Line	Affiliation	Section	Comment	SCHEER response
1.	European Society of Endocrinology	1. Introduction	GENERAL COMMENTS WITH REGARDS TO THE INTRODUCTION, CONCLUSION AND/OR THE DOCUMENT IN GENERAL 1.The precautionary principle must be always followed, and any risk benefit analysis must acknowledge that lack of data does not equate lack of toxicity. 2.All scientific literature must be used for all risk assessments described in the document so that it encompasses both regulatory and non-regulatory measures of adversity. 3.Provide more clarity as to how often risk assessments will be updated.	1.It is not common to use the precautionary principle for substances in the field of medical devices, because benefit risk assessments must be performed for medical devices. In addition, the manufacturer has to demonstrate that the device conforms with the essential requirements of Annex I of the MDR (EU 2017/745). Section 4 of Annex I of the MDR (EU 2017/745) describes the various control measures manufacturers have to follow to eliminate or reduce risks as far as possible through safe design and manufacture. Medical devices have to comply with the general safety and performance requirements as presented in Annex 1 of the MDR (EU 2017/745). 2.All available information needs to be considered in the BRA of a medical device. The SCHEER recommends using a weight of evidence (WoE) approach for performing a BRA. Text added on section 1. introduction: "*For this literature review all available information needs to be considered, including peer reviewed publications and regulatory studies*". Text added under step 3 and 7 of the guidelines' approach section 3 and under step 7 section 5. "*For the risk assessment all available information needs to be used including peer reviewed publications and regulatory studies. The SCHEER recommends using a WoE approach for performing the risk assessmen*t". Text added under step 3 section 4: "*by using all the available information, including peer reviewed publications and regulatory studies. The SCHEER recommends the application of WoE methodology*". 3.The frequency of the update is stated in the MDR (EU/2017/745). Technical documentation of a marketed medical device has to be reviewed by a Notified Body at least once every five years according to section 3.4 of Annex IX. In addition, based on clinical performance and vigilance reports (*e.g.* adverse effects), intermediate reviews may also be performed. Based on this newly added information, the

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				risk assessment may need to be adapted to include the most recent scientific and clinical developments.
			4.When there are is high-quality data available the medical device should not be allowed on the market on the basis of the precautionary principle. To avoid any harmful exposure.	4. The SCHEER disagrees (see also the answer to comment #1-1 above). For medical devices, a risk benefit evaluation is part of the total evaluation. Even when harmful substances like DEHP are used as a constituent of a medical device, the manufacturer should demonstrate that the benefit outweighs the risk. For very minimal amounts present *(e.g.*, as process residues), the principle of Threshold of Toxicological Concern (TTC) may be used to demonstrate negligible or no risk for the presence of this substance in the device. SCHEER recommends using a WoE approach for the evaluation of the available information.
			5.Avoid any loopholes and do not consider and compare “adverse effects caused by medical diagnostic, interventive and treatment measures” to those of phthalates, EDC and mixture exposures in the medical uncertainty analysis.	5. The SCHEER also considers alternative treatment modalities in which phthalates are no longer present in any used instrument/equipment as possible alternatives for medical devices containing phthalates. For alternative treatment modalities, just as for medical devices containing phthalates, conformity to the MDR, including to all safety regulations, has to be demonstrated.
2.	European Society of Endocrinology	B. REFERENCES	"IN GENERAL - missing literature that should be taken into account for the overall development of this guidance Leaching of Phthalates from Medical Supplies and Their Implications for Exposure - https://doi.org/10.1021/acs.est.2c09182 Occurrence of phthalates in facemasks used in India and its implications for human exposure - https://doi.org/10.1080/09603123.2022.2135691 Wearing face masks as a potential source for inhalation and oral uptake of inanimate toxins - A scoping review - https://doi.org/10.1016/j.ecoenv.2023.115858 "	Thank you for the references. • Wang and Kannan 2023 is now cited in Annex 6 on Use of phthalates in medical devices. • Shende *et al.* 2024 is now cited in Annex 8 section 8.2 on human exposure to DEHP and alternative plasticisers. • Kisielinski *et al.* 2024 is cited in Annex 8 section 8.2 Analytical methods, and 8.3 on human exposure to DEHP and alternative plasticisers.
3.	European Society of Endocrinology	Annex 6: Use of phthalates in medical devices	"Page 69 1. Lines 33-39: consider to also include peripubertal girls. 2. We also wonder about IVF procedures. Are embryos ""sensitive individuals""?"	1. The SCHEER agrees with the comment: peripubertal males has been changed into peripubertal individuals”. 2. All equipment, instruments and utensils used in an IVF procedure may result in the release of toxic substances.

