 23  
Jakarta Pusat 10560  
Phone (021) 4244691

ISBN 978-602-415-024-2  
First Edition  
MAY 2020

## **FOREWORD**

Thanks to the grace and guidance from Allah SWT, the Recommendation on Supervision of the Use of Convalescent Plasma and Immunoglobulin Concentrates in COVID-19 Therapy and Technical Guidelines for Quality Assurance of COVID-19 Convalescent Plasma Processing, can be prepared and completed properly.

In dealing with COVID-19 as mandated by Mr. President Ir. Joko Widodo through Presidential Decree Number 9/2020 on Amendment to Presidential Decree Number 7/2020 on the Task Force for the Acceleration of COVID-19 Handling, NADFC is strongly committed to give contribution in accordance with the main tasks and authorities in monitoring the aspects of the efficacy, safety and quality of therapeutic products used in the treatment of COVID-19 patients.

Various efforts in the developing treatment of COVID-19, including the use of convalescent plasma as a potential alternative therapy need to be supported. Considering that the evidence for the use of convalescent plasma as a treatment for COVID-19 still needs to be proven, especially in the Indonesian population, certain clinical trials need to be conducted. For this reason, NADFC has made recommendations regarding the use of convalescent plasma in COVID-19 therapy, to provide assurance in efficacy, safety, and quality.

The use of convalescent plasma in COVID-19 therapy requires a plasma processing activity in accordance with the Standards of Good Manufacturing Practices for

Pharmaceutical Products (CPOB) for processing blood products in order to produce safe therapeutic products. In line with the Recommendation, NADFC established Technical Guidelines for Quality Assurance of COVID-19 Convalescent Plasma Processing, which can be used as a guide for Blood Transfusion Units (BTU) involved in the use of Convalescent Plasma both in conducting research and in the therapy of COVID-19 patients.

These guidelines are dynamic and very open to the possibility of refinement to match the findings and new data that supports the use of the most recent convalescent plasma.

Finally, we would like to extend our gratitude to all those who have contributed to the preparation of this Recommendation and Technical Guidelines. Hopefully, this guideline provides maximum benefits in providing health protection for Indonesians.

Jakarta, May 2020

Head of National Agency of Drug and Food Control

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**RECOMMENDATION**

**ON**

**SUPERVISION OF THE USE OF CONVALESCENT PLASMA**

**AND IMMUNOGLOBULIN CONCENTRATES IN COVID-19 THERAPY**

**I. BACKGROUND**

In order to support the COVID-19 pandemic countermeasure action, National Agency of Drug and Food Control, which is mandated to conduct tasks in the field of Drug and Food control in Indonesia, has the responsibility to oversee and ensure that drugs and therapies used in the treatment of COVID-19 patients meet the standards and requirements of safety, efficacy/benefit, and quality.

At present, there has been no specific drug or therapy available for COVID-19, but several potential drugs have been used to treat patients with COVID-19 in the status of a test drug<sup>1</sup>. In addition, from various references, it is known that the use of convalescent plasma and immunoglobulin concentrates, is thought to have potential modalities in the treatment of COVID-19 patients, based on experience of their use in cases of infection due to SARS-CoV-1 (2003), EBOLA virus (2014-2015), H1N1 flu virus (2009-2010) and MERS-CoV (2012)<sup>2,3</sup> and COVID-19 therapy in China<sup>4,5,6</sup>. Convalescent plasma is blood plasma obtained

from individuals who have recovered (survivors) from an infection and contains neutralizing antibodies against the infection. Immunoglobulin Concentrates for intravenous use (IVIg) is globulin concentrates from a collection of blood plasma, a product that is more uniform than plasma and can be utilized in small volumes.

The United States Food and Drug Authority (US FDA) has listed the use of COVID-19 convalescent plasma with a high neutralizing antibody titer against SARS Cov-2 from recovered individuals (survivors) as an emergency investigation product (emergency Investigational New Drug - eIND) ) for COVID-19 patients with severe conditions<sup>7</sup>. In addition, the European Union has also published guidelines for the COVID-19 convalescent plasma utilization program in the European Union<sup>8</sup>.

