Eucomed
Medical Technology

April 2011

Backgrounder: Medical device classification in the area of blood

1.0 Summary

This paper provides information on the legal frameworks covering medical devices (not *in-vitro* diagnostics) associated with the collection, processing, and storage of blood and blood components. Four product groups are presented along with the classification rules that have been applied according to the current Medical Devices legislation and guidance. The results of a Eucomed member survey show that, currently the majority of their products are classified as Class IIb. A section on donor safety and potential for solutions miss-connections is presented. Eucomed members, and other interested stakeholders are working together on a new connector design to ensure this risk is reduced. Finally, some points are listed on considerations for future application of classification rules regarding this group of products. Eucomed's position on classification for medical devices in the area of collection, processing and storage of blood and blood components is that the current rules in the Medical Devices Directive are appropriate to ensure safety. However, considering emerging medical device technologies, especially solutions, further clarification of the rules will enable better understanding and harmonization of the applicable rules.

2.0 Introduction

Eucomed's Blood Safety Group (BSG) brings together medical device suppliers involved in the design and/or oversight of manufacturing medical devices for collection, processing and storage of blood and blood components.

The Medical Devices Directive is currently going through a 'recast' process and classification issues will be reviewed as part of this process. Specifically, The European Commission's Medical Device Expert Group (MDEG) (1) has indicated that they will be reconsidering the classification of blood bags containing anticoagulant or other solutions. The current Borderline Manual (2) clearly states that the views expressed in the manual are not legally binding. Furthermore, a recent European Parliamentary question and answer (3) indicated that since 2005 the Commission has not taken any legally binding decision with regard to the reclassification of medical devices. A reclassification, which is a derogation from the classification criteria of Directive 93/42/EEC, requires an implementing measure to be adopted by the Commission in accordance with the relevant provisions of the directives. As a final point, the French blood service, Etablissement Français du Sang (EFS) have indicated that the French Regulatory Agency (AFSSAPs) is considering that all aphaeresis systems are made Class III. This has been triggered by a donor death in France in 2009.

This document aims to put together the rationale that suppliers have used to justify the classification for their current products according to the existing regulatory framework. To support this rationale, Eucomed has conducted a brief survey of its members active in the manufacturing of medical devices in the area of blood. From the responses received, it can be observed that the majority of products within the scope of this paper are in Class IIb. For a summary of the responses received, please see Annex 1.

Consideration is also given to providing some practical guidance for logical mechanisms in determining classification in this area that will lead to more clarity and transparency for customers (blood services), suppliers and regulators in the future.

Finally, an overview is provided on the project that the European Blood Alliance (EBA) and suppliers have undertaken to re-design connectors so that miss-connections (such as the one causing the donor death in France) will not occur in the future.

3.0 Definitions

See Annex 2.

4.0 Legal frameworks covering blood and blood components, blood bags, other bags and solutions associated with the collection, processing and storage of blood and blood components

Since the introduction of the Medical Devices Directive nearly 20 years ago, a whole new regulatory framework specifically addressing the safety and quality of blood collections, processing and storage has been developed and implemented. This framework reinforces aspects of the European Directorate for the Quality of Medicines & HealthCare (EDQM) guide to the preparation, use and quality assurance of blood components. In addition, the current version of the European Pharmacopoeia provides monographs for solutions and blood bags. Most recently, with the implementation of the Medical Devices Directive amendments in 2010, some Essential Requirements of the Machinery Directive 2006/42/EC might become relevant in the assessment of some of the products at stake (specifically Annex 1, point 1.5.4, connections are covered). Standardization of critical aspects of these products is achieved through specifications from standardization bodies such as the European Committee for Standardization (CEN), the International Electrical Committee (IEC) and the International Organization for Standardization (ISO). These legal frameworks and guidance documents lead to robust and extensive regulations covering the products discussed in this paper. Consideration must be given to **all these frameworks** in addressing issues concerning blood collections and treatments.

An outline of these legal frameworks and guidance is provided in **Figure 1** below.