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				Therefore, the whole IVF procedure should be carefully monitored for toxic effects.
4.	European Society of Endocrinology	7. Justification for the use of CMR/ED phthalate	"Page 34 Lines 11-17: Do these criteria include price? Can financial aspects be a part of the risk benefit analysis? "	The risk should be reduced to a level as low as reasonably practicable, which may be achieved by reducing exposure (ISO 10993-17: 2023), according to the principles of risk management as described in ISO 14971 (2019) and its accompanying guidance ISO/TR 24971 (2020). When the risk cannot be reduced to a satisfactory level, a benefit risk analysis can be performed to determine if the risk is acceptable against the benefit of using the device. The benefit risk assessment is included in the risk management file of the medical device. Ultimately costs can also be an important consideration for deciding whether or not to use an alternative substitution, but in general, the Benefit Risk Assessment (BRA) is the more important factor.
5.	European Society of Endocrinology	4. Assessment of the presence of phthalates in a medical device	1."Page 22 Lines 11-12: also take into account other chemicals beyond phthalates to asses mixture effects. 2.Page 23 Footnote 6: consider to also include embryos within IVF settings 3.Page 24 Lines 34-46: Possible low dose effects must be acknowledged and taken into consideration as phthalates are EDCs. Also important to note that smaller doses of EDCs do not always guarantee less harm, sometimes exposure to a lower dose can be more harmful than to a higher dose. 4.Page 25 Line 38: This paragraph is based on linear dose-response, unclear how the sensitive populations are accounted for.	1.These guidelines describe the approach for the BRA of alternative substances to replace CMR-ED phthalates. It should be noted that the risk assessment of a medical device includes all constituents of that medical device, including other chemicals. 2.Please see the answer to comment #3-2. 3.In the hazard characterisation, an essential part of the risk assessment, along with the description of the hazard, is the dose response relationship that identifies the lowest dose inducing any adverse effect. For endocrine activity, the dose inducing an adverse effect needs careful evaluation, including a wide range of doses, as well as evaluation for any other relevant adverse effect. 4.In the risk assessment for a medical device, the intended use of the device is of utmost importance, both regarding exposure (to which the paragraph is referring to) and effects. So, when a medical device is intended to be used by sensitive (sub)populations, this aspect needs to be integrated in the risk assessment, or when necessary, needs to be specifically addressed in the studies performed for the

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				risk assessment (e.g. reproduction toxicology studies), as stated in the guidelines.
			5.Page 26 Line 10: Are mixture effects included as ""uncertainty factors""	5.Mixture Assessment Factor (MAF) is not used here. The SCHEER is aware of the ongoing policy discussions regarding the use of additional assessment factors (MAF) for chemical mixtures. However, the SCHEER would like to caution against an a priori addition of a MAF until an agreed framework for such a use in risk assessment is established. As indicated above, the risk assessment for a medical device should include all constituents of that device. The SCHEER also recommends that whenever the risk associated to combined exposure has to be considered, the approach described in the SCCS, SCENIHR SCHER Opinion (2012) and in the EFSA guidance (2019) should be followed, as stated in the guidelines.
			6.Page 30 Line 3: replace ""on literature"" with ""on all academic literature""	6.The SCHEER disagrees with limiting the literature search to only academic literature. All available information should be included and evaluated (after an adequate and transparent quality check) in the hazard identification and characterisation of the constituents of a medical device, as requested by the WoE approach (see above answer to comment #1-4).
			7.Page 32 Lines 5-8: Would it be possible to conduct studies to obtain the missing data?"	7.Yes. When all available information is evaluated, missing data can be obtained by performing studies on exposure *(e.g*. migration studies) or on effects (Toxicological studies). The ISO 10993 series of standards provide information to perform a biological and clinical evaluation of a medical device. The ISO 10993 series can be used to comply with the essential requirements as included in the MDR EU (2017/745).
6.	European Society of Endocrinology	3. Framework for Benefit-Risk Assessment	“Page 19 1. Line 17-18: Ensure that patient exposure is measured following tests among different patient groups including children and young adults.	1. For any risk assessment, the exposure of patient groups for which the medical device is intended has to be estimated. This is already clearly indicated in the guidelines. This exposure estimation is part of the risk assessment of the medical device. Leakage properties of a substance from a medical device is an important aspect of the exposure estimation. When specific subgroups of patients (*e.g*.