According to a study conducted by the WHO Blood Regulators Network<sup>9</sup>, the use of convalescent plasma from survivors of COVID-19 disease is a valuable alternative empirical intervention in pandemic emergencies and the absence of specific drugs or vaccines. However, it is very important to obtain data on the effectiveness and safety of its use from clinical trials or structured special uses that can be conducted simultaneously.

## **II. OBJECTIVES**

This recommendation was established with the objective of supporting the development of COVID-19 convalescent plasma and immunoglobulin concentrates specifically for quality assurance and proof of product efficacy and safety as an alternative to COVID-19 therapy. The approach taken is therapy for patients with acute conditions or have a worsening risk to become acute conditions through the following proof:

1. Randomized Controlled Trial (RCT) and/or case-controlled study design;
2. Observational studies for use with specific monitoring.

## **III. SCOPE**

As a New Development Drug (OPB), NADFC supervision is conducted through the implementation of regulatory assistance and the establishment of technical guidelines for quality assurance of convalescent plasma processing.

The regulatory supervision and assistance is conducted in the following stages:

1. Implementation of convalescent plasma clinical trials to ensure efficacy and safety: development of protocols, implementation of clinical trials and evaluation of clinical trial results.
2. Quality assurance of Convalescent Plasma products used.

## **IV. PRINCIPLES OF THE USE OF COVID-19 CONVALESCENT PLASMA AND IMMUNOGLOBULIN CONCENTRATES IN INDONESIA**

### **4.1. Scheme for Using Convalescent Plasma and Immunoglobulin Concentrates**

The use of convalescent plasma and immunoglobulin concentrates needs to be based on evidence of a positive balance between the risk and efficacy, and supported by safety standards for the use of blood products in accordance with prevailing legislations. In addition, the use of convalescent plasma and immunoglobulin concentrates must follow the OPB scheme in accordance with the Regulation of Head of NADFC Number 16/2015 on Management and Evaluation of New Development Drugs.

The scheme for using COVID-19 convalescent plasma and immunoglobulin concentrates is as follows:

#### **a. Clinical Trials**

The implementation of clinical trials should be carried out with a randomized controlled design or Randomized Controlled Trial (RCT). However, in a pandemic emergency in handling COVID-19, other research designs may be considered. Researchers who will

participate in the implementation of clinical trials can submit an application to National Agency of Drug and Food Control to obtain Clinical Trial Approval (PPUK) and the National Agency of Drug and Food Control will oversee the implementation of clinical trials according to the guidelines of Good Clinical Trial Methods (CUKB).

Documents for submission of clinical trial approval need to be accompanied by information about COVID-19 convalescent plasma used, which includes sources of COVID-19 convalescent plasma. The collection, storage, labeling and use of convalescent plasma shall consider the CUKB guidelines a research drug. Researchers are also required to give priority to the principles of patient ethics and safety including, among others, donor and patient informed consent, institutional approval, and special labels on product packaging and commitment to give reports on objective data outcome.

b. Use with specific monitoring

This scheme is made possible by the mechanism of observational studies, especially for COVID-19 patients who do not meet the criteria or cannot (non-eligible) to participate in RCT clinical trials. In addition, non-study mechanisms can also be used for patients with acute conditions or have a worsening risk to acute conditions through

the request of a doctor who treats these patients, with strong justification based on scientific evidence.

#### **4.2. Patient Criteria**

Clear and objective parameters need to be set for criteria for patients who can be eligible for convalescent plasma and immunoglobulin concentrates based on adequate risk benefit considerations.

#### **4.3. Donor Eligibility**

1. Donors must be voluntary and meet general requirements in accordance with Regulation of Minister of Health Number 91/2015 on Blood Transfusion Service Standards.
2. COVID-19 convalescent plasma and immunoglobulin concentrates shall be collected from patients who have been recovered based on the verification of the recovery level and medical history in accordance with applicable clinical management guidelines and meet specific requirements related to COVID-19 convalescent plasma with the following qualifications:
  - a. A prior diagnosis of positive COVID-19 documented by a laboratory test result with a diagnostic test (naso/oro-pharyngeal swab) at the time of illness or for individuals that have not been tested but have a clear history of COVID-19 symptoms;