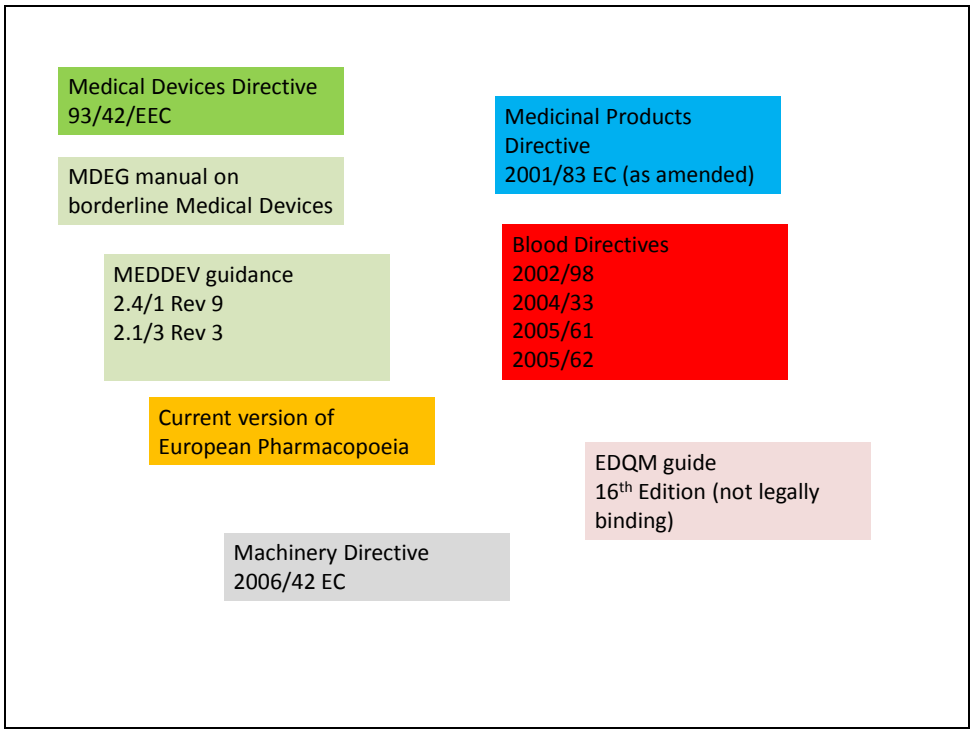

Figure 1: Legal frameworks and guidance documents

5.0 Medical Device Products in the area of blood

Four groups of medical devices are considered:

Group 1 – 'Plastic collapsible containers for human blood and blood components' without integrated solutions
Whole blood storage bags, RBC storage bags, Platelet storage bags, Plasma storage bags, WBC storage bags, Cord blood bags, Cryo-conservation bags, Transfer/Processing bags, Aphaeresis disposable sets

Group 2 – Stand-alone solutions
2.1. Potential for donor exposure: Anticoagulant Solutions, Saline Solutions
2.2. Potential for patient exposure: Anticoagulant Solutions, Saline Solutions, Platelet Additive Solutions, Red Blood Cell Additive Solutions, Washing Solutions and Freezing Solutions

Group 3 –'Plastic collapsible containers for human blood and blood components' with integrated solutions

Group 4 – Overall 'systems'
4.1. Whole blood processing systems
4.2. Aphaeresis systems

Outside the scope of this Paper
Pathogen Reduction Technology (PRT) and Pathogen Inactivation (PI) Technology
Stand alone equipment
Stand alone software

6.0 Classification rules applied to products in Group 1

Group 1 – 'Plastic collapsible containers for human blood and blood components' without integrated solutions

Whole blood storage bags, RBC storage bags, Platelet storage bags, Plasma storage bags, WBC storage bags, Cord blood bags, Cryo-conservation bags, Transfer/Processing bags, Aphaeresis disposable sets.

