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GUIDELINES

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Recommendations for in vitro evaluation of blood components collected, prepared and stored in non-DEHP medical devices

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Abstract

Background and Objectives: DEHP, di(2-ethylhexyl) phthalate, is the most common member of the class of ortho-phthalates, which are used as plasticizers. The Medical Device Regulation has restricted the use of phthalates in medical devices. Also DEHP has been added to the Annex XIV of REACH, "Registration, Evaluation, Authorisation and Restriction of Chemicals" due to its endocrine disrupting properties to the environment. As such, the sunset date for commercialisation of DEHP-containing blood bags is May 27th 2025. There are major concerns in meeting this deadline as these systems have not yet been fully validated and/or CE-marked. Also, since DEHP is known to affect red cell quality during storage, it is imperative to transit to non-DEHP without affecting blood product quality. Here, EBA members aim to establish common grounds on the evaluation and assessment of blood components collected, prepared and stored in non-DEHP devices.

[Correction added on 23 December 2022, after first online publication: The Abstract section was corrected in this version.]

Materials and Methods: Based on data as well as the input of relevant stakeholders a rationale for the validation of each component was composed.

Results: The red cell components will require the most extensive validation as their quality is directly affected by the absence of DEHP, as opposed to platelet and plasma components.

Conclusion: Studies in the scope of evaluating the quality of blood products obtained with non-DEHP devices, under the condition that they are carried out according to these recommendations, could be used by all members of the EBA to serve as scientific support in the authorization process specific to their jurisdiction or for their internal validation use.

Keywords
blood collection, blood components, blood safety, plasma, platelet components, red cell components

INTRODUCTION

Di(2-ethylhexyl) phthalate (DEHP) has been used in blood bags since 1955 to make PVC blood bag systems flexible to allow processing of the drawn donor blood in a closed system into various blood components for the treatment of patients. Concerns about the health effects of plasticizers that could lead to endocrine disruptive consequences have resulted in European legislation aiming to diminish or ban the use of phthalate plasticizers. The new Medical Device Regulation of the European Union (EU) (EU 2017/745 MDR) defines the restrictions relating to the presence of phthalates and other endocrine-disrupting substances in medical devices, such as blood bag collecting systems.

For new devices, the application date for CE marking under the new MDR was due on 21 May 2021, whereas current CE certificates are valid until 26 May 2024. In case the benefit risk assessment (BRA) demonstrates that alternatives would be more hazardous to health, or could be a threat, then an exemption for DEHP may be provided for specific applications.

The European Chemical Agency (ECHA) has, however, recently submitted (10 July 2019, into force 23 November 2021) a recommendation to the European Commission to amend the Authorization List (Annex XIV of REACH, 'Registration, Evaluation, Authorization and Restriction of Chemicals') entries by adding the endocrine-disrupting properties of four phthalates, including DEHP, meaning that some previously exempted uses will require (market) authorization. ECHA indicates that for three of the four phthalates, the endocrine-disrupting properties concern human health only, and so, for blood bags, REACH defers to the medical device legislation for these. Concerning DEHP, however, the endocrine disrupting properties relate to human health and the environment, and therefore, REACH does not defer to the medical device legislation. Consequently, this results in a sunset date for the commercialization of DEHP-containing products after 27 May 2025 (as opposed to 26 May 2024 as per MDR). The European Commission, in collaboration with the Member States and the European Parliament, will make the actual amendment of the entries; companies must apply before 27 November 2023 for authorization to ECHA on exemptions of uses.

In light of this, various DEHP alternatives are being explored that are capable of maintaining similar physical characteristics of the blood bag set, as well as maintaining similar blood component quality (see Appendix S1 for extra background information). Although the various plasticizers that may both derive from the collection, as well as storage bag, do not seem to have a different impact on platelet or plasma quality during storage, they do have a considerably variable impact on the red cell storage lesion. DEHP is lipophilic, allowing DEHP to leach into the storage medium, mainly associating with plasma and red cells, albeit to a lesser degree. Moreover, DEHP incorporates into the red cell membrane [1], resulting in its stabilization [2], and surprisingly, leading to a strong reduction of haemolysis during storage. Also, DEHP was found to reduce microvesicle formation while favourably impacting osmotic resistance and morphology. These changes were found to result in increased survival after transfusion [3]. Replacing legacy storage solutions (for Europe, mainly SAGM) with other additive solutions (Table 1) has been shown to mitigate increased haemolysis levels to varying degrees [4, 5] with some evidence for complete mitigation.

In the last decade, with the upcoming DEHP ban, a range of plasticizer alternatives have been explored (Table 2), with promising candidates in bold. The European Pharmacopoeia of November 2017 has already incorporated four suitable alternatives: BTHC, DINCH, DEHT and TOTM/TEHTM to be used in containers meant for plasma for fractionation. The proposed DEHP alternatives confer satisfactory physical characteristics towards the PVC bags while simultaneously leaching into blood products to a lesser degree. Also, the toxicity of these plasticizers in rodents is decreased by tens to hundreds of folds (SCENIHR report on the safety of medical devices containing DEHP plasticized PVC, 2015). The consequence, however, of the absence of the membrane stabilizing plasticizer DEHP is that RBC haemolysis levels increase during storage (Table 3).

