

POSITION PAPER

ON THE CLASSIFICATION OF BLOOD BAG SETS WITH CITRATE-BASED ANTICOAGULANT SOLUTIONS

in response to the publication of the MDCG classification guidance document

24 December 2021

On 4 October, the MDCG guidance document on classification of medical devices (MDCG 2021-24) was published to define classification rules under the new Medical Device Regulation (MDR). In BTA's view, the final guidance document still leaves room for interpretation related to the wording of the definitions and examples of Rule 2 and Rule 14 and whether blood bag sets containing citrate-based anticoagulant solutions would be classified as Class IIb or Class III medical devices. The purpose of this position paper is to demonstrate why citrate based anticoagulant solutions should not be understood as medicinal products and consequently why blood bag sets incorporating these anticoagulant solutions should stay as Class IIb medical devices, in line with public health needs.

Background and problem context of blood bag sets containing citrate-based anticoagulant solutions

The vast majority of blood bag sets used on the EU market incorporate an anticoagulant solution integrated during the manufacturing process. This is considered as a "processing agent", designed only to ensure optimal storage conditions for the blood and blood components as well as to facilitate cell viability and the function of blood components. Almost all Blood bag sets sold in the EU contain a citrate-based anticoagulant solution with the following compounds: citrate, phosphate, and dextrose (CPD), sometimes with added adenine (CPDA-1). The citrate moiety prevents the coagulation and ensures the free circulation of the blood in the extracorporeal set. Without an anticoagulant solution, blood bag sets cannot be used for whole blood collection and processing.

Under the Medical Device Directive (MDD), blood bag sets incorporating citrate-based anticoagulant solutions have been categorised as Class IIb medical devices. However, the recently adopted MDCG guidance document on the classification of medical devices under the Medical Device Regulation (MDR) 2017/745 classifies the use of blood bag sets in two separate rules with specific examples:

Rule 2	Example
All non-invasive devices intended for channeling 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 channeling	



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.	Blood bags without a substance which, if used separately, can be considered to be a medicinal product

Rule 14	Example
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.	Blood bags incorporating heparin or other substances as anticoagulant agents which, if used separately, can be considered to be a medicinal product

What is more, the document states in the ‘General explanation of the rules’ paragraph that the meaning and application of ‘*a substance which, if used separately, can be considered to be a medicinal product*’ and of ‘*has an action ancillary to that of the device*’ will be clarified in the separate section of the MDCG Guidance document on the borderline between medical devices and medicinal products. However, this clarification is yet to be determined by the respective body (Working Group 6) within the MDCG.

The current wording of Rules 2 and 14 as well as their corresponding examples do not sufficiently clarify the classification of blood bag sets. The classification document specifically mentions “Heparin” as an example for an anticoagulant substance used in blood bags. However, heparin – due to its intrinsic properties – is not used for anticoagulation during storage of whole blood or blood components in blood bag systems. In fact, the vast majority of blood bags in the EU incorporate citrate-based solutions, as these solutions allow for the safe transfusion of blood products due to their low citrate concentration and short half-life (see explanation below). While the classification guidance singles out heparin as an example for a medicinal product in blood bags and a reason for a Class III designation, this may inadvertently suggest that citrate-based solutions should also fall under the same category.

For a substance to constitute a medicinal product, it needs to meet one or both criteria of the corresponding text of the Pharmaceutical Legislation (Article 1 (2) of the Directive 2001/83/EC):

As per the definition of Article 1(2) of Directive 2001/83/EC, a medicinal substance:
“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.”

This position paper explains in detail why citrate-based anticoagulant solutions do not fulfil either of the main criteria of the medicinal product definition above, as well as how a potential upclassification could have dire unintended consequences going against the spirit of the EU Treaties.

Citrate-based solutions in blood bag sets have no properties for treating or preventing disease in patients

The sole function and principal intended purpose of citrate-based solutions in the blood bag sets is to ensure optimal storage conditions for the blood and blood components. Sodium citrate prevents the clotting cascade and ensures the blood's free circulation in the extracorporeal blood bag set. While some of the citrate-based solution may get transfused into patients' bloodstream through the standard transfusion processes, it is not done with a "view" (intended use) to have properties for treating or preventing diseases in human beings (nor are they used to make a medical diagnosis). As such, the use and intended action of citrate-based solution do not meet the definition of a medicinal product according to Paragraph a) of Article 1(2) of Directive 2001/83/EC.