- b. Have not shown any clinical COVID-19 symptoms for at least 14 days prior to the donation documented by a negative test result for SARS-CoV-2 through naso/oro-pharyngeal swab;
  - c. Donors without a history of blood transfusion and female donors who have never been pregnant. If the female donors were pregnant, they need to be tested and found negative for anti-HLA/HPA/HNA antibodies using a validated assay.
  - d. Donors with SARS-CoV-2 neutralizing antibody titers, if available of at least 1:160. The neutralizing antibody titers of 1:80 may be considered acceptable if an alternative matched unit is not available. When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.
  - e. Donors shall re-donate their plasmas every 14 days, with a maximum donation of 12 L a year, if they are collected with a plasmapheresis procedure and meet the specific requirements related to COVID-19 convalescent plasma.
3. Donors shall be recruited from hospitals that treat COVID-19 patients and have been given the informed consent.

## **V. QUALITY ASSURANCE OF THE USE OF CONVALESCENT PLASMA AND IMMUNOGLOBULIN CONCENTRATES**

### **5.1. Product Requirements**

The convalescent plasma and immunoglobulin concentrates used must meet the safety and quality requirements specified as a test drug in accordance with Regulation of Head of National Agency of Drug and Food Control Number 16/2015 on Management and Evaluation of New Development Drugs.

### **5.2. COVID-19 Convalescent Plasma Collection and Processing Facility**

1. Convalescent plasma processing activities should be carried out at BTU facilities that have complied with GMP requirements to avoid risks from products that do not meet quality and safety requirements. If this is not possible, it can be obtained from BTU which already has a quality assurance system, as a minimum requirement.
2. Specifically for the immunoglobulin concentrate processing; it should be carried out in GMP-certified pharmaceutical industry facilities.

### **5.3. Documentation**

A proper computerized or manual documentation system should be available for donor recordkeeping, processing, use of convalescent plasma and patient data. This is to ensure the traceability of all plasma

donation processes, processing, and the use. The record must have a unique identification number to make the look-back activity possible.

#### **5.4. Labeling**

Considering that COVID-19 convalescent plasma is a product that is under investigation, for which its usefulness and safety are unknown, the container for convalescent plasma storage should be labeled: "For Clinical Trials - COVID-19 Convalescent Plasma". It is recommended to use a uniform and labeled container containing important information, including unique donation number, test results during donor selection, date of collection and processing, and storage temperature.

## **VI. MONITORING OF RESULTS WITH THE ORIENTATION ON PRODUCT SAFETY AND EFFICACY ESTABLISHMENT**

### **6.1. Monitoring and Reporting**

Patient treatment outcomes that include safety and product efficacy indicators use a case report form (CRF) in both manual and electronic forms. The CRF can contain information on gender, age, time of transfusion (days since disease onset), number, volume and volume of convalescent plasma antibodies, other therapies that are given in parallel to the patient, clinical symptoms and laboratory check

parameters (before transfusion, during treatment and after patients recover or according to established protocols), other side effects that may be related to transfusion, and length of hospital stay. The data can be used to determine product characteristics and effective dosage regimens that provide the most benefits. Communication and dissemination of information on the monitoring result must be carried out immediately.

In addition to CRF documentation as a clinical trial document, the administration of convalescent plasma to patients in the Scheme of Specific Monitoring is recorded in hospital medical record documents.

## **6.2. Storage of Document Records**

The documents as referred in point 6.1 must be kept as clinical trial documents in accordance with CUKB regulations. Documents are kept in a cupboard or place that is given a clinical trial identity, has controlled access and is recorded every time the document is borrowed or returned. Documents in the form of electronic records, such as electronic CRF (e-CRF) must have a password that is only known by members of the research team who are authorized to have controlled access and back-up data available. Documents are stored for at least 5 (five) years after the clinical trial is complete.

Storage of hospital medical record documents shall follow the existing provisions in each institution. The provisions for document storage must be set forth in a fixed procedure.

## **VII. DEVELOPMENT POTENTIAL OF COVID-19 CONVALESCENT PLASMA AND IMMUNOGLOBULIN CONCENTRATE PRODUCTION**

### **7.1. Use of Small Scale Immunoglobulin Concentrates**

The processing of immunoglobulin concentrates requires effective and efficient technology to obtain an effective dose of relevant antibodies. The use of immunoglobulin concentrates, is possible to obtain products that are more uniform than plasma and can be used in small volumes to increase the specific antibodies of the virus in patients.