Importantly, and in parallel to the ECHA recommendations, blood bag systems will most likely upgrade to MDR (Medical Device Regulations) Class III, implying that a clinical evaluation will be required for any new blood bag system (from 21 May 2021). In April 2019, EBA answered a consultation by the EU Scientific Committee on Health,

TABLE 1 Additive solutions

Constituents	SAG-M	AS-1	AS-3	PAGGS-M	AS-5	AS-7 (SOL-X)
NaCl (mmol/L)	150	154	70	72	150	
Na_2HPO_4 (mmol/L)				16		12
$NaHCO_3$ (mmol/L)						26
NaH_2PO_4 (mmol/L)			15.5	8		
Citric acid (mmol/L)			2			
Na-citrate (mmol/L)			20			
Adenine (mmol/L)	1.25	2	2	1.4	2.2	2
Guanosine (mmol/L)				1.4		
Glucose (mmol/L)		111	61	47		80
Dextrose anhydrous (mmol/L)	41				41	
Na-gluconate (mmol/L)						
Mannitol (mmol/L)	30	41		55	45.5	55
pH	5.7	5.5	5.5	5.7	5.5	8.5
Osmolarity (MOsm/L)	376	462	291	345	372	237

Environmental and Emerging Risks (SCHEER) on 'Preliminary guidelines on benefit-risk assessment of phthalates' and in June, EBA presented its position at a European Commission Stakeholders meeting in Brussels, as follows:

- There are currently no commercially available validated non-DEHP devices for red blood cell collection and storage with comparable quality to DEHP-containing devices.
- Both recipients and donors (only in case of aphaeresis) are exposed to DEHP.
- An orderly (validation of the whole chain) transition to non-DEHP blood bag systems is needed to guarantee the sufficiency and safety of blood transfusion and transplantation.
- A concerted action between manufacturers, blood establishments and users is needed.
- Time is needed for the proper assessment of alternatives and validation of the blood supply chain from the donor to the final recipient.

In this context, and as there are major concerns in meeting the sunset date, some of the European manufacturers plan to apply for authorization for the continued use of DEHP beyond the sunset date. The intention is to push prolonged authorization for the use of blood bag sets towards the end of this decade in order to allow for an orderly transition to a European non-DEHP portfolio and prevent risks of supply gaps. The authorization strategy has been presented successfully to ECHA, as well as to the European Commission and was well received by both parties.

NON-DEHP BLOOD COMPONENT EVALUATION PHASES

Evaluation of blood components prepared using non-DEHP medical devices can be run through three successive phases.

A **Phase 1** study should be carried out based on positive Phase 0 data (where the manufacturer tests for ISO 3826 compliance and also obtains some [biochemical] quality data) and pertains an initial investigation of the blood components (in vitro evaluation), which should be carried out on a certain minimum number of components (see chapter 4.2). CE-certification of the blood bag system is usually not yet required at this stage. The study should include at least a worst-case scenario to validate biochemical quality parameters and maximum shelf life (which might be combined with a best-case scenario). Components produced during this stage should not be used for transfusion. A Phase 1 study may be restricted with regards to study size and number of quality parameters tested based on the existence of extensive Phase 1 studies from other blood establishments testing the same blood bag system of the same manufacturer (or from Phase 0 data, including biochemical quality data; see Table 4). A restricted Phase 1 study may, for example, be suitable in case of differences between jurisdictions in the maximum allowed overnight hold (48 h vs. 72 h), cold versus warm filtration, and so forth, or when jurisdiction-specific quality requirements are not covered by the adopted results. A restricted Phase 1 study, and the extent of tests performed, may depend on the differences in processing, and as such, comprises a restricted selection of tests as listed in chapter 5.

In a **Phase 2** study, an operational validation should be carried out on a larger number of blood units. CE certification in this stage is usually required in most jurisdictions. Data under routine conditions are gathered. Standard routine quality tests, as required by Guidelines (EDQM Guide and/or local guidelines) are performed. It is advised to already start collecting data on, for example, leakage issues and ease of handling in this phase, although a much larger study size is most likely to be required to be able to statistically compare the incident frequency of the new with current blood bag systems. Components produced during this stage can be used for transfusion if they comply with the routine quality parameters (depending on jurisdiction regulation or authorization process). Usually, Phase 2 is started with

TABLE 2 DEHP alternatives

Plasticizer short name	Full name	Leaching potential	Toxicity	Comments
ATBC	Acetyl tri-*n*-butyl citrate	Higher leaching observed compared to DEHP in medical devices.	Rapidly metabolized. No obvious toxic effects noted in animal models, and no human studies available.	Used in cosmetics and as a plasticizer for PVC. Used in food applications. Has been used in medical devices, including blood bags and tubing.
BTHC	*n*-Butyryl-tri-*n*-hexyl citrate	Slightly lower leaching rates than DEHP (limited data)	Rapidly metabolized. Low toxicity in animal models, and no human studies available.	Uses similar to ATBC, in use in commercially available platelet storage bags.
COMGHA	Castor-oil-mono-, glycerides, hydrogenated, acetates	Slightly lower leaching rates than DEHP	Not completely metabolized, possibly due to limited absorption in the GI tract. Low toxicity in animal models, and no human studies available.	Similar use as DEHP. Approved in EU for food packaging. Listed in the European List of Notified Substances (ELINCS) as no. 451-530-8
DEHA	Di(2-ethylhexyl) adipate	Slightly higher leaching rates than DEHP (limited data)	Reproductive toxicity noted	Has been put on the Community rolling action plan by REACH based on concerns of toxicity
DINCH	1,2-Cyclohexane dicarboxylic acid diisononyl ester	Lower than DEHP	Low toxicity in animal models, limited human studies available. Adverse effects of DINCH metabolites on Human reproductive health. GreenScreen classification is Moderate due to endocrine activity	Shows potential. Similar use as DEHP. Approved in EU for food packaging. Currently in use in commercially available RCC and platelet storage bags. CE certified medical devices for paediatric use
DINP	Di-iso-nonyl phthalate	No data	Similar to DEHP toxicity in animal models, and no human studies available.	Not used in medical devices. Listed in Regulation (EU) No 1907/2006 Annex XVII, 52 and 10/2011. Restrictions on use in toys.
DEHT	Di(2-ethylhexyl) terephthalate	Lower than DEHP	Possibly lower than DEHP in animal models. Only two skin irritation and sensitization studies in humans with no evidence found. GreenScreen classification is low	Shows potential. Similar use as DEHP. Used in toys and other consumer products. No information on use in medical devices, other than some explorative studies
TOTM/TEHTM	Trioctyltrimellitate	Unclear leaching rates compared to DEHP (limited data)	Poorly absorbed and metabolized. Low toxicity in animal models. Some skin sensitization in human skin studies.	Used as plasticizer in electrical wires but also on commercially available platelet and plasma blood bags. Not approved in Europe for food contact.

