Quality Assurance and Good Manufacturing Practice In Respect of Plasma Fractionation

Kamran Mousavi Hosseini[1], Zohreh Sharifi[1]*

1. Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran.,Corresponding Author: Kamran Mousavi Hosseini, Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran., Phone: 0098 21 82052160, E-mail: mkmousavi@yahoo.com

Abstract

The Quality centers shall build up a quality system. This comprises all activities in the blood center intended to ensure that all blood and all components have a quality corresponding to the intended use.

Quality Assurance shall cover all aspects of manufacture starting with selection of donors, blood bags, anticoagulant solutions and including collection, storage, transportation, processing, quality control and delivery of the finished component. Good Manufacturing Practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. Good manufacturing Practice is concerned with production and quality control.

In order to monitor the implementation and compliance with the blood establishment quality management system, regular internal audits need to be in place. These should be conducted independently by trained and competent persons from within the organization, according to approved protocols.

All audits results should be documented and reported to management. Appropriate corrective actions should be taken. Corrective and protective actions should be documented and assessed for effectiveness after implementation.

Key words: Quality Assurance, GMP, Qualification, Validation, Internal audit.

Introduction

Production of medicinal products for both human and veterinary use in every country must be in accordance with local legislations. Patients whom are prescribed a medicine usually does not know much about the drug effectiveness or its side effects, so patients just trust the physicians and pharmacist to take the drug. That is

why there are a lot of regulations and requirements for the physicians and pharmacist, because based on the following triangle patient is not able to choose the medicine directly. Figure 1 shows this triangle.

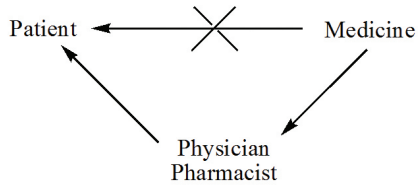

Figure 1- Procedure of receiving medicine

Most of the countries ask for quality assurance and Good Manufacturing Practice requirements, to be implemented within the process of producing blood products or plasma derived biological drugs by manufactures. (1, 2) Plasma fractionators have to produce their plasma derived products in a way to ensure that they are fit for their intended use and comply with the local regulations and do not place patients at risk due to inadequate safety, quality, or efficacy. Human plasma derived medicine quality depends on the preparation method and it can be different from batch to batch due to the nature of source starting material which is plasma. (3, 4)

In order to achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and therefore Quality control. (5)

In a Good Manufacturing Practice environment everything should be fully documented and its effectiveness has to be monitored. Quality Assurance System should monitor that all facilities are adequate, and premises and equipments are sufficient. Quality Assurance System also has to make sure that personnel are competent and qualified.

Quality Assurance, Good Manufacturing Practice and Quality Control are conceptually inter-related.

As far as all blood products and plasma derived products which have been produced by blood fractionation companies are known as drugs, all international requirements with notice to the local regulations apply to all processes of manufacturing them.

In most pharmacopeia such as British Pharmacopeia (BP) (6) and United State Pharmacopeia (USP) (7) there are several monographs for the blood or plasma derived products as drugs. In accordance with Iran local regulations all drugs should be released by responsible pharmacist.

All biological medicinal products derived from human blood or plasma quality depend on the nature of source material. The source material may be contami-

nated by disease transmitting agents such as viruses. Therefore the safety of medicinal products derived from human blood or human plasma depend on the way of controlling source materials and their origin as well as on the subsequent manufacturing procedures, including virus removal and virus inactivation methods. (8-10) Effective virus removal and virus inactivation methods shall be taken to prevent the transmission of infectious diseases and the requirements and standards which have been defined by local authorities regarding plasma fractionation and biological medicinal products derived from human blood or plasma shall be applicable. (11, 12)

The main point is, the quality of the final biological medicinal products can be affected by all the steps in their manufacturing process from A to Z, including the blood collection or plasma collection, all methods of fractionation, precipitation, filtration, sterilization, and packaging; (13, 14) therefore all operations should be done in accordance with an appropriate system of Quality Assurance and Good Manufacturing Practice. (5)

Local authorities in order to monitor the implementation and compliance with Good Manufacturing Practice principles, conduct inspections.15,16 For example Good Manufacturing Practice inspections are performed in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA); in the South Korea by the Korea Food & Drug Administration (KFDA); in Australia by the Therapeutical Goods Administration (TGA); in South Africa by the Medicines Control Council (MCC); in Brazil by the Agencia Nacional de Vigilancia Sanitaria (ANVISA); and in Iran inspections are carried out by the Food & Drug Organization (FDO) which is an state organization affiliated to the Ministry of Health and Medical Education.

Quality Assurance System

The concept of Quality Assurance has wide range. The concept of quality in transfusion medicine depends on how safe and efficacious blood, blood components, and plasma derived biological drugs, and all activities which can influence the quality are exactly monitored by quality assurance system. (5) The quality history can be shown by table 1.