Classification of the individual components if CE marked separately	Rule	Class
Surgically invasive needle used for less than 60 minutes (transient use)	6	IIa
Surgically invasive needle, used for less than 30 days to channel blood into the extracorporeal blood circuit (short term use)	7	IIa
Non-invasive tubing to channel blood and other body liquids in the extracorporeal circuit and which might be intended to be connected to an active medical device in Class IIa	2	IIa
Non-invasive tubing with filters	3	IIa
Bags intended for short-term storage of whole blood, RBCs, platelets, plasma, WBCs for eventual administration	18	IIb
Bags intended for long-term storage	18	IIb
Blood Bag	18	IIb

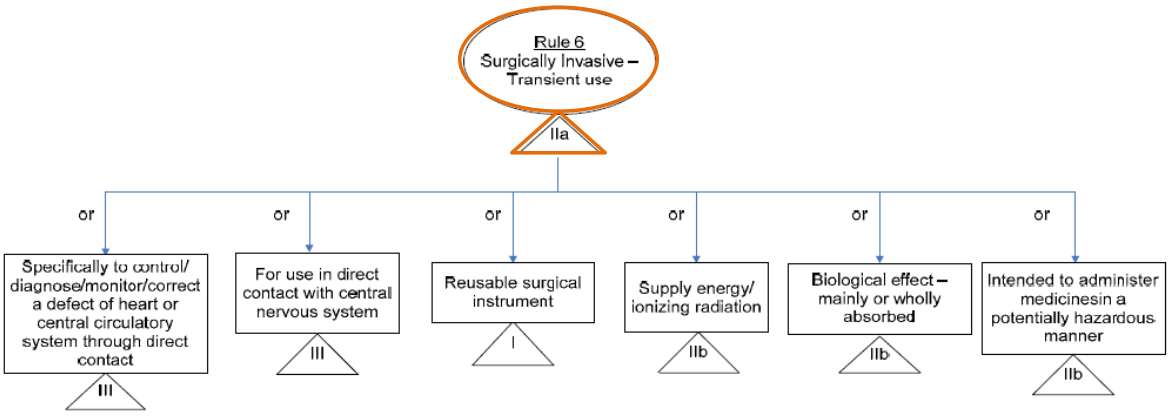

Figure 2: Rule 6 applicable to surgically invasive needles used for less than 60 minutes

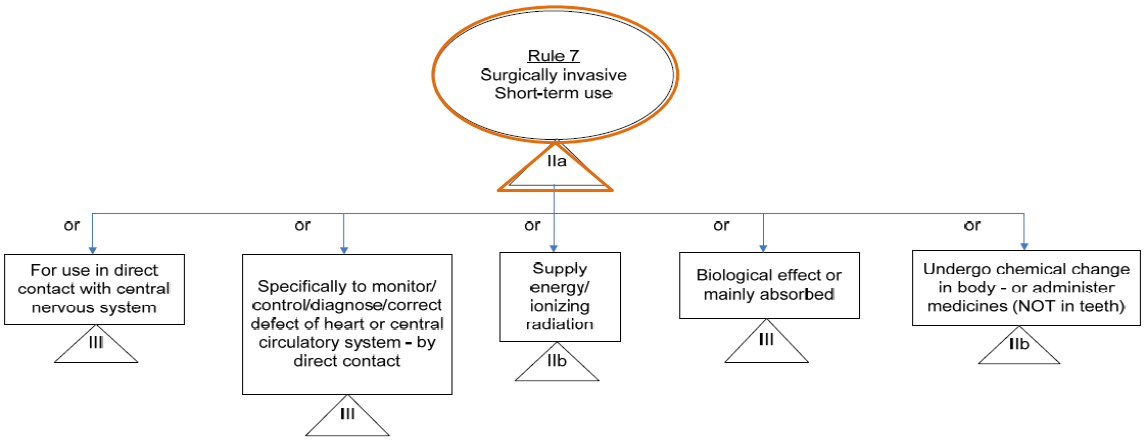

Figure 3: Rule 7 applicable to surgically invasive needles used for less than 30 days