TABLE 3 Blood bag system considerations

Collection/processing step	Requirements[a]
Blood collection	• Compatibility with mixers, sampling with vacutainer tubes/corresponding sampling
Blood bag systems	• Bottom-and-top and top-top systems • 2-component (whole blood filtration) and 3-component (generation of buffy coat, filtration of separated components) • Apheresis and whole blood systems
Post-collection, pre-processing rest/transport	• Cooling down (37–20°C, butane-1,4-diol plates or similar) • Transport from collection site to processing site • Same-day processing or pre-processing overnight hold in RT
Centrifugation	• Speed up to ~5000 × *g* without leakage: ○ RT for whole blood systems and platelet components ○ Cold (4°C; certain plasma/cryoprecipitate/serum components)
Component separation	• Separation on automated, semi-automated and manual blood component extractors, including compatibility with features such as clamping, sealing, RBC detectors, RBC mixers, hanging/mounting of bag, pressure on bag, breaking of breakaway cannulas • Whole blood separation and manual platelet concentrate processing
Filtration	• RBC • Whole blood • Whole blood/platelet sparing • Plasma • Platelets
Tube sealers	• Sterile closing and easy, ergonomic separation of tube ends, weld integrity
Sterile docking devices	• Sterile docking/welding and easy, ergonomic opening of weld of ○ Same plasticizer tubes ○ Different plasticizer tubes (all combinations of plasticizers in use)
Storage equipment	The material should be suitable for storage in the below-mentioned temperatures, including withstanding relatively fast temperature changes, frozen transport or RT agitation without breaking/leakage etc. • Plunge freezing devices (from RT to −40°C or below within 60 min or similar) • Freezers, <−30°C, FFP storage • Freezers, from −60 to −80°C, cryopreservation of RBC • Refrigerators 2–6°C, RBC storage • Platelet agitators 20–24°C, platelet storage • Plasma thawers (from −70°C to liquid [RT] FFP)
Labelling	• BE labels and manufacturer labels should be easy to attach and stick to the material during the above-mentioned temperature changes.
Secondary processes and sampling	• Compatibility with connection to sets for automated platelet production, pathogen reduction, cell wash and so forth, which may have connection tubes of different plasticizers (see also Sterile docking devices). • Overall quality of secondary processing after storage in new plasticizers/additive solution combinations.
Transfusion	• Compatibility with spikes of transfusion sets, blood warmers and so forth (according to ISO 1135)

[a]Results for the various aspects mentioned in this table should be obtained by manufacturers. Some have to be, however, confirmed in a Phase 2 study (operational validation), such as the ease of use and leakage frequency.

increased frequency of quality control, which can be decreased to standard frequency if the results are satisfactory.

A **Phase 3** study may comprise passive or active haemovigilance surveillance, which depends on the criticality of the change. Also, a Phase 3 study might entail a recovery study. For critical changes, such as a change of plasticizer, active haemovigilance may be required in which a patient population size, monitoring points and alert and termination levels are defined such that unexpected severe increases in adverse event frequency will be detected as early as possible.

Upon implementation of a non-DEHP blood bag system, the question is whether all components are to be validated (i.e., be subjected to Phase 1 and 2 studies) or whether validating a subset of components within each group (i.e., within the RBC, platelet or plasma group) is sufficient. In Table 4, suggestions for the evaluation and validation of the components, as well as the underlying rationale, are provided.

Number of assays and statistical analysis

Currently, the EDQM guide defines no requirement on the minimum number of components to be tested for quality during storage other than suggesting an 'appropriate' number to be defined by the institution itself. One of the reasons why it is difficult to propose a certain minimum number is that based on the variability of certain parameters, as well as study design (paired/unpaired), different study group sizes are required. As such, the minimum number of components to