-60's	Final control
-70's	Quality system
-80's	Quality Assurance
-90's	GMP development
2000's	Finding right quality standards

Table 1- Quality history

Quality Assurance covers all activities which can individually or collectively influence the quality of medicinal product. In other words the quality assurance system should ensure that all critical processes such as the purchase of raw materials, starting materials, selection of donors, collection of blood / plasma, production of plasma, storage, laboratory testing, dispatch and associated quality control measures, are specified in appropriate instructions and are performed in accordance with the principles of Good Manufacturing Practice and comply with the appropriate regulations.

Quality Assurance has to make sure that medicinal products are of the quality required for their intended use. It is important to know that quality should be the responsibility of all persons involved in manufacturing.

There should be a quality department that is independent of production and that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control units or in single individual or group, depending upon the size and structure of the organization.

Quality Assurance System responsibility

The Quality Assurance System for the manufacturing medicinal products should ensure that:

Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice and Good Laboratory practice.

Production and control operations are clearly specified and Good Manufacturing Practice adopted.

Managerial responsibilities are clearly specified.

Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.

All necessary controls on intermediate products and any other in process controls and validations are carried out.

The finished product is correctly processed and checked, according to the defined procedures.

Medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorization and any other regulations relevant to the production, control and release of medicinal products. By Food and Drug Organization in Iran Responsible Pharmacist is the Qualified Person who has to do this job.

Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life.
There is a procedure for Self Inspection and quality audit regularly check the effectiveness and applicability of the Quality Assurance System.

Good Manufacturing Practice

Good Manufacturing Practice guidelines are not series of instructions saying how to manufacture products. GMP does not say by which method the medicinal product has to be produced. But GMP has general principles that must be observed during producing medicinal products. (17, 18) Every company has to set up its own quality program and manufacturing process. (19) May be in different ways can fulfill GMP requirements. It is the responsibility of the company to implement the most effective and efficient quality process. Sometimes GMP is being referred as cGMP. (20,21) The letter "c" stands for "current", which means that manufacturer must employ technologies and systems which are up to date. (22) Good Manufacturing Practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization or product specification..
There are some other good practice systems such as Good laboratory Practice (GLP) for laboratories, and Good Clinical Practice (GCP) for hospitals and clinicians.

Main aim of GMP

The main aim of Good Manufacturing Practice is to minimize risks affecting the produced medicinal products and to give assurance that the risk of error is minimum.
We should always remember that those systems and equipments we were using two decades ago to prevent contamination, mix up, and errors may be less than adequate today standard.

GMP basic requirements

Good Manufacturing Practice is concerned with both production and quality control.
All manufacturing processes are clearly defined, systematically reviewed with notice to experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications.
Critical steps of manufacturing processes and significant changes to the process should be validated.

All necessary facilities for good manufacturing practice should be provided.
Instructions and procedures should be written in an instructional form in clear unambiguous language. All SOPs should have a similar format.
Operators should be trained to carry out procedures in a correct way.
Records should be made manually or by recording instruments, during manufacture which demonstrates that all steps required by the defined procedures and instructions were in fact taken.
The distribution of the products minimizes any risk to their quality.
Recall system should be available to any batch from sale to supply.
Complaints about marketed products have to be examined; the causes of quality defects have to be investigated and appropriate measures taken in respect of the defective products and to prevent recurrence.

Qualification

Qualification is the action proving that any equipment is working correctly and actually leads to expected results. (23) The word validation is sometimes widened to incorporate the concept of qualification. Instrument Qualification means checking an instrument for compliance an instrument with previously defined functional and performance specifications, (24,25) which includes:
Design Qualification (OQ) - The documented verification that the purposed design of the facilities, systems and equipment is suitable for the intended purpose.
Installation Qualification (IQ) - The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.
Operational Qualification (OQ) - The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.
Performance Qualification (PQ) - The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Validation

Validation is action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results. (26, 27) All virus inactivation and virus

removal methods must be validated. (28) Any validation project associated with new equipment, assays, processes, materials, operations or systems should be first discussed within the departments'validation/ quality team. The team should then assign project responsibility to members. All equipment installed in the laboratory must first be safety checked. Once installed IQ, OQ and PQ should be performed prior to any method validation being performed.

References

1. Slopecki A, Smith K, Moore S. The value of Good Manufacturing Practice to a blood service in managing the delivery of quality. Vox Sang. 2007; 92(3): 187-196.

2. Food and Drug Administration, HHS. Current good manufacturing practice for blood and blood components. Fed Regist. 2007; 72(164): 487765-801.

3. Mousavi Hosseini K, Pourmokhtar M, Dinarvand R Rezvan H, Jalili MA. Preparation of enriched immunoglobulin M and immunoglobulin A from human plasma. Medical Journal of the Islamic Republic of Iran. 2004;17(4): 315-318.

4. Nasiri S, Rezvan H, Mousavi Hosseini K, Roostaei MH. Preparation of highly purified S/D coagulation F VII and F IX concentrate from PPSB. Medical Journal of the Islamic Republic of Iran. 2001; 15(2): 103-108.