Furthermore, the European Medicines Agency (EMA) publishes information on all authorised medicines authorized in the European Economic Area as part of the Article 57 database,ⁱ according to which CPD/CPDA-1 is not registered as a medicinal product on its own on the European market.ⁱⁱ The database shows citric acid or citrate salts used intravenously or as parenteral products containing citrate and these substances are not indicated for anticoagulation. Anticoagulants should only be considered as medicinal products if placed on the market in their own right for administration to a patient. This is not the case for neither CPD nor CPDA-1, which is an additional argument as to why these anticoagulant solutions cannot be categorised as medicinal substances.

A detailed breakdown of the ingredients, purpose and intended effects of both CPD and CPDA-1 can be found in Annex I below.

Citrate-based solutions do not restore, correct or modify physiological functions or make medical diagnosis

Based on Annex I, the primary mode of action of citrate-based anticoagulant solutions is not intended to be on the human body, although these solutions – as mentioned above – may indirectly have a secondary effect when the blood products are transfused to patients.

Blood bags usually contain citrate-based anticoagulant solutions for the collection of whole blood in a ratio of 1 part citrate-based anticoagulant solutions to 7 parts whole blood. Based on a maximum collection of 500ml of whole blood, this means a total of 70 ml citrate-based anticoagulant solutions included in the blood bag.ⁱⁱⁱ The citrate infusion in the body lowers ionized calcium and magnesium concentrations. According to Bolan et al^{iv}, ionized calcium and magnesium will only be minimally affected with an infusion rate of 0.02 mg/kg/min (red cell concentrates) and only during a 90 min period. Also, for the infusion of plasma (0.6 mg/kg/min for 30 min), or platelets (0.6 or 0.4 mg/kg/min for 30 min), the effects on ionized calcium and magnesium will be borderline and rapidly restored.

Apart from – or rather because of – the minimal concentration of citrate when using citrate-based anticoagulant solutions, these substances have a very short half-life (approximately 37 minutes), effectively meaning that by the end of a typical 2 hours long transfusion process most of the citrate will have been dispersed from the human body.^v As such, the concentrations in which citrate-based anticoagulant solutions are calculated and controlled, even with residual citrate, do not have an anticoagulant effect within the human body. This fact alone renders these substances inadequate to restore, correct or modify physiological functions by exerting a pharmacological, immunological or

metabolic action ancillary to the device within the human body. This is a key difference between heparin and citrate-based anticoagulant solutions that is not reflected properly in the example of Rule 14.

Therefore, the use and intended action of citrate-based anticoagulant solutions also do not meet the definition of a medicinal product according to Paragraph b) of Article 1(2) of Directive 2001/83/EC.

Annex II provides a detailed breakdown of the calculations on the minimal concentration of citrate during transfusion.

Up-classifying blood bags containing citrate-based anticoagulant solutions to class III would have unintended negative public health and internal market consequences

A potential upclassification of blood bag sets to Class III would have two major negative unintended consequences.

First, it would negatively affect public health in the EU. Blood bag sets have demonstrated a high level of safety for decades, and their use for the collection and transfusion of blood is strictly regulated. Whole blood collection devices ensure a unidirectional blood flow to the collection bag, as such, donors are not exposed to the anticoagulant solution at any point during the collection process. In this regard, the upclassification of blood bag sets to Class III does not seem to provide additional justification for the protection of the donor. Coupled with the low concentration and half-life of citrate in the human body after transfusion (see above), it is clear that patient safety has long been guaranteed with the use of blood bag sets containing citrate-based anticoagulant solutions under Class IIb.

In addition, it should be noted that the Blood, Tissues and Cells Legislation (Directives 2002/98/EC and 2004/33/EC) regulates the processing of labile blood components and includes very strict patient safety clauses that pertains to the use of blood bag sets. As the European Commission has already demonstrated in its evaluation of the directives in 2019^{vi}, they have managed to ensure patient safety over the past two decades.

Hundreds of millions of blood components containing citrate-based anticoagulant processed out of whole blood collection systems have been safely transfused during the past several decades. Changing the classification of blood bag sets from Class IIb to Class III because of the use of citrate-based solutions does not justify public health needs, does not increase the products' safety profile, and would not benefit neither donors nor patients. On the contrary, due to the additional regulatory requirements, a potential upclassification would actually hamper the safe supply of blood products in the coming years, a key issue area identified in the 2019 Commission evaluation, threatening public health in the EU. This would be contrary to the spirit of the Medical Devices Regulation (MDR) that upholds Article 168 of the Treaty of the Functioning of the European Union (TFEU) on the protection of public health.