TABLE 4 Extent of validation per blood component

Red blood cells	
Standard RBCs, leucoreduced from BC-removed WB (RBC leucofiltration) or from WB (WB leucofiltration).	An extensive study is required (i.e., full phase 1–3) per combination of plasticizer and storage medium per manufacturer, preferentially with two different process variables (e.g., processing within 8 h and processing after overnight hold). Based hereon, other blood establishments from other EU countries may adopt the results and internally perform a restricted qualification (Phase 1), taking into account the impact of, for example, possible variation in processing operations between blood establishments.
• Standard RBCs, irradiated (x-ray and gamma) • Standard RBCs, irradiated (x-ray and gamma) and washed	Given acceptable data from a Phase 1 study on the standard RBC component (i.e., similar quality), in which the new and current blood bag sets are compared side by side in a worst-case scenario, a restricted Phase 1 qualification can be performed with a lower number of units (Section 3) and analysis of fewer biochemical parameters (chapter 5.1). Although data is available showing that irradiation of DEHT/PAGGSM RCC leads to a comparable increase of haemolysis levels as compared to its DEHP/SAGM control counterpart [9], little data is available on other combinations, warranting a restricted Phase 1 qualification.
Derived from standard RBCs/other • RBCs, split (paediatric) units • RBCs, washed • RBCs, cryopreserved • RBCs, for intrauterine transfusion • RBCs, for neonatal exchange transfusion • RBCs, from apheresis	Given acceptable Phase 1 data on standard RBCs and Standard RBCs, irradiated (x-ray and gamma; i.e., similar quality), and provided the foil of the bags are identical, an operational change control (Phase 2 study) only as there is no indication these components will be affected.
Platelets	
• Platelets, leucoreduced, pooled from BC • Platelets, leucoreduced, apheresis	Platelets are currently already being stored in non-DEHP storage bags; as such, only DEHP from the collection bag and tubing may leach into the final platelet product. Taking into consideration previous evidence on the minor effect of DEHP plasticizer on platelet components [4, 5], only an operational validation (Phase 2 study) is required unless unconventional DEHP alternatives or storage solutions are used. In such a case, Phase 1 validation is required, as specified in Tables 7 and 8.
Derived from the platelet products above • Platelets, leucoreduced, pooled irradiated • Platelets, leucoreduced, pooled, pathogen reduced • Platelets, leucoreduced, apheresis, pathogen reduced • Platelets, leucoreduced, apheresis, irradiated • Platelets, split (paediatric) units • Platelets, washed • Platelets, cryopreserved	Taking into consideration the argumentation with regards to the standard platelet products from pooled BCs and apheresis, only an operational change control with underlying argumentation is required, followed by routine data collection (Phase 2).
Plasma	
• Plasma, fresh frozen, (leucoreduced), from WB • Plasma, fresh frozen, from apheresis	Plasma factor content stability is not influenced by the plasticizer. As such, various DEHP alternatives are endorsed in the Ph. Eur. An operational validation (Phase 2 study) is required to ensure bag characteristics and processing compliance in the absence of DEHP.
Derived from the plasma products above • Plasma, fresh frozen, pathogen reduced • Plasma, fresh frozen, irradiated • Cryoprecipitate • Cryoprecipitate, irradiated • Cryoprecipitate, pathogen reduced	Taking into consideration the argumentation with regard to the standard plasma product, only routine testing is required (Phase 2).
Whole blood	
• Whole blood (Leucoreduced, platelet reduced) • Whole blood (Leucoreduced, platelet sparing filter)	Whole blood storage for transfusion purposes is gaining renewed attention. Little is known about the effect of alternative plasticizers on the individual components during prolonged contact with other components. Also, little is known of the effect of, for example, lipaemia in the absence of DEHP on whole blood component quality. These uncertainties warrant a thorough approach through a full phase 1–3 validation.

(Continues)

TABLE 4 (Continued)

Red blood cells	
Granulocytes	
• Granulocyte concentrate	Considering the absence of any level of proof of a beneficial effect of DEHP on granulocyte concentrates, we propose that the change of plasticizer of the collection devices (whole blood or apheresis) be assessed according to routine testing (Phase 2, chapter 5.6).

be tested differs somewhat between blood establishments and has become the norm based on historical experience. From an EBA survey among member states, it has become clear that a Phase 1 study containing at least 15 units is acceptable for all participating blood establishments, although some require less. As such, it is suggested to include at least 15 units in a Phase 1 study. Pairing is advised when possible (in case of, e.g., comparing best/worst case scenarios). Based on the results of this study, other blood establishments aiming to use the same non-DEHP blood bag system (i.e., same plasticizer, storage solution and manufacturer) can perform an operational Phase 2 validation (with some destructive testing to check shelf life) and a Phase 3 study.

RATIONALE FOR REQUIRED QUALITY AND PROCESS PARAMETER ANALYSIS PER BLOOD COMPONENT

RBC component quality and process parameters

Haemolysis rates have been reported to increase during storage in DINCH, DEHT and BTHC. Interestingly, for red cells stored in DINCH-PVC and DEHT-PVC in the storage medium SAGM, although resulting in increased haemolysis rates, this was not found to be associated with enhanced potassium leakage and ATP reduction [4, 5]. In another study using the storage medium SAGM, similar haemolysis levels were found when comparing DEHP and DINCH, while BTHC haemolysis rates doubled or tripled [6]. This study also reported a higher rate of osmotic fragility, as well as decreased deformability when storing in BTHC and DINCH. Yet another study [7], also using SAGM, found no differences when comparing haemolysis between DEHP and a di (2-ethylhexyl) 4-cyclohexene-1,2-dicarboxylate (DOTH)/DINCH combination. In this study, baseline haemolysis rate ($t = 0$) was, however, already substantial (0.4%), while some units were close to exceeding 0.8% haemolysis in the third week of storage, which is the maximum amount of haemolysis that European countries adhere to in their guidelines when storing up to 6 weeks (Guide to the preparation, use and quality assurance of blood components, EDQM, 2020). This study also reported comparable ATP, glucose, sodium and potassium levels. These are but a few of the studies that have been conducted, but it exemplifies the heterogeneous results even with the same storage medium. What seems to be clear although is that haemolysis rates are affected slightly to substantially affected in most cases. This seems to be, however, independent of a loss of intracellular homeostasis but mainly a consequence of the absence of membrane stabilization that used to be fulfilled by DEHP. Indeed, osmotic fragility may increase, and deformability may decrease slightly, but glucose consumption, lactate production, ATP levels, 2,3-DPG concentration and sodium/potassium levels are largely unaffected. Although ATP levels may be similar when stored in SAGM-DEHP, SAGM-DINCH, SAGM-DEHT or SAGM-BTHC, it remains that they decrease during storage.