5. Sondag D, Salpeteur C. Quality assurance and blood transfusion. Acta Anaesthesiol Belg. 2002; 53(2): 125-127.

6. British Pharmacopoeia 2011. British Pharmacopoeia Commission Seceterial of the Medicine and Healthcare product Regulatory Agency. The Stationary Office (TSO). 2011. UK.

7. United States Pharmacopeia. 2011; Rockville, Maryland USA.

8. Mousavi Hosseini K, Dinarvand R, Pourmokhtar M, Rezvan H, Jalili MA.Pasteurization of IgM-enriched immunoglobulin. DARU. 2004; 12(1): 40-43.

9. Rezvan H, Nasiri S, Mousavi Hosseini K.Inactivation of polio-virus type-1 and HSV-1 in human coagulation factor VII concentrate by pasteurization. Archives of Iranian Medicine, 2001; 4(1): 10-13.

10. Rezvan H, Motallebi Z, Jalili M, Mousavi Hosseini K, Pourfatholah AA.Safety of blood and plasma derivatives: pathogen reducing technologies. Medical Journal of the Islamic Republic of Iran. 2006; 20(2): 86-92, 2006.

11. Gerlich WH, Glebe D. Methods for validation of hepatitis B virus inactivation. Dev Biol. 2004; 118: 113-122.

12. Dichtelmuller H, Rudnik D, Breuer B, Ganshirt KH, Validation of virus inactivation and removal for the manufacturing procedure of two immunoglobulin and a 5% serum protein solution treated with beta-propiolactone. Biologicals. 1993; 21(3): 259-268.

13. Pourmokhtar M, Dinarvand R, Mousavi Hosseini K, Rezvan H, Jalili MA. Solvent-detergent treatment of IgM-enriched immunoglobulin.DARU. 2003; 11(2): 47-51.

14. Mousavi Hosseini K, Rezvan H, Motallebi Z, Chabokpeh S, Mirbod V. Study of the heat treated human albumin stabilization by caprylate and acetyltryptophanate. Iranian Biomedical Journal, 2002; 6(4): 135-140.

15. Jennings TA, Scheer A, Emodi A, Puderbach L, King S, Norton T. Inspection qualification and operational qualification for a

vacuum freeze-dryer (Part I). jJ Pharm Sci Technol. 1996; 50(3): 180-188.
16. Jennings TA, Scheer A, Emodi A, Puderbach L, King S, Norton T. Inspection qualification and operational qualification for a vacuum freeze-dryer (Part II). J Pharm Sci Technol. 1996; 50(4): 205-212.
17. Edwards LD, Fletcher AJ, Fox AW, Stoiner PD. Principles and Practice of Pharmaceutical Medicine. 2007; John Wiley & sons Ltd. Chichester England.
18. The rules governing medicinal products in the European Union. European Commission. 2007; Luxembourg.
19. Tomic S, Filipovic Sucic A, Ilic Martinac A. Good manufacturing practice: the role of local manufacturers and competent authorities. Arh Hig Rada Toksikol. 2010; 61(4): 425-436.
20. Food and Drug Administration, HHS. Current good manufacturing practice and investigational new drugs intended for use in clinical trials. Fed Regist. 2008; 73(136): 40454-63.
21. Harolds J. What is now current good manufacturing practice for PET drugs? Clin Nucl Med. 2010; 35(5): 329.
22. Food and Drug Administration, HHS. Amendment to the current good manufacturing practice regulations for finished pharmaceuticals. Fed Regist. 2007; 72(232): 68064-70.
23. Kaminiski L, Degenhardt M, Ermer J, Feussner C, Hower-Fritzen H, Link P, Renger B, Tegtmeier M, Watzig H. Efficient and economic HPLC performance qualification. J Pharm Biomed Anal. 2010; 51(3): 557-564.
24. Buffaloe V. Process validation: achieving the operational qualification phase. Biomed Instrum Technol. 2004; 38(5): 384-386.
25. Rambhatla S, Tchessalov S, Pikal MJ. Heat and mass transfer scale up issues during freeze-drying: control and characterization of dryer differences via operational qualification tests. Pharm Sci Tech. 2006; 7(2): 39.
26. Parentral Drug Association. Validation of moist heat sterilization processes: cycle design, development, qualification and ongoing control. J Pharm Sci Technol. 2007; 61(1 Suppl): 2-51.
27. Soncin S, Lo Cicero V, Astori G, Soldati G, Gola M, Surder D, Moccetti T. A practical approach for the validation of sterility, endotoxin and potency testing of bone marrow mononuleated cells used in cardiac regeneration in compliance with good manufacturing practice. J Transl Med. 2009; 7: 78.
28. Rezvan H, Nasiri S, Mousavi Hosseini K, Golabi M. A study on the application and efficacy of solvent-detergent treatment in the process of purifying F VII from prothrombin complex.Medical Journal of the Islamic Republic of Iran. 2002; 16(3): 179-182.