### **7.2. Production of Large Scale Immunoglobulin Concentrates**

The production of large-scale immunoglobulin concentrates in the early stages of the epidemic is not possible given the limited availability of donors as a plasma source. Production on an industrial scale must be carried out in adequate facilities and have a production license and comply with GMP regulations. In a recurrent epidemic situation, consideration should be given to identifying potential donors who are not sick and who have been previously exposed to the epidemic virus

through serosurvey. These donors can be recruited on a large scale for the availability of starting material in the production of immunoglobulin concentrates from plasma that is specific to COVID-19.

## **VIII. CLOSURE**

In accordance with various global references, including Position Paper from the WHO Blood Regulators Network, recommendations from the United States Authority (US-FDA) and European Union guidelines on COVID-19 convalescent plasma programs, convalescent plasma and immunoglobulin concentrates from COVID-19 survivors can be considered as alternatives COVID-19 therapy in pandemic emergencies and the unavailability of specific drugs and vaccines.

However, for quality assurance and proof of its effectiveness and safety, the use of convalescent plasma and immunoglobulin concentrates in principle must go through a clinical trial research scheme in accordance with Regulation of Head of National Agency of Drug and Food Control Number 16/2015 on Procedures and Evaluation of New Development Drugs, and use schemes with specific monitoring. In addition, it is important to consider the application of other key component requirements in accordance with prevailing legislations, such as the criteria for eligible patients for convalescent plasma therapy and immunoglobulin concentrates, donor eligibility, product requirements, and their collection and processing facilities.

To that end, NADFC with the mandate in the field of Drug and Food control will conduct the supervision in the use of convalescent plasma and immunoglobulin concentrates, specifically related to the mechanism of New Development Drug, by providing regulatory assistance and establishment of technical guidelines for its implementation.

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## **ANNEX**

### **TECHNICAL GUIDELINE**

#### **QUALITY ASSURANCE ON PROCESSING**

#### **CONVALESCENT PLASMA OF COVID-19**

#### **I. INTRODUCTION**

Convalescent plasma and immunoglobulin concentrate of COVID-19, which used as an alternative therapy for patients COVID-19, come from the blood donors according to specific criteria. The result is a plasma-derived product as an investigational drug following the patient's needs who receive it.

To ensure the quality and safety of investigational drugs, align with the acceleration and expansion utilization of convalescent plasma and immunoglobulin concentrates, the processing activities should be carried out in a GMP certified blood establishment facility. Other facilities, GMP uncertified, are acceptable as long as implement a robust quality system to mitigate the risk of defective products that do not meet the quality and safety requirements. Notably, for immunoglobulin concentrate manufacturing, it should be carried out in a GMP certified pharmaceutical industry facility and do not be further discussed in this technical guideline.

## **II. OBJECTIVES**

1. Promote the development of COVID-19 convalescent plasma through quality assurance monitoring; and
2. A guideline of convalescent plasma quality assurance for blood establishments, which are operated by the central or regional government, in the hospital and other facilities, and also managed by Indonesian Red Cross (PMI) of which be involved in the processing and utilization of COVID-19 convalescent plasma which covers activities from donor recruitment, processing to distribution.

## **III. SCOPE**

This technical guideline is an integral part and adheres to the Recommendation on the Monitoring the Use of Convalescent Plasma and Immunoglobulin Concentrates for COVID-19 therapy as it contains critical aspects and specific requirements that must be fulfilled by blood establishment facilities which enrolled in the processing and utilization of convalescent plasma for COVID-19 therapy.

The GMP uncertified blood establishment facility should establish and implement a quality assurance system under blood processing and blood component guidelines, including plasma, which refers to the Regulation of the Head of Indonesia FDA Number 10/2017 on Good Manufacturing Practices in Blood Establishment.

The recruitment donor procedures, processing, quality attribute, and distribution of convalescent plasma must be carried out under the Minister of Health Regulation Number 91/2015 on Blood Transfusion Service Standards. Other specific requirements that should also be covered are the processing and utilization of convalescent plasma from donors who have recovered from COVID-19.