That changing storage media may compensate for the increased haemolysis levels due to the absence of DEHP is exemplified well in a study performed by Graminske et al. [8]. In this study, a substantial increase in haemolysis upon storage in AS-1-DEHT as compared to AS-1-DEHP was reported, while storing in PAGGSM-DEHT resulted in mean haemolysis close to AS-1-DEHP control (0.38% vs. 0.32%) [8]. Although these results seem promising, this study used a DEHP-containing collection set. As collection set-derived DEHP leaches into the whole blood to a certain degree, this will contaminate the produced red cell concentrate, which may affect haemolysis levels during storage. Similar results were reported in two studies by Larsson et al. in which non-DEHP collection sets were used to compare DEHP/DEHT and SAGM/PAGGSM combinations in a regular setting [5] and a corresponding irradiation setting [9]. They reported promising results with haemolysis only slightly higher in PAGGSM-DEHT (0.27 ± 0.03) as compared to 0.23 ± 0.04 in its SAGM-DEHP counterpart 49 days post-collection in the non-irradiated setting. A slightly larger difference was found after irradiation, with 0.35 ± 0.07 in PAGGSM-DEHT as compared to 0.28 ± 0.04 in SAGM-DEHP after a total of 28 days of storage. Last, a recent study by Vermeulen et al. showed very promising results, with PAGGSM-BTHC haemolysis levels being comparable to SAGM-DEHP (0.38 ± 0.12 vs. 0.36 ± 0.17, respectively) [10]. In the same study, a haemovigilance surveillance was performed to track adverse event frequency. No indication for higher rates of adverse event frequency was found in patients receiving non-DEHP RCC transfusions as compared to patients receiving the standard DEHP-containing product.

Clearly, the number of studies that are performed on this subject are numerous but many more combinations of blood bag system, plasticizers and storage media are to be explored. Ongoing research is required to identify and optimize the best possible combination of plasticizer and storage solution. It is critical that the non-DEHP era will not come at the cost of an RBC product that is more rapidly degraded, possibly more harmful for the patient or will lead to reduced storage times and as a consequence, results in more outdating. This would, overall, negatively affect the blood supply. A reduced RBC shelf life could jeopardy the continuous blood supply, especially during crisis, such as the COVID-19 pandemic [11].

TABLE 5 RBC quality parameters

Parameter	Novel additive solution	Novel plastic/ plasticizer
Unit volume (ml)	Required	Required
Haematocrit (L/L) or %	Required	Required
Haemoglobin (Hb) (g/unit)	Required	Required
MCV (Mean corpuscular volume)	Required	Required
Residual WBC (10^6/Unit)	Recommended	Required
Supernatant K^+ (mmol/L)	Required	Required
Haemolysis (%)	Required	Required
ATP	Required	Required
2,3-DPG[a]	Recommended	Recommended
pH	Required	Required
Lactate (mmol/L)	Required	Required
Glucose (mmol/L)	Required	Required
pCO_2 (kPa)	Recommended	Recommended
pO_2 (kPa)	Recommended	Recommended
RMV: RBC microvesicle	Required	Required
Erythrocyte morphology	Recommended	Required
Leachables from plastic film in supernatant and cells[b]	/	Required
Osmotic fragility	Recommended	Recommended
Deformability	Recommended	Recommended
Oxidative haemolysis	Optional	Optional

[a]2,3-DPG analysis kits are currently unavailable.
[b]To be carried out by the manufacturer.

Key considerations

- The absence of DEHP may severely impact RBC quality during storage.
- Many plasticizer and storage solution combinations are available that may affect a range of storage parameters.

Proposal

Considering these elements, we recommend for each unique combination of plasticizer and storage solution to analyse and assess the critical quality and process parameters listed in Tables 5 and 6, respectively, in a Phase 1 study for the standard RBC components listed in Table 4. The quality parameters of RBC are verified throughout the storage period with four control steps between the day of preparation of the final product and the expiry date (date of preparation of the final product (T1) and four checks during storage; i.e., D14, D28, D35 and D42). As mixing due to sampling may, however, potentially affect haemolysis, it is advised to minimize sampling frequency. Also, other control points may be suitable in the case of, for example, irradiated RBC.

TABLE 6 RBC process parameters

Parameter	Novel additive solution	Novel plastic/ plasticizer
Collection time and volume	Required	Required
Storage temperature between collection and processing	Required	Required
Time delay between collection and processing into BC	Required	Required
Temperature during processing steps (collections, transportation, use of cooling plates, etc.)	Required	Required
Centrifugal force (RCF)	Recommended	Required
Centrifugation time	Required	Required
Centrifugal temperature	Required	Required
Time for separation	Required	Required
Temperature at filtration	Required	Required
Height of filtration	Required	Required
Filtration time	Recommended	Recommended
Storage temperature	Required	Required
Mixing during storage (no, yes, number of mixing)	Required	Required
Storage time	Required	Required

PC component quality and process parameters

Platelet concentrates have been stored for decades in devices providing optimum gas permeability, a characteristic for which PVC-DEHP is not suitable. The devices currently used for the preparation and storage of platelets are therefore already devoid of DEHP: PVC-BTHC, PVC-TOTM and polyolefin plastic films. To date, platelet concentrates are likely to contain only a very low concentration of DEHP, its origin being reduced to the transitional phase of collection and storage of the collections. The contact time with the collection device is, in all cases, less than 24 h and equal to the time of collection for apheresis platelets (less than 2 h). For the apheresis process, it can be considered, given the extremely short timeframe of the apheresis procedure, that the contact time is insufficient to represent a significant concentration of DEHP in the final PC, although significant amounts of DEHP from the tubing may still leach into the product.