Ironically, up-classifying blood bag sets containing citrate-based anticoagulant solutions to Class III despite their demonstrated safety profile would actually harm public health needs and weaken

achieving a harmonised EU internal market without actually achieving any added value to patient safety and at the same time going against the spirit of the EU Treaties.

CONCLUSION: clarification is required in the upcoming guidance document on borderline between medical devices and medicinal products

In our view, the goal of MDCG guidance documents is to provide an adequate level of specificity and clear guidance to authorities for the classification and use of medical devices. However, the recently published classification guidance document still leaves room for interpretation as to how blood bag sets containing citrate-based anticoagulant solutions should be classified.

Without proper clarification, manufacturers would have to individually negotiate and agree on the classification of their devices with their respective Competent Authorities prior to CE marking. It is estimated that this clarification process would take an additional 8-12 months which cause a serious delay to the certification of blood bag sets and would render keeping key regulatory deadlines untenable (e.g. expiry of MDD certificates). This would create a serious supply issue of blood bag sets in the EU and risk the proper functioning of public health systems. Additionally, the lack of clear EU-level guidance would potentially also lead to a situation where essentially the same devices would be put on the EU market as Class IIb products in certain Member States and as Class III in others. This would also mean that the same products would be available sooner in certain regions but only later in other countries. Therefore, lack of clarification would not only create a more disharmonised blood bag set market in the EU but would also exacerbate unequal patient access and weaken EU public health.

For this reason, it is of paramount importance that the upcoming *MDCG guidance on borderline between medical devices and medicinal products* clarifies the meaning behind ‘a substance which, if used separately, can be considered to be a medicinal product’ and ‘has an action ancillary to that of the device’ to the greatest extent to allow for the harmonised and proper classification of blood bag sets containing citrate-based anticoagulant solutions.

Taking into account the above argumentation that citrate-based solutions should not be understood as a medicinal product, the BTA would furthermore suggest that the upcoming guidance document should use CPD and CPDA-1 as specific examples in the case of blood bag sets for falling out of the scope of the definition of Rule 14 – on the same account that heparin was used as a specific example for a substance that falls within that same scope. CPD and CPDA-1 are the most frequently used anticoagulant compounds in blood bags in the EU. This should warrant these solutions to be mentioned as specific examples for compounds that cannot be considered as a medicinal product.

In conclusion, the Blood Transfusion Association recommends that the upcoming MDCG guidance on borderline between medical devices and medicinal products should:

- 1. Clarify the definition of Rule 14 to the greatest degree, and**
- 2. Mention CPD and CPDA-1 as specific examples of substances that do not fall under the Rule 14 definition of a medicinal product.**

We believe that proper clarity and correct classification of blood bag sets containing citrate-based anticoagulant solutions can still be achieved through the upcoming borderline guidance document.

BTA remains at the disposal of Working Group 6 of the MDCG and any other relevant stakeholders in case further information or expert input needed on these matters.

Annex I

Specifications of CPDA-1 and CPD in terms of ingredients, purpose and intended effects on the human body.

Product	Ingredient	Purpose	Is the ingredient intended to affect the structure and function of the body?
CPDA-1	Water for Injection, EP	To solubilize the other ingredients	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Sodium Citrate Dihydrate EP	The citrate moiety in CPDA-1 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. Also serves as a pH buffer and osmotic stabilizer in the collected blood product	No, the intended purpose is to maintain anticoagulation and to maintain blood component in active state. The ingredient is naturally occurring in the blood.
	Citric Acid Anhydrate EP	pH buffer; membrane and osmotic stabilizer in the collected blood product	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Monobasic Sodium Phosphate monohydrate, EP	Building block of ATP; helps maintain phosphate gradient lost during storage of the blood product; buffer in the collected blood product	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Dextrose Anhydrous EP	Supports red blood cell and platelet metabolism via ATP generation by glycolysis in the collected blood product	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.