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				children) are indicated for the intended use, specific information (e.g. on exposure or on age-related toxicity of some constituent) must be provided and/or specific studies must be performed.
			2. Line 20: Ensure that the latest insights from peer reviewed literature are being used to determine hazard characterisation.	2. This is already included in RA for constituents of medical devices. The RA of a medical device starts with a characterisation of the medical devices for its constituents. After the characterisation of the medical device (*e.g.* materials, constituents, process residues), the literature search regarding the constituents (including all type of information - see the answers to comment #5-4 and #9-6) is the starting point for the risk assessment of a medical device. See also ISO 10993-17 (2023) and ISO 14971 (2019). This was already included in the guidelines as part of the RA.
			3. Line 21-24: If there is no or insufficient data available, the precautionary principle should be applied until the required data has been obtained.	3. The SCHEER disagrees (see above comment #1-1). When insufficient information is available, the manufacturer has to perform additional studies for the risk assessment of the medical device. For medical devices, a risk benefit evaluation is part of the total evaluation of the device. Even when potentially harmful substances like DEHP are used as a constituent of a medical device, the manufacturer should demonstrate that the benefit outweighs the risk. When very minimal amounts are present (*e.g*. as process residues), the principle of Threshold of Toxicological Concern (TTC) may be used to demonstrate negligible or no risk for the presence of this substance in the device.
			4. Lin 36-40: Avoid regrettable substitution! Alternatives need to have testing data / information on risks.	4. The SCHEER agrees that regrettable substitutions should be avoided. For alternatives, as for the substance it is replacing (*e.g.* DEHP), the safety of use has to be demonstrated according to the MDR, including a risk benefit evaluation. This is exactly the aim of these BRA guidelines.
			5. Page 20 Line 7-16: use all peer reviewed literature available and do not only rely on regulatory tests AND apply	5.As indicated above (please see the answers to comments #1-4, #5-6, #6-2), all available information (including peer-reviewed publications as well as regulatory studies) needs to be evaluated for

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			precautionary principle if there is no or insufficient data available. Extensive testing should be a pre requirement before an alternative is allowed on the market. Regrettable substitution should be avoided at all costs.	quality and, when appropriate, considered in the assessment. When data are not available, they can be obtained by performing additional studies. SCHEER disagrees with using the precautionary principle for medical devices. The risk assessment is the basis for using or not using an alternative to avoid regrettable substitution (please see the answer to comment #6-4).
			6. Line 41-43: regular revisions are a necessity to keep the guidance up to date with the quickly evolving research in this area.	6. Regular revision of these guidelines is mandatory as presented in the MDR Annex I, Chapter II, art 10.4.3. (EU 2017/745). Based on scientific progress, but at least every 5 years these guidelines need to be revised.
			7. Page 21 Figure Regrettable substitution must be avoided, do not replace a known hazardous chemical with an alternative for which no or insufficient data is available. Also here peer reviewed literature should be used and exposure levels should be tested for different population groups including children and young adults. Mixture effect should be taken into account when assessing the ""acceptable dose"". And again, regular reviews are critical following the many studies that are being done in this area."	7. The Figure is presented to give a short overview of the procedure to be followed for the justification of continued use of a CMR/ED phthalate in a medical device. All points mentioned are addressed above in answers to comments #6-1-5.
7.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	On page 97, it should be imperative to underscore the significance of Commission Regulation (EU) 2023/2482, which amended Regulation (EC) No 1907/2006 to align the sunset date for DEHP in medical devices with the transitional periods specified in the Medical Device Regulation (MDR). This regulatory amendment allows for the continued usage of DEHP until 2030, demonstrating a harmonisation with the principle of meticulous risk assessment. Originally slated for May 2025, the sunset date for DEHP has been extended to July 1, 2030, under Regulations (EU) 2017/745 and (EU) 2017/746. This is especially important for blood bag sets as it allows the development, regulatory and validation of new materials and storage solutions in European blood establishments.	The SCHEER agrees with the comment. Specific information for the postponement of the exemption date (sunset date) for medical device constituents has been added to Annex 5. To emphasise this important aspect for blood bags, Annex 5 is specifically indicated and added as a reference to Annex 10. that this important information can be added in Annex 10. Text added to Annex 10: *"It should be noted that the sunset date for the continued use of DEHP in medical devices has recently been extended to 1 July 2030 (Commission Regulation (EU) 2023/2482) as described in Annex 5 of these guidelines. After this date, authorisation according to REACH (Regulation (EC) No. 1907/2006) is required, in addition*