Many studies published in the 1980s focused on the preservation of non-DEHP PVC platelet concentrates (PVC-TOTM, PVC-BTHC), but with the objective of demonstrating that the increased permeability to gas (O_2, CO_2) of these plastic films represented a real benefit in maintaining the homeostasis, metabolism and functionality of platelets. Even if an effect of drastically reducing DEHP concentration in concentrates was to be observed, it would have been largely masked by the effect of increased gas exchange.

To the best of our knowledge, no study has supported any benefit of DEHP in maintaining platelet homeostasis, or in reducing the effects of aging or in platelet functionality. A first study published by

TABLE 7 Platelet quality parameters

Parameter	Novel plastic/ plasticizer
Volume (dl)	Required
Platelet concentration (g/L)	Required
Platelet content ($\times 10^{11}$/unit)	Required
pH	Required
Mean platelets volume (MPV; fl or μm^3)	Required
Residual WBC (10^6/unit) (dl)	Required
Morphology, for example, Swirl score	Required
Activation/apoptosis, for example, beta thromboglobulin, CD62P (expression or soluble), phosphatidylserine exposure (Annexin V)	Required
Lysis, for example, LDH	Required
Residual red cell count (dl)	Recommended
Plasma/PAS ratio (dl)	Recommended
Metabolic activity: ATP, pH, lactate, glucose, pCO_2, pO_2	Recommended
Function, for example, aggregation thromboelastography/thromboelastometry	Recommended
Cytokines/chemokines	Recommended
Platelet microvesicles	Recommended
Residual content of 'added substances' (e.g., pathogen reduction agent)	Recommended
Leachables from plastic film in supernatant and cells[a]	Required

[a]To be determined by the manufacturer.

Valeri [12] in 1973 shows that the accumulation of DEHP in platelet concentrates has no benefit on platelet viability.

The few studies available show that in the presence of DEHP, the generation of aggregates appears to be reduced [13–15]. The presence of DEHP has no influence on the development of LDH or resistance to hypotonic shock. Labow [16] observed, at the start of the storage period, a difference in the morphological index of platelets in the presence of DEHP, but this observation could not be linked to an effect on functionality. Lagerberg [4] found no significant effect on platelet concentrates prepared from whole blood collected and processed in 100% DINCH devices. That DEHP alternatives do not impact platelet quality was supported by L. Larsson [5], who monitored platelet quality prepared from whole blood collected and processed in a DEHT device. The study did not show any significant difference in quality between platelet concentrates produced with the DEHP device and concentrates obtained with the DEHT device.

Key considerations

- The current contact duration during which the diffusion of DEHP is possible is relatively low for PCs, resulting in only a trace of DEHP in the current platelet components.
- There is a lack of documented benefit provided by the DEHP on the quality and conservation of the PCs.

TABLE 8 Platelet process parameters

Parameter	Apheresis platelets novel plasticizer	Pooled WB platelets novel plasticizer
Collection time	Recommended	/
Storage temperature between collection and processing	Recommended	Recommended
Time delay between collection and processing	Recommended	Recommended
Centrifugal force (RCF)	Required	Required
Centrifugation time	Required	Required
Centrifugal temperature	Required	Required
Temperature at filtration	Recommended	Recommended
Height of filtration (if applicable)	Recommended	Recommended
Filtration time (if applicable)	Recommended	Recommended
Total platelet/storage bag volume ratio	Required	Required
Storage temperature	Required	Required
Storage time	Required	Required

Proposal

Considering these elements, as well as the considerations listed in Table 4 for this product group (i.e., the use of unconventional plasticizer/ storage medium), only an operational validation (Phase 2 study) is required unless unconventional DEHP-alternatives or storage solutions are used. Platelets are currently already often being stored in BTHC or DINCH. As such, only when unconventional DEHP alternatives are being used do we recommend for each unique combination of plasticizer and resuspension medium of platelets to analyse and assess the critical quality and process parameters listed in Tables 7 and 8, respectively, in a Phase 1 study for the platelet components listed in Table 4. The quality parameters of PCs are verified throughout the storage period with two control steps between the day of preparation of the final product and the expiry date (i.e., D2, D5, D7). Other control points can be added.

Plasma component quality and process parameters

Plasma, either as FFP by quarantine or for fractionation (PDMPs) is stored frozen in a PVC-DEHP bag. An exception is the plasma treated with amotosalen, as the final storage bag is made of EVA. It is described that the diffusion of DEHP is much higher in plasma than in other components due to the presence of lipoproteins and triglycerides. DEHP is degraded in liquid plasma to MEHP, which is, in fact, a toxic compound. To the best of our knowledge, no study supports any benefit of the presence of DEHP or MEHP during the freezing stages, during storage in frozen form, or in its liquid form after thawing on the in vitro properties of plasma.