#### **IV. ARRANGEMENT OF TECHNICAL GUIDANCE**

This technical guideline consists of the following aspects:

1. Donor Recruitment and Requirements
2. Blood/Plasma Collection Facility Requirements
3. Blood/Plasma Collection
4. Processing
5. Testing and Quality Attribute
6. Documentation
7. Labelling and Storage
8. Distribution and Application
9. Monitoring
10. Contract Processing, Testing and Services

## **V. QUALITY ASSURANCE ON PROCESSING CONVALESCENT PLASMA OF COVID-19**

### **1. DONOR RECRUITMENT AND REQUIREMENTS**

#### **Donor Recruitment**

1.1. The blood establishment should perform donor recruitment activities which include socialization and campaign of a voluntary (unpaid) blood donor to improve the willingness and awareness of survivors to donate their blood and provide the needs of convalescent plasma as an alternative therapy for COVID-19 pandemic. If donor recruitment is conducted at the blood establishment of PMI or Local Government, the data of donor candidate should be obtained from hospitals that have treated COVID-19 patients.

#### **Donor Registration**

1.2. Upon present at the blood establishment, donor candidate should provide their identity with a photograph and stating their full name, National Identification Number (NIK), address and date of birth. Each donor should also provide proof of permanent residence, including telephone numbers where appropriate so that they can be contacted after donating blood or plasma, if necessary.

- 1.3. A thorough check on the donor identity should be repeated before each step that is relevant to the quality of the products and the safety of donors, or at least before donor selection and venipuncture.

### **Donor Selection**

- 1.4. Blood or convalescent plasma should be voluntarily collected from patients who have been declared recovered from COVID-19 based on confirmation of their recovery rate and medical history by the authorized doctor following applicable clinical practices guidelines.
- 1.5. Every donor should be tested on infectious of transfusion-transmitted diseases (TTD).
- 1.6. Donor selection should be carefully conducted according to a validated systematic process, consisting of a donor health assessment and lifestyle history (obtained from the donor questionnaire) and a medical examination. This evaluation, along with a review of the results of the infectious disease screening laboratory test, should be used to ensure, prior the release of the plasma, that the donor presents no increased risk for transmission of infectious agents. Donor selection should be carried out at least one day before the blood/plasma collection.
- 1.7. The donor should meet general requirements under the Minister of Health Regulation Number 91/2015 on Blood Transfusion Service

Standards, and fulfill other specific requirements relevant to COVID-19 convalescent plasma with the following qualifications:

- a. A prior diagnosis COVID-19 based on a laboratory test result (naso/oro-pharyngeal swab) at the time of illness or a clear history of COVID-19 symptoms when testing was not available;
- b. No clinical symptoms of COVID-19 for at least 14 days prior donation followed by a negative test result for SARS-CoV-2 through naso/oro-pharyngeal swab;
- c. Donors without a history of blood transfusion, or female donors who have never been pregnant, If the female donors have been pregnant, they should be tested and found negative for anti-HLA/HPA/HNA antibodies using a validated assay.
- d. SARS-CoV-2 neutralizing antibody titer, if available of at least 1:160. The neutralizing antibody titer of 1:80 might be considered if an alternative matched unit is not available. In an emergency, convalescent plasma can be released without prior neutralizing antibody testing, and the retained sample should be tested immediately. If there is sufficient correlation between neutralizing antibody testing and other specific antibodies testing, i.e. Enzyme-Linked Immunosorbent Assay (ELISA); therefore, other specific antibodies can replace neutralizing antibody testing;

- e. Complete the informed consent for convalescent plasma; and
  - f. Donors can re-donate their plasma every 14 days, with a maximum donation of 12 L a year, if it is collected with a plasmapheresis procedure and fulfilled the specific requirements related to COVID-19 convalescent plasma.
- 1.8. Initial plasmapheresis and at 4-month intervals for donors undergoing serial plasmapheresis (donating plasma more than once every four weeks), should be tested for albumin and total protein, results must be within normal limits.
- 1.9. Physical examination should be conducted by an authorized doctor, using a complete level 2 personal protective equipment, under procedures established before the first blood donation and before the next donation, as well as in a periodic specific plasmapheresis program.
- 1.10. An appropriate computerized recording system (if not available, a manual system can be used) should be available for donor recording (including medical history and health status) and to ensure the traceability of all blood donation processes. Such information may present a perspective of the donor medical history, including the previous deferral and contribute to reinforce the decision whether such donation will pose a risk to the quality and safety of convalescent plasma.