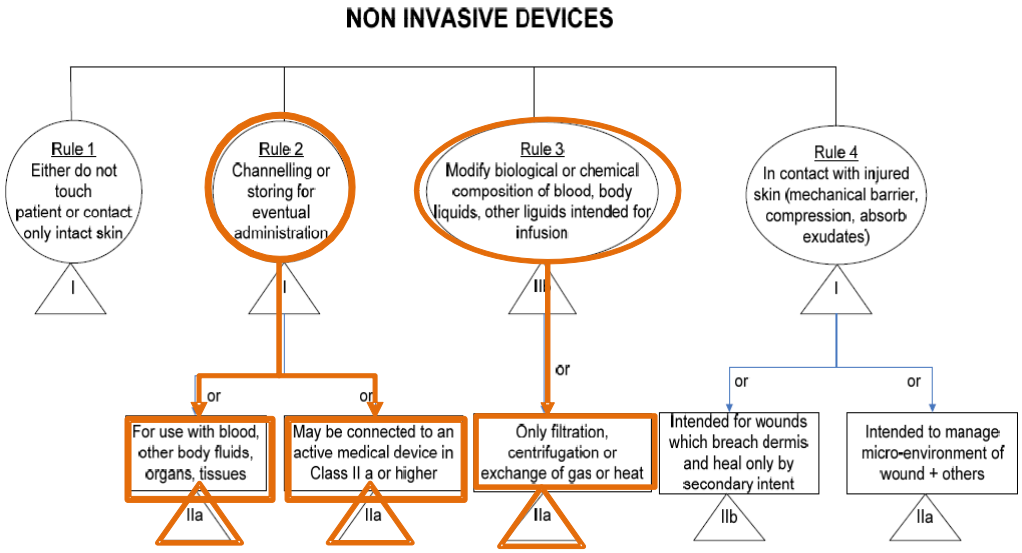

Figure 4: Rules 2 & 3 applicable to non-invasive tubing

The needle attached to all of the bags and sets is surgically invasive and sterile. It is intended for either transient (less than 60 minutes) or short-term use (less than 30 days). The applicable rule for the needle is Rule 6 (transient use) or Rule 7 (short-term use). In both cases the needle is **Class IIa.**

The disposable sets are not intended to be invasive but are intended, in some instances of use to be connected to an active device. Under Rule 2, whether the selection is for use with blood or other body fluids, or for use with an active medical device in Class IIa or higher, the classification is **Class IIa**.

Rule 3 is considered to apply to non-invasive tubing equipped with filters which under Rule 3 are for filtration of blood and are **Class IIa**.

From the reading of these rules, it can be derived that sets are generally in Class IIa, however if they are part of a CE marked device which includes as a component a blood bag, then Rule 18 prevails and the set will therefore be **Class IIb.**

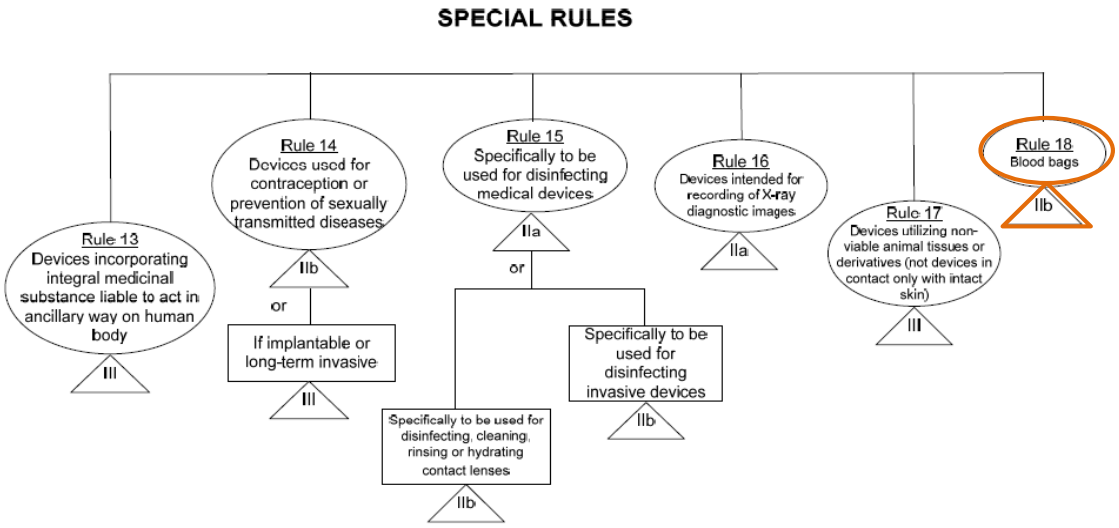

Figure 5: Rule 18 applicable to Blood Bags on Set

7.0 Classification rules applied to products in Group 2

Group 2 – Stand-alone solutions

2.1 Potential for donor exposure: Anticoagulant Solutions, Saline Solutions
2.2 Potential for patient exposure: Anticoagulant Solutions, Saline Solutions, Platelet Additive Solutions, Red Blood Cell Additive Solutions, Washing Solutions and Freezing Solutions

Most of these solutions are considered as devices in their own right.