TABLE 9 Plasma quality parameters

Parameter	Novel plastic/ plasticizer
Volume (ml)	Required
Residual WBC (dl)	Recommended
Protein after thawing (g/L)	Required
Immunoglobulin (G, M, A) (g/L)	Required
FVIII:C (IU/ml)	Required
Residual platelets (dl)	Recommended
Residual red cells (dl)	Recommended
PT ratio (prothrombin time)	Recommended
Thromboelastography/ thromboelastometry	Recommended
APTT ratio	Required
Fibrinogen (g/L)	Required
FII, V, VII, IX, X, XI (UI/ml)	Recommended
vWf:Ag	Recommended
vWf:RiCof	Recommended
AT III (Antithrombin), Protein C, Protein S	Recommended
TAT/Frag1.2/FPA + FXIIa	Recommended
C3a (mg/L) and C5a (µg/L)	Recommended
C1 inhibitor	Recommended
Alpha-2 anti-plasmin	Recommended
Plasminogen	Recommended
ADAMTS13	Optional
Leachables from plastic film[a]	Required

[a]To be determined by the manufacturer.

Lagerberg concludes that there is no significant effect on the haemostasis parameters of plasma derived from whole blood collected and processed in a DINCH device [4]. In addition, the available in vitro data show that amotosalen-treated plasma stored in a bag devoid of DEHP is fully compliant in terms of regulatory requirements, as well as for in vitro attributes. Larsson monitored the quality of plasma derived from whole blood collected and processed in a DEHT device after preparation on D0 and on D0 and D7 after frozen storage and thawing in a DEHT device [5]. The study did not show any significant difference in haemostasis and biochemistry parameters between the DEHP and the DEHT devices.

Key considerations

- There is a lack of documented benefit provided by the DEHP on the quality and conservation of plasma and its factors.
- Some DEHP alternatives are already authorized in the Ph. Eur.

Proposal

As mentioned in Table 4, no effect of DEHP on plasma factor stability has been documented, and various DEHP alternatives are already listed in the Ph. Eur. As such, only an operational validation (Phase 2 study) is required. If regulatory bodies require Phase 1 validation data, we, however, recommend the below parameters to be tested. The below parameters should be tested throughout the storage period (four control steps between the day of preparation of the final product) and the expiry date (date of the application of a new process [T1] and three checks after frozen storage-thawing on D1–14, at 6 months and at 12 months, respectively T2, T3 and T4). Other control points can be added for the validation of the extension of storage. Tables 9 and 10 list the required quality and process parameters to be assessed for plasma. For each parameter, mean, SD, min, max and median values should be reported.

TABLE 10 Plasma process parameters

Parameter	Apheresis plasma	Whole blood plasma
Collection time and volume	Required	/
Storage temperature between collection and processing	Required	Required
Time delay between collection and processing	Recommended	Recommended
Delay between collection and filtration if applicable	Required	Required
Height of filtration	Recommended	Recommended
Filtration time	Recommended	Recommended
Time between collection and freezing	Required	Required
Storage temperature	Required	Required
Storage time	Required	Required
Time of thawing	Required	Required

WB component quality and process parameters

There is growing interest in the use of whole blood for the treatment of major haemorrhages. In reality, this component is either (a) a unit of whole blood that has been leucoreduced (also removing most of the platelets) resulting in a unit of red cells in plasma, or (b) a unit of whole blood that has been leucoreduced using a platelet-sparing filter so that the majority (>70%) of platelets remain in the final component along with the red cells and plasma. The requirements for validation of WB containers with novel plasticizers will, therefore, be similar to those outlined for red cells, plasma and platelets above. However, the shelf life of WB components is a compromise of the conditions for each component when stored separately. For WB, the shelf life is commonly 14–21 days of refrigerated storage, which is shorter than usual for red cell storage but longer than usual for plasma and longer than usual for platelets but at a lower temperature. It would therefore be appropriate to study the quality parameters of each component within the stored WB, as it is not known whether there is an additive effect of the plasticizer on the components during longer storage or through prolonged contact with other components.

Key considerations

- The effect of DEHP is thought only to have a significant impact on RBCs.
- The storage of whole blood components may be of the duration when the effects of DEHP start to be observed on the reduction of haemolysis of RBCs (14–21 days).
- The presence of a high proportion of plasma in the suspension media of the red cells may allow significant diffusion of DEHP.
- It is possible that a change in plasticizer may have a significant effect on the quality of red blood cells within a whole blood component.

Proposal

Considering these elements, we propose that the effect of changing the plasticizer for whole blood components be assessed in accordance with the tables for the individual components therein.

Cryoprecipitate component quality and process parameters

Cryoprecipitate is manufactured from FFP by slowly thawing plasma at 1–6°C and centrifugation to collect the precipitate. Excess liquid (cryopoor plasma) is removed, and the precipitate is resuspended in a small amount of residual plasma and is then re-frozen for storage. As with FFP, cryoprecipitate is currently stored frozen in a PVC-DEHP bag.

Key considerations

- To the best of our knowledge, no studies have been performed to study the effect of non-DEHP collection systems/storage bags on cryoprecipitate.
- It is assumed that cryoprecipitate will be produced from adequately validated FFP from non-DEHP collections. Therefore, investigators will be aware of any specific losses of clotting factors, which should be particularly considered.

Proposal

Considering these elements and the absence of any level of proof of a beneficial effect of DEHP on cryoprecipitate, we propose that the change of plasticizer of the collection devices (whole blood or apheresis) be assessed as a simple verification of conformance only (Phase 2). Tables 11 and 12 specify the required quality and process parameters for cryoprecipitate. For each parameter, mean, SD, min, max and median values should be reported.

TABLE 11 Cryoprecipitate quality parameters

Parameters	Novel plastic/plasticizer
Volume (ml)	Required
FVIII:C (IU/ml)	Required
Fibrinogen (g/L)	Required
Leachables from plastic film[a]	Required

[a]To be determined by the manufacturer.