## **2. BLOOD/PLASMA COLLECTION FACILITY REQUIREMENTS**

- 2.1. Blood/plasma collection facility should be at the blood establishment that complies with GMP requirements.
- 2.2. Blood establishment facility that does not meet the GMP requirements should have the following:
  - a. The quality assurance system; and should implement it in the organization, personnel and qualified person for quality assurance, documentation systems and other relevant functions;
  - b. Sufficient room for each critical stage of donor selection, blood/plasma collection, processing, testing and the storage for released products that meet quality assurance requirements;
  - c. Competent personnel to conduct critical processes which include selection, establishment and determination of donor suitability, plasma processing, donor infectious disease screening, ABO and Rhesus blood grouping, blood type antibodies test, labelling, storage and distribution.
- 2.3. Look-back
  - a. Blood/plasma collection facilities should have a look-back system procedure. This process should be able to trace back products

collected from the donor to the final recipient and from the recipient back to the donor, preferably using a computer database.

- b. The procedure should be effective for monitoring the safety status of convalescent plasma given to the patients from all registered donors. Please note the re-donation requirements for COVID-19 convalescent plasma as listed in section 1.7 (f). The data on the system should always be updated according to the latest information.

- 2.4. Equipment used for plasmapheresis or whole blood collection should be maintained, calibrated, qualified and utilized following the designation of the process.
- 2.5. The existing laboratory equipment should be qualified and calibrated by the test objectives and confirmed using a validated test method for TTD screening tests and the requirements test related to the quality of COVID-19 convalescent plasma.
- 2.6. All critical processes in the processing of convalescent plasma should be validated following the validation protocol before being applied.
- 2.7. Waste Management should follow the guidelines for waste handling and management, specifically for infectious waste, hazardous and toxic substance, and general waste.

### **3. BLOOD/PLASMA COLLECTION**

- 3.1. The collection preferably carried out by plasmapheresis. However, where that is not possible, convalescent plasma can also be processed from the whole blood.
- 3.2. Plasma collection by plasmapheresis:
  - a. The total plasma volume collected from donors in one procedure and the duration of plasma collection should be regulated by internal policy based on the latest medical knowledge under prevailing legislation.
  - b. Plasma collection process with plasmapheresis procedure should apply a validated method. Any deviation from established procedures and processes may fail to comply with the product specifications. Therefore, appropriate handling procedures for defective products should be available, and these products cannot be released for distribution.
- 3.3. Whole Blood Collection:
  - a. The collection of one standard unit of whole blood should be achieved less than 12 minutes, as longer duration may result in the activation of coagulation factors and cellular components. Blood collected above the maximum period should be recorded and discarded.

- b. The volume of whole blood collection to produce 200 mL of plasma is 450 mL.
- 3.4. The collection system should be carried out following the operating instructions of the used device.
- 3.5. Standardized and validated procedures for the preparation of the phlebotomy site should be followed using a suitable disinfection solution which should be allowed to dry according to the disinfectant type. The expiry date of the disinfectant should be checked. If refillable bottles are used for disinfectant, they should be cleaned before being refilled. The date of manufacture and the opening date for in-house disinfectant should be stated on the label. The prepared skin area should not be touched after disinfection and before the needle has been inserted. Care should be taken not to lean over or speak over the disinfected skin.
- 3.6. Records should be kept for each activity associated with the donations, including identification of the person who performs the venipuncture. Records should also show any unsuccessful donation, adverse reactions or adverse events.

#### **4. PROCESSING**

- 4.1. If the obtained convalescent plasma by plasmapheresis is deemed to be divided into 2-3 separate units @ 200 ml or according to the transfusion

needs, then the process should be conducted in a closed system using a sterile connecting device and using an appropriate bag for plasma.