Rule 3 is applied to these solutions because they modify the biological or chemical composition of blood intended for infusion.

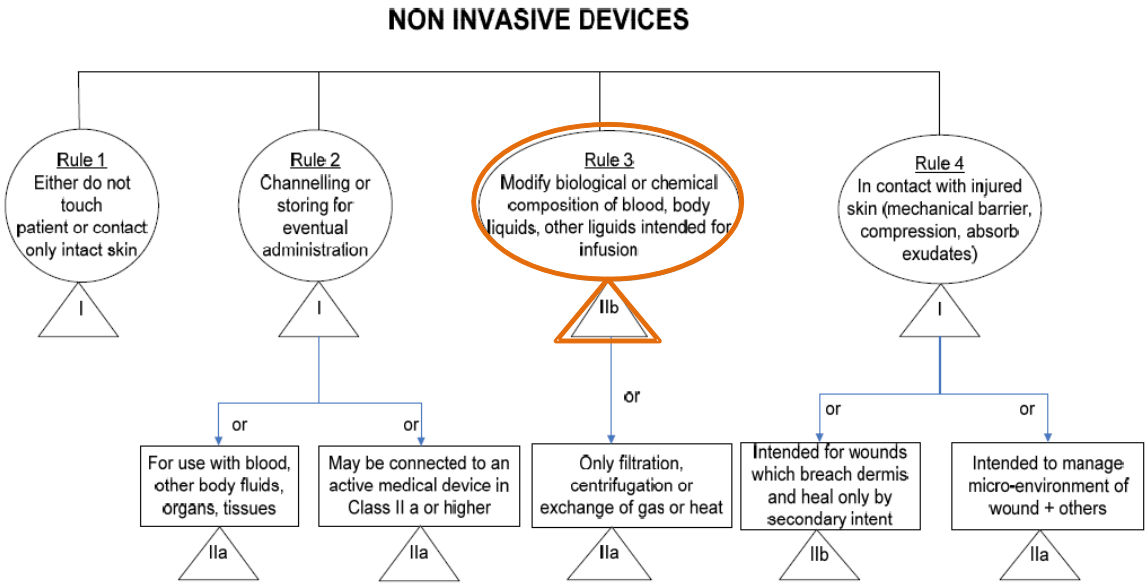

Figure 6: Rule 3 applicable to stand-alone solutions

All solutions currently used in the collection, processing and storage of blood and blood components are **specifically intended for use outside the human body** and **not for the treatment of a disease** within the human body. None of these solutions are used **with a view** to modifying physiological functions by exerting a pharmacological, immunological or metabolic action within the human body.

Annex 3 provides tables of examples of the chemical compositions of these solutions. Most of the listed substances are not considered as active ingredients of any medicinal product but rather as excipients. To date the majority of these solutions have not fallen under Rule 13.

The primary action of the constituents of the solutions is not intended to be on the human body, however, these solutions may indirectly have a secondary effect when the blood products are collected from donors and transfused to patients. The concentrations in which these solutions are used are calculated and controlled in order not to exert any effect on the human body.

Blood products and components are regulated by Blood Directive 2002/98/EC. The potential effect of these solutions is therefore assessed as a whole along with the blood product and/or component. It is therefore not necessary to assess the effect on the body of these individual solutions under the Medical Devices Directive.

The only exception to this latter point, is for anticoagulant solutions where the donor may be exposed and thus for future discussions on legislation in the area of blood, consideration should be given specifically to donors and donor safety.

If new substances are used in the future, then the applicability of Rule 13 should be considered on a case by case basis.