TABLE 12 Cryoprecipitate process parameters

Parameters	Novel plastic/plasticizer
Collection time	/
Storage temperature between collection and processing	Required
Centrifugal force[a]	Required
Centrifugal time[a]	Required
Centrifugal temperature[a]	Required
Time delay between collection and processing	Recommended
Time between collection and freezing	Required
Storage temperature	Required
Storage time	Required
Time of thawing	Optional
Time of storage at +1°C	Required

[a]If applicable, that is, siphon or centrifugal method.

Granulocyte component quality and process parameters

Granulocyte components/concentrates are blood components that are currently only produced by a relatively small number of blood establishments. They can be manufactured from whole blood or collected specifically by apheresis and are currently stored in either standard DEHP plasticized PVC bags or in bags designed for the storage of platelets, of which the latter are already devoid of DEHP. These components are stored for 24–48 h due to a decrease in activity and viability.

Granulocyte components stored in non-DEHP platelet bags manufactured from whole blood are likely to contain a relatively low concentration of DEHP, its origin being reduced to the collection and intermediate storage of whole blood/buffy coats. The contact time with the collection device/intermediate storage is likely less than 24 h. For granulocyte components collected by apheresis, the amount of DEHP is also likely to be relatively low, as processing and transfusion are performed as quickly as possible after collection. To the best of our knowledge, no study has supported any benefit of DEHP in maintaining granulocyte activity or viability. In a controlled study, Miyamoto and Sasakawa reported that DEHP decreased both chemotaxis and bactericidal activity, including a comparison to TOTM-PVC [17, 18]. In contrast, Drewnaik et al. described that G-CSF mobilized

TABLE 13 Granulocyte concentrate quality parameters

Parameters	Novel plastic/plasticizer
Volume (ml)	Required
Granulocyte content (10^{10})	Required
Haemoglobin content (g/U)	Recommended
Haematocrit (%)	Required
Platelet content (10^{11})	Recommended
Leachables from plastic film	Recommended
Granulocytes viability	Required

TABLE 14 Granulocyte process parameters

Parameters	Apheresis granulocyte	WB pooled granulocyte
Collection time	Required	/
Storage temperature between collection and processing	Required	Required
Centrifugal force	/	Required
Centrifugal time	/	Required
Centrifugal temperature	/	Required
Time delay between collection and processing	Recommended	Recommended
Time between collection and pooling	/	Required
Added solutions (PAS/Plasma)	Required	Required
Time delay between processing and irradiation	Recommended	Recommended
Storage time	Required	Required
Storage temperature	Required	Required

neutrophils stored for 24 h, have a normal function when tested in assays of respiratory burst, chemiluminescence, phagocytosis, chemotaxis and superoxide anion production [19]. This suggests no harmful effect of DEHP, although this study and others like it were not designed to specifically look at the effect of DEHP. It must, however, be acknowledged that granulocyte components can contain a significant number of both red cells and platelets; however, given the short shelf life of these components (≤48 h), it is not considered that the presence of either red cells or platelets in these components require any special consideration.

Key considerations

- The effect of DEHP is thought to have a significant impact on RBCs only.
- The storage of granulocyte concentrates is of short duration, ≤48 h, and much less than the period from which the effects of DEHP start to be observed on the reduction of haemolysis of RBCs (14–21 days).
- The current contact duration during which the diffusion of DEHP is possible should result in only small amounts of DEHP in granulocyte-containing components.
- There is a lack of documented benefit of DEHP on the activity and viability of granulocytes, with one paper suggesting a negative effect.

Proposal

Considering these elements and the absence of any level of proof of a beneficial effect of DEHP on granulocyte concentrates, we propose that the change of plasticizer of the collection devices (whole blood or apheresis) be assessed as a simple verification of conformance only (Phase 2). Tables 13 and 14 specify the required quality and process criteria for Granulocyte Concentrates. For each parameter, mean, SD, min, max and median values should be reported.

CONCLUDING REMARKS

The deadlines for the transition to DEHP-free blood components are rapidly approaching. A multitude of studies has been performed aiming to address the impact of DEHP absence on the quality of the various blood components. It is clear that mainly red cell components are affected by this change, while platelet and plasma components are seemingly unaffected. It is clear that red cell component quality reduction in the absence of DEHP may be dampened through the use of next-generation storage solutions. Still, many combinations of plasticizer and storage solution alternatives are to be tested to ensure a transition to an optimal non-DEHP product. So far, studies have mainly focused on the major blood components, with little data on the successive impact of, for example, irradiation, pathogen reduction and so forth. As such, in this article, we have aimed to propose a framework, which allows blood establishments to share and rely on extensive international investigations to more efficiently enrol the same non-DEHP blood bag sets across countries. Also, we have aimed to provide a rationale, as well as guidance for the requirement of studying sub-component quality and process parameters so that most jurisdictions' quality requirements are covered and so that they may adopt internationally obtained results. We have refrained from defining quality criteria thresholds, as it is up to the blood establishments themselves to judge whether potential increments in critical blood quality criteria that are still within the ranges specified in the EDQM Guide are acceptable. International adoption of blood product quality data would significantly reduce time constraints in view of the DEHP deadlines, as well as reduce the cost associated with this change. It is clear that the main effort has to be focused on erythrocyte-containing products and that not all sub-components require extensive validation, especially those derived from platelet or plasma components. Even so, ensuring that all blood and subcomponents remain of quality is of prime importance during this large-scale transition. We propose that through extensive international collaboration, the best possible result is to be obtained.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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