4.2. Processing of convalescent plasma from whole blood:

a. Whole blood from the donor should experience centrifugation and separation.

b. Centrifugation

1) Centrifugation parameters (revolutions per minute, temperature, time, acceleration, and deceleration) are essential for the composition and characteristics of the specific components.

These critical parameters should be defined based on validation data that demonstrate a process that consistently produces quality products.

2) For each process, the centrifugation record should identify the operator and confirm that the centrifugation process was performed according to specifications.

c. Separation

After centrifugation, the bag system should be carefully removed from the centrifuge and placed into a plasma expressor or blood separation system. Plasma should be transferred into the satellite bags within the closed system, using a designated method to optimize the harvest of desired plasma.

## **Virus Inactivation Process**

- 4.3. If possible, virus inactivation should be carried out under appropriate and validated method<sup>5</sup>.

## **Freezing**

- 4.4. Plasma may be frozen while waiting for the testing results of antibody titer or if it is not immediately given to the patient, in the form of Fresh Frozen Plasma (FFP).
- 4.5. FFP becomes an alternative if convalescent plasma distributed to areas far from the plasma processing location.
- 4.6. The freezing process cannot be conducted on plasma collected by partially closed system plasmapheresis.
- 4.7. The plasma freezing process is conducted by rapidly freezing plasma using a contact shock freezer or blast freezer or other validated devices. Maximum plasma freezing should be done within 6 hours, counted from the completion of the blood/plasma collection up to the core temperature below -30°C for 1 hour.
- 4.8. Keeping in mind that the freezing speed will be influenced by the type of plasma container, the freezing equipment and loading pattern as well as the plasma volume.
- 4.9. The freezing process validation should consider the worst-case scenario, including minimum and maximum load and position in the

freezer. Recording of plasma bag temperature and freezing time during the freezing process makes it possible to evaluate the capacity of the freezing device and ensure a standardized freezing process. Validation studies should be available and should be able to demonstrate that the freezing temperature of the product reaches the desired storage temperature according to specifications.

4.10. FFP can be stored for the period as follows:

<b>Storage Temperature</b>	<b>Expiration Date</b>
- 20 to 24°C	3 months
- 25 to -29°C	6 months
- 30 to -39°C	1 year

## **5. TESTING AND QUALITY ESTABLISHMENT**

- 5.1. SARS-CoV-2 neutralizing antibody titer should meet the recommended minimum value requirements. Testing of retained samples should be conducted at a facility with a Bio Safety Level 3 (BSL) standard.
- 5.2. Plasma retained samples allocated for the study were taken during donation and stored at -80°C.
- 5.3. TTD screening tests should be performed on each prospective donor, which includes screening tests for infection markers:
  - a. Hepatitis B surface antigen (HBsAg);
  - b. HIV 1/HIV 2 antibody (anti-HIV1 / HIV2);
  - c. Hepatitis C antibody (anti-HCV); and

d. Syphilis.

- 5.4. The blood donors should be free from hepatitis B, HIV, Hepatitis C, and syphilis primarily by the Chemiluminescence Immuno-Assay (ChLIA) method and the Nucleic Acid Amplification Test (NAT) for HIV, HCV, and HBV. If the blood establishment does not have NAT testing equipment, analysis can be contracted to third parties.
- 5.5. Donors who have been proven to be reactive to the TTD test at the initial screening should be retested in duplicate by the same assay.
- 5.6. NATs require a particularly sophisticated laboratory environment and equipment, and well-trained laboratory personnel. Mainly, because of an extraordinary risk of false-positive results due to the so-called carry-over (inadvertent transfer of the amplification product DNA to neat donor samples), very stringent handling and logistic are mandatory.

#### **Release of COVID-19 Convalescent Plasma**

- 5.7. The specification of product released should be set for COVID-19 convalescent plasma.
- 5.8. The release of COVID-19 convalescent plasma is performed by reviewing and ensuring that all processes are carried out correctly starting from donor selection, convalescent plasma collection, testing, documentation, and labelling. Where appropriate, this process is assisted by a validated computerized system.

5.9. The decision release of plasma should be carried out by the authorized qualified person, and fully documented with confirmed traceability.

## **6. DOCUMENTATION**

6.1. Proper documentation ensures that work is performed in a standardized, uniform manner and ensures traceability of all steps.