- ## Anticoagulant Solutions

The mode of action of anticoagulant solutions is to bind calcium thus preventing the clotting cascade and keeping the blood freely circulating in the extracorporeal set.

The binding of calcium modifies the chemical composition of the blood which is intended for infusion. This is only applicable to those anticoagulants where there is a claim associated with blood collection and blood processing.

- ## Platelet Additive Solutions

These solutions modify the chemical composition of the blood by acting as a plasma extender.

The additive solution is intended to maintain the pH and glucose levels of the platelets and provide a medium to allow platelet storage for 5-7 days (depending on local regulations). It maintains the chemical composition of platelets intended for infusion.

- ## Red Blood Cell Additive Solutions

These solutions are intended to maintain the pH and glucose levels of the Red Blood Cells (RBCs) and reduce lysis thereby preventing their degradation up to 42 days in refrigerated storage. It maintains the chemical composition of RBCs intended for infusion.

- ## Washing Solutions

The washing solutions are intended to reduce the amount of substances in blood components regarded as harmful for the patients' health (e.g. cold agglutinin antibodies, cytokines, freezing agents, etc.).

- ## Freezing Solutions

The freezing solutions are intended to prevent storage lesions to blood cells during the freezing process and deep freezing storage. The freezing of blood components is intended to build up a stock

of blood products with special properties like rare blood groups, etc. They contain glycerol or other chemicals that replace water and thereby modify the chemical composition of blood.

8.0 Classification of products in Group 3

Group 3 - 'Plastic collapsible containers for human blood and blood components' with integrated solutions

The same rules apply as for Groups 1 and 2, however for anticoagulant solutions integrated into the disposable sets Rule 18 is applicable because Rule 18 states that blood bags containing or coated with anticoagulant are Class IIb. (6).

9.0 Classification of products in Group 4

Group 4 – Overall 'systems'

4.1. Whole blood processing systems
4.2. Aphaeresis systems

For these two systems there is a significant difference in the operation and risk associated with their use. Under the Medical Devices Directive, extensive analysis of these risk factors is evaluated according to the Essential Requirements and relevant standards. Appropriate assessments according to the principles of Good Automated Manufacturing Principles (GAMP) are taken into consideration.

These systems generally consist of:

Equipment
Software
Plastic Disposable sets
Solutions

The classification of the plastic disposable sets and solutions has already been covered by the classification rules set out for groups 1, 2 and 3.

Regarding the equipment, this is considered as an 'active' device and Rule 11 is the most applicable:

Classification of equipment if CE marked separately	Rule	Class
All active devices intended to administer, and or remove medicines, body liquids or other substances to or from the body are in Class IIa, unless this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are in Class IIb	11	IIb