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				to justification for the use of CMR/ED phthalates according to the MDR (Regulation (EU) 2017/745).” The regulatory measures according to replacement of ED substances in medical devices in relation to the REACH regulation are indicated in Annex 5. Text added to Annex 5. *“Regarding the exemption of medical devices from the REACH restriction requirements several changes have been published recently. Regulation (EU) 2021/2045 amending the REACH regulation (EC No 1907/2006) extended the scope of several phthalates including DEHP, uses in the EU. Since this modification of entry n°4 of the REACH authorisation list to include DEHP's endocrine disrupting (ED) properties, use of DEHP in medical devices (previously exempt from the REACH authorisation) will be subject to an authorisation requirement.”* *Originally, the use of DEHP was to be subject to authorisation requirements after May 2025, but the new regulation (EU) 2023/2482, issued in November 2023 postpones this deadline. This amendment aligns with the extended transitional periods for medical device regulations (EU) 2017/745 (MDR) reflecting the need for a gradual shift to DEHP-free medical devices.* *Under the new Regulation (EU) 2023/2482, users of DEHP in medical devices will no longer be able to use DEHP from July 2030, unless they apply for authorisation before January 2029. After 2030, this authorisation will add an authorisation process to the current requirements in the MDR that includes for the use of DEHP above 0.1% in a medical device a justification and comparison with potential alternatives for which the revised guidelines can be used.”*
8.	GE Healthcare	5. Assessment of possible alternative substances, materials, designs or medical treatments	Evaluation of each alternative requires extensive research and testing. This involves time and resources and eventually the validation process for the identified alternative may take multiple years to complete. Recommend changing line 35 from “three” to “two” alternatives.	The SCHEER agrees with the need for a careful evaluation of any alternative. Please see the answer to comment #6. The SCHEER disagrees with lowering the number of alternatives to be evaluated in the guidelines.