6.2. The Standard Operating Procedures (SOPs) should include all applicable methods and procedures, well trained to personnel before the application, and be accessible to all authorized personnel.

6.3. If appropriate documentation concerning the convalescent plasma is needed, then the recording system should be available following the procedures in Good Clinical Practices (GCP).

6.4. All critical procedures such as purchasing and receiving raw materials, donor recruitment, donor selection, blood/plasma collection, blood component preparation, laboratory testing and quality control, product labelling, storage, release, distribution, transportation, recall and destruction of products should be described in details in the SOP following relevant regulations.

6.5. Specific procedures should be in place for a series of convalescent plasma processes ranging from donor selection to convalescent plasma

distribution, which ensures the safety and prevents the risk of disease transmission.

- 6.6. Critical laboratory processing and testing records should be reviewed for completeness, legibility and, when appropriate, accuracy by the designated person.
- 6.7. Documents should be reviewed and approved by authorized personnel.
- 6.8. All records, including raw data, which are critical to the safety and quality of blood or blood components, should be kept in a secured storage area according to relevant regulations, or preferably for at least 5 (five) years.

## **7. LABELING AND STORAGE**

- 7.1. The collected plasmas should be labelled with relevant information regarding their identity and release status. Whenever possible, machine-readable labels (barcodes) should be used. The label at least contains the following information:
  - a. Unique donation number (through the use of this number there should be traceability to the donor and all records of the manufacturing steps through to the final product);
  - b. The required storage conditions;
  - c. The expiry date;

- d. The date of collection of the donation(s) from and processing date and time;
  - e. Inactivation date and time (if applicable);
  - f. ABO and RhD blood group;
  - g. Results of TTD screening and erythrocyte antibody screening;
  - h. Name or other identification that indicates the location of component preparation;
  - i. If the utilization for a clinical trial scheme, there should be labelled "For Clinical Trials - COVID-19 Convalescent Plasma";
- 7.2. Convalescent plasma should be stored in an area that is controlled and monitored, and effective in preventing mix-ups, damage and contamination. All controls should be documented.

## **8. DISTRIBUTION AND APPLICATION**

- 8.1. Before distribution, the convalescent plasma should be visually inspected.
- 8.2. There should be a record that identifies the person distributing, and the hospital receiving it and the patient receiving convalescent plasma.
- 8.3. Dispatch of the convalescent plasma should be made by authorized personnel.

- 8.4. The SOP on packaging should be available stating how the contents should be packaged, the material to be used and the amount of any cooling elements and their storage conditions before use. The distribution system should be conducted in a validated cold chain.
- 8.5. Convalescent plasma should be distributed to hospitals to be given to patients who have met the criteria and obtained informed consent.
- 8.6. Convalescent plasma can be used immediately after the collection/processing for up to 24 hours (under 2 - 6°C storage conditions) or taken from frozen deposits.
- 8.7. The process of frozen convalescent plasma thawing (FFP) should consider the temperature and duration according to the standard. Convalescent plasma can only be used for a maximum of 6 hours after thawing.

## **9. MONITORING**

- 9.1. Monitoring data is required to evaluate the entire manufacturing process and use of convalescent plasma.
- 9.2. Facilities that conduct convalescent plasma transfusion should report data on the use of convalescent plasma and adverse events.

## **10.CONTRACT-BASED PROCESSING, TESTING, AND SERVICE**

- 10.1. All activities that have a potential impact on the quality or safety of convalescent plasma and which are performed for hospitals or blood establishment (contract giver) by blood establishment or other laboratories (contract acceptor) should be arranged in contract detail.
- 10.2. The contract should ensure that the contract acceptor complies with and implement a quality assurance system for all aspects relevant to the contract giver's activities.
- 10.3. The contract giver should be responsible for ensuring that processes are in place to assure the control of activities by the contract acceptor and the quality of the convalescent plasma.
- 10.4. The details in the contract should cover technical quality agreements, particularly on the critical steps performed by different parties.
- 10.5. The contract giver should provide all necessary information to the contract acceptor.
- 10.6. The contract should be approved and signed by representatives of both parties, and it must be kept up to date.

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