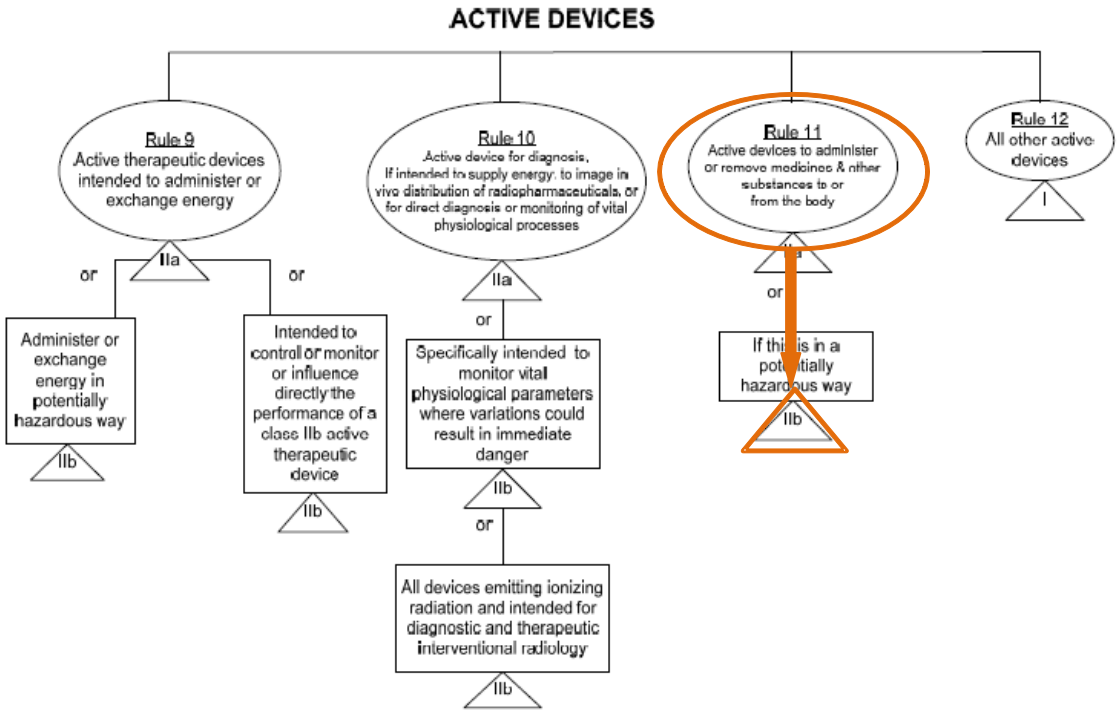

Figure 7: Rule 11 applicable to equipment

The software follows the overall classification of the system which is **Class IIb.**

10.0 Donor safety

A donor died in France in 2009 due to the miss-connection of ACD-A, instead of saline, to a plasmapheresis disposable set. Following this event, an immediate, temporary modification was made to designs of French disposable sets and solutions to meet the French regulatory requirements. However, the modification is not ideal because miss-connections between PAS (Platelet Additive Solutions) and RAS (Red Blood Cell Additive Solutions) can still occur. Suppliers, together with the European Blood Alliance, EFS and AFSSAPs have been collaborating on the development of a new connector design to prevent this problem in the future. Several meetings have taken place including a meeting with the European Commission in December 2010. ISO (through ISO TC210 JWG4) have been requested to consider, including an aphaeresis module, to set specifications for a new connector.

Since the occurrence of this tragic fatality, other similar incidents have been reported in France as in other countries retrospectively and also prospectively (i.e. after the French adverse reaction). From the French experience, it could be deduced that the frequency of such human errors could be as high as 1/10.000 plasmapheresis procedures. And up to now, although no report on frequency of adverse reactions in donors and patients has been made available, misconnections of medical devices have been acknowledged as a potential cause of adverse reactions both in donors and in patients.

11.0 Future application of classification rules for medical devices in the area of blood

When determining the classification of medical devices in the area of blood, together with Notified Bodies, a case by case approach must be applied and the following considerations should be made:

- Intended use of the device
- Mode of action of the device
- Action inside or outside the human body
- Inclusion of active/non-active ingredients
- Other legal frameworks
- Donor and patient risk benefit

References

(1) Borderline and Classification Medical Device Expert Group (MDEG)
http://ec.europa.eu/consumers/sectors/medical-devices/documents/borderline/index_en.htm
(2) Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices, Version 1.8 of 01-2011, Appendix 9, page 40, Para 8.4
(3) Parliamentary questions, Answer given by Mr Dalli on behalf of the Commission, 18 January 2011.
http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=P-2010-011041&language=EN
(4) COMMISSION DIRECTIVE 2004/33/EC of 22 March 2004 implementing Blood Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components
(5) European Pharmacopoeia 6.0
(6) MEDDEV 2.4/1 Rev. 9 June 2010, Classification of medical devices, Guidelines relating to the application of the Council Directive 93/42/EEC on Medical Devices

Annex 1

Current classification of products

Eucomed has conducted a brief survey of its members active in the manufacturing of medical devices in the area of blood. The survey was conducted during the month of February 2011 and responses were received from 5 members[1] regarding the classification of their current product portfolios.

Below is a brief summary of the response:

Member	Products/Groups of products
1	6
2	14
3	18
4	6
5	6

All products/groups of products of members 1-4, regardless of the Notified Body used or whether or not the product contains a solution (integral part of device or not), are **Class IIb**. Concerning Member 5, 1 group of products out of 6 products have been classified as **Class III**.

