Blood Transfusion Association

PROPOSED CLASSIFICATION OF BLOOD BAG SETS

MEDDEV 2.4/1 rev. 9, issued by the Commission as part of the implementation of the Medical Devices Directive (MDD), includes guidance for the application of the classification rules for medical devices including blood bag sets: "*Blood bags **(including those containing or coated with an anticoagulant)** [are in Class IIb]. Where blood bags have a function greater than for storing purposes and include systems for preservation other than anti-coagulants then other rules (e.g. rule 13) may apply*".

Although the device's risk profile and its intended purpose have not changed over the past two decades, the recent European Commission's draft guidance document on the classification rules of the Medical Devices Regulation (MDR) stipulates that according to rule 14 "*all devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the devices, are classified as class III*".

The draft guidance specifies that "*blood bags incorporating Heparin as an anticoagulant*" would be class III. This proposed up-classification of blood bag sets under the new MDR from class IIb to class III is due to misalignment on the interpretation of the changes in the classification rules, which poses a challenge from a public health perspective.

The use of blood bag sets for the collection of donor blood is strictly regulated. In addition to the European legislation on Medical Devices, blood bag sets are subject to ISO standards and the European Pharmacopeia and are also regulated by three EU Blood Directives[1] which define quality and safety standards for the collection, testing, processing, storage and distribution of human blood components. From a safety point of view there is no reason to up-classify blood bag sets to class III and special rules under the MDR are not applicable to the intended use of blood bag sets.

Furthermore, the combination of classification rules, as well as their interpretation, makes classification of blood bag sets unclear. For instance, rule 2 of the MDR classification rules state that blood bag sets that are intended for the channelling or storing of blood or blood components should be classified as Class IIb devices. This is also applicable to blood bag sets which include an anticoagulant and/or preservative solution without a medicinal function, as is the case for 90% of blood bag sets:

Rule 2

All non-invasive devices intended for channelling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa:

- *if they may be connected to a class IIa, class IIb or class III active device; or*
- *if they are intended for use for channelling or storing blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags; **blood bags are classified as class IIb**. In all other cases, such devices are classified as class I.*

[11] Directive 2002/98/EC (European Blood Directive), Directive 2004/33/EC on the technical requirements for blood and blood donation, and Directive 2005/61/EC on the traceability requirements and notification responsibilities in case of serious adverse reactions and events

Blood bag sets are also surgically invasive devices intended for transient use of less than 60 minutes and therefore potentially subject to rule 6, which classifies them as Class IIa devices. The MDR classification rules further include a specific rule (rule 14) on devices incorporating, as an integral part, an ancillary medicinal product, and medicinal products derived from human blood or blood plasma. Rule 14 would only apply for blood bags incorporating substances with a function greater than for storing purposes (or with medicinal function as defined by Directive 2001/83/EC).

Rule 14

"All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the devices, are classified as class III."

Based on rule 14, the European Commission's draft guidance document on Classification of Medical Devices regulation 2017/745 includes example 10 (Blood bags incorporating Heparin as an anticoagulant) to show that blood bag sets with an anticoagulant should be considered as Class III. Heparin fulfils the criteria of being a medicinal product (see below), and as such, blood bags containing heparin should be classified as Class III (or blood bags incorporating substances with a function greater than for storing purposes should be classified as Class III).

Heparin is very different from the CPD anticoagulant solutions being typically used in standard blood bag systems across Europe. Citrate as a substance is NOT to be considered as medicinal product per Directive 2001/83/EC (point 2 and point 10 of Article 1) as described below:

a. Citrate is not presented (nor used) as having properties of a therapeutic effect in human beings, and it is not intended for direct intravenous administration to human beings nor to be used in human beings with a view to make a medical diagnosis or affect normal physiological functions in the human body, as defined in point 2 of Article 1 of Directive 2001/83/EC, or including a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive.
b. Heparin is a long-lasting anticoagulant and is used for systemic anticoagulation. Citrate on the other hand has a very short half-life (37min only)[1] and is therefore not use as a systemic anticoagulation. There is no intent for citrate based anticoagulants to act on the human body in vivo as the **residual anticoagulant and/or preservative** solutions transfused into patient does not have any pharmacological, metabolic or immunological action in human beings. They are designed for ex vivo anticoagulation.
c. The citrate-based solutions and/or preservative solutions can be considered as 'excipients'/'starting materials' or 'processing agents' used ONLY in the preparation of blood components with the principal intended purpose to ensure optimal storage conditions for the blood and blood components. The blood bag sets with citrate-based solutions and/or preservative solutions have no function greater than for storing purposes.
d. The mode of action is as follows: The citrate moiety in CPD prevents coagulation through reversible chelation of circulating divalent cations in whole blood, including calcium and magnesium, and sequestration of these ions from their normal physiological function in the coagulation cascade. The dextrose component of the solution is required to support

red blood cell and platelet metabolism during blood storage. Citrate is a normal molecule in the body—being an obligate step in the Krebs Cycle.

The European Commission's guidance should clarify this distinction in order to avoid diverging interpretation among Member States. In light of the above, blood bag sets with and without anticoagulants and/or preservative solutions which are not considered as medicinal product as defined by Directive 2001/83/EC should remain in Class IIb.

[1] Kramer L, Bauer E, Joukhadar C, et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. Crit Care Med. 2003; 31:2450–5.