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	Adenine is not purchased to EP but is tested and meets EP	Building block of ATP; replaces adenine nucleotides broken during storage of the blood product; extends the shelf-life of red cells to 42 days.	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
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Product	Ingredient	Purpose	Is the ingredient intended to affect the structure and function of the body?
CPD	Water for Injection	To solubilize the other ingredients	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Sodium Citrate Dihydrate, EP	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. Also serves as a pH buffer and osmotic stabilizer in the collected blood product	No, intended purpose is to maintain anticoagulation and to maintain blood component in active state. The ingredient is naturally occurring in the blood.
	Citric Acid Anhydrate, EP	pH buffer; membrane and osmotic stabilizer in the collected blood product	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Dextrose Monohydrate, EP	Supports red blood cell and platelet metabolism via ATP generation by glycolysis in the collected blood product	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.
	Monobasic Sodium Phosphate monohydrate, EP	Building block of ATP; helps maintain phosphate gradient lost during storage of the blood product; pH buffer	No, the intended purpose is to maintain blood component in active state during storage. The ingredient is naturally occurring in the blood.

Annex II

Calculation of citrate concentration in the human body during transfusion of a blood product^{vii}

- Typically, 70ml CPD anticoagulant solution in a blood bag system is diluted in 500 mL (1 part CPD per 7 parts blood). Some systems are for collection of 450 mL, these contain 63 mL of CPD.
- As a result the citrate concentration in plasma of a whole blood collection is about 22 mM. After processing, a Red Cell Concentrate contains between 10 and 40 mL plasma (lowest for buffy coat depleted, which is the standard in Europe, highest for PRP removed which is hardly not use in Europe). We took worst case: 40 ml in a circulation of 3 litre, based on the calculation that an adult has a typical whole blood volume of 5-6 l with an average Htc 42%.
- Calculation RBC transfusion: with infusion of 1 unit of RCC (about 300 mL, with 40 mL plasma of 22 mM citrate) you infuse 170 mg citrate. If all citrate remains in the circulation this would give an increase of 0.3 mM in the circulation. For the standard RCC product used in Europe it is at least 50% lower. The half-life of citrate in the circulation is very short (37 min; and 20% is immediately cleared by the kidney), with an infusion rate of 150 mL/hour (average) most of the citrate is already cleared before the whole unit is infused and/or a next RCC is transfused (on average patients receive 2 units). The infusion of citrate is for a 70 kg person and transfusion time of 120 min in total 0.02 mg/kg/min.
- Calculation for a platelet concentrate transfusion: For platelet concentrates (either pooled buffy coats or pooled PRP derived) this is somewhat higher and patients receive 1 product in a time from of about 30 min. A platelet concentrate in plasma is about 300 mL, this means that about 1.3 grams of citrate is infused, resulting in an increase of 2.2 mM citrate in the circulation if all citrate would remain in circulation. For the standard platelet product in Europe, which is in a mixture of additive solution (65%) and plasma (35%) this is lower, as the additive solution contains only 12 mM citrate (1/3 22 mM and 2/3 12 mM; about 1.5 mM increase or 900 mg citrate). The infusion rate of citrate is for a 70 kg person and a transfusion time of 30 min in total 0.6 mg/kg/min (for a unit in additive solution this is 0.4 mg/kg/min).
- Calculation for a plasma unit transfusion: The same calculation is applicable for a unit of plasma: 0.6 mg/kg/min.

REFERENCES

ⁱ <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database>

ⁱⁱ An ACD sodium citrate anticoagulant – which is different from CPD – was registered as a medicinal substance in Italy as per their national pharmacopeia requirement, but has since been withdrawn on April 2021 and was under permanent cease of marketing since 2018. As such, this product is not in circulation anymore.

ⁱⁱⁱ European Directorate for the Quality of Medicines and Healthcare (EDQM), 20th Edition of the Guide to the preparation, use and quality assurance of blood components

^{iv} Bolan et al, Comprehensive analysis of citrate effects during plateletpheresis in normal donors. *Transfusion* 2001; 41:1165-1171

^v For further references on citrate half-life please see:

Kramer L, Bauer E, Joukhadar C, Strobl W, Gendo A, Madl C, Gangl A., Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 2003;31: 2450-5;

Kozik-Jaromin J, Nier V, Heemann U, Kreymann B, Bohler J., Citrate pharmacokinetics and calcium levels during high-flux dialysis with regional citrate anticoagulation. *Nephrol Dial Transplant* 2009;24: 2244-51;

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^{vi} Commission Staff Working Document on the Evaluation of the Union legislation on blood, tissues and cells,

https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf

^{vii} Bolan et al, Comprehensive analysis of citrate effects during plateletpheresis in normal donors. *Transfusion* 2001; 41:1165-1171