Please note: for further detailed information on the analysis of classification for specific products, please contact Eucomed.

[1] The Eucomed members collectively represent the majority share of the medical device suppliers to the blood banking sector.

Annex 2

Definitions

Aphaeresis: a method of obtaining one or more blood components by machine processing of whole blood in which the residual components of the blood are returned to the donor during or at the end of the process. (4)

Anticoagulant and Preservative Solutions for human blood are sterile and pyrogen-free solutions prepared with water for injections, filtered, distributed in the final containers and sterilized. (5)

Blood bags – Sterile plastic containers for human blood and blood components. Plastic containers for the collection, storage, processing and administration of blood and its components are manufactured from one or more polymers, if necessary with additives. (5)

Disposable sets – Sets for the transfusion of blood and blood components. Sets for the transfusion of blood and blood components consist principally of plastic tubing assembly to which are fitted the parts necessary to enable the set to be used for transfusion in the appropriate manner. (5)

Whole blood processing systems: a method of obtaining one or more blood components by machine processing of whole blood in which the residual components of the blood are not returned to the donor during or at the end of the process.

Annex 3

Examples of chemical compositions of solutions

Platelet additive solution (PAS) names and formulations are as described in the table below. See Appendix A for an explanation on the use of platelet additive solutions terminology.

Table of Platelet Additive Solutions

New Name	Citrate	Phosphate	Acetate	Magnesium	Potassium	Gluconate	Glucose	Alternate Names	Previous *ISBT 128* Name
PAS	NS	NS	NS	NS	NS	NS	NS		Not named
PAS-A	X	X			X			PAS (1)	Not named
PAS-B	X		X					PAS II, PAS-2, SSP, T-Sol	PASII
PAS-C	X	X	X					PAS III, PAS-3, Intersol	PASIII
PAS-D	X		X	X	X	X		Composol PS	PAS IIIMgK (note, Composol PS should not have been called PASIIIMgK)
PAS-E	X	X	X	X	X			PAS IIIM, SSP+	Not named
PAS-F			X	X	X	X		PlasmaLyte A, Isoplate	Not named
PAS-G	X	X	X	X	X		X		Not named

Source: Ringwald, J., Zimmerman, R., and Eckstein, R: The New Generation of Platelet Additive Solution for Storage at 22°C: Development and Current Experience, Transfusion Medicine Reviews, Vol 20, No 2 (April), 2006: pp 158-164.

Anticoagulant-Preservative Solutions (mg in 63 mL) for Collection*

Variable	CPD	CP2D	CPDA-1	ACD-A	ACD-B	4% Citrate
pH	5.3-5.9	5.3-5.9	5.3-5.9	4.5-5.5	4.5-5.5	6.4-7.5
Ratio (mL solution to blood)	1.4:10	1.4:10	1.4:10	1.5:10	2.5:10	0.625:10
FDA-approved shelf life (days)	21	21	35	Automated collection of RBCs, platelets, and FFP		Automated collection of plasma and for plasma exchange
Content						
Sodium citrate	1660	1660	1660	1386	832	2520
Citric acid	206	206	206	504	504	As needed for pH adjustment
Dextrose	1610	3220	2010	1599	956	
Monobasic sodium phosphate	140	140	140			
Adenine	0	0	17.3			

*For collection of 450 mL whole blood (or automated collections).
CPD = citrate-phosphate-dextrose; CP2D = citrate-phosphate-dextrose-dextrose; CPDA-1 = citrate-phosphate-dextrose-adenine; ACD-A = acid-citrate-dextrose (formula A); ACD-B = acid-citrate-dextrose (formula B); FDA = Food and Drug Administration; FFP = Fresh Frozen Plasma.

16th edition of the AABB Standards

Content of Additive Solutions (mg/100 mL)

Constituent	AS-1 (Adsol)	AS-3 (Nutricel)	AS-5 (Optisol)
Dextrose	2200	1100	900
Adenine	27	30	30
Monobasic sodium phosphate	0	276	0
Mannitol	750	0	525
Sodium chloride	900	410	877
Sodium citrate	0	588	0
Citric acid	0	42	0

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