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				A lower number of evaluations is possible with appropriate and scientifically sound justification and documentation: this is already indicated in the guidelines.
9.	Haemonetics Corporation	A. UPDATE of the GUIDELINES on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	"Page 8, line 36, “Indeed, the call for information also revealed that the guidelines were also applied for other listed CMR/ED substances as indicated in Annex I Chapter II Section 10.4.4, notably cobalt (Co).” This comment should be expanded to suggest that this guidance document benefit risk assessment approach should be used for other substances of high concern. “This guidance document benefit risk assessment approach should be used for other substances of high concern.”"	These guidelines are drafted on request of the Commission, based on the MDR Annex I, Chapter II art 10.4.3., and are therefore limited to the justification for the use of CMR/ED phthalates. The SCHEER has acknowledged, already in the guidelines adopted and published in 2019, that the approach as described for phthalates also might be applicable for justification of the use of other CMR/ED substances. The MDR also indicates the possibility to draft similar guidelines for other substances as indicated in art 10.4.4. Indeed, some answers to the call for information on the use of the guidelines published in 2019, indicated its use for other CMR/ED substances, notably cobalt.
10.	Haemonetics Corporation	Annex 9: Health hazards of CMR/ED phthalate alternatives	Page 88, line 1, For Table 9.1, there is one edit we suggest making. TOTM is listed as having “liver toxicity and reproductive effects” in the “Critical toxicological endpoint for NOAEL derivation” column but the “Developmental and/or Reproductive Toxicity” column says “no up to 1000 mg/kg bw/day in rats”. The referenced CPSC 2018c, Bernauer and Fromme 2022 support the statement that TOTM does not have reproductive toxicity up to 1000 mg/kg. So, we suggest “liver toxicity and reproductive effects” should be changed to “liver toxicity” alone.	Thanks for highlighting this. The SCHEER agrees: Table 9.1 has been modified accordingly.
11.	Haemonetics Corporation	2. Methods	On page 16, line 3, table 3 the alternative plasticizers are listed.	The SCHEER agrees. However, Table 3 identifies the results of the literature search for possible alternatives. Table 3 is not an exhaustive list but identifies the most common substances that might be used as alternatives for DEHP depending on the functional characteristics needed.
12.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	Page 96/ Lines 35-36, agree with the author’s conclusion that PAGGSM reduced hemolysis in non-DEHP systems compared to other red blood cell storage solution, however, I do not agree with their conclusion that PAGGSM had a similar membrane stabilizing effect as DEHP. The mechanism of action is different and the publication does not support that conclusion. I would recommend a rewording of this conclusion. Proposed rewording:	The SCHEER agrees that it is important to remain factual when reporting literature. The sentence was modified for clarification: “*Interestingly, both studies showed that the PAGGSM storage solution reduced hemolysis associated with the usage of DEHT-PVC bags, when compared to AS-1 or SAGM”*.

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			"Interestingly, both studies showed that RBC storage in PAGGSM additive solution was associated with lower end-of-storage hemolysis, compared to other storage solutions that are in routine use today (ie SAGM, AS-1). This improvement may at least in part compensate for the increase in end of storage hemolysis that results from the removal of DEHP, which has been shown to incorporate into and stabilize the RBC membrane."	
13.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	Page 97, line 6, to enhance clarity, it is suggested that the term "blood bag sets" be utilised. This adjustment captures the true representation including apheresis sets as well as whole blood collection and processing sets.	The SCHEER agrees that term 'blood bag sets' is to be used when referring to the whole system allowing collection, processing and storage of red blood cell concentrates. The sentence was modified: "*Polyvinyl chloride (PVC) plasticised with di(2-ethylhexyl) phthalate (DEHP) has been the material of choice for blood bag sets used for the collection, processing and storage of red blood cell concentrates since the mid-20th century*".
14.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	Page 97, lines 5 – 8, report overall conclusions on studies performed on the use of alternative plasticisers to DEHP for red blood cell storage. It is suggested to acknowledge that further studies are needed to confirm available data on a larger basis and to fully elucidate all possible impacts of substitutes for DEHP in blood bag sets on blood components processing, storage and blood establishments logistic/validations.	The SCHEER agrees. The conclusion was modified: "*However, a careful benefit risk assessment extending beyond hemolysis needs to be performed before replacing DEHP by any alternative in blood bag sets. These guidelines are intended to provide information how to perform such BRA*." The SCHEER has indicated at several locations throughout the guidelines that an adequate (benefit) risk assessment has to be performed before an alternative for phthalates can be introduced in any medical device. Annex 10 is intended to raise awareness that research for replacements of DEHP as a plasticiser in blood bags is well underway. In addition, text was added to Annex 5 and Annex 10 on the Regulatory context on CMR and/or ED phthalates to inform the reader that the exemption period for the use of several phthalates in medical devices was recently prolonged to July 2030 (Regulation (EU) 2023/2482). See also comment #7. Text was added to Annex 10 referring specifically to Annex 5 regarding the sunset date for phthalates.
15.	Blood Transfusion	Annex 10: Recent progress in the use of alternative plasticisers	Page 96, line 6 and 16, to enhance clarity, it is suggested that the term "blood bag sets" be utilised. This adjustment	The SCHEER agrees that "bags" can be replaced by "bag sets". Please see the answer to comment #13

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	Association (BTA)	to DEHP for red blood cell storage	captures the true representation including apheresis sets as well as whole blood collection and processing sets.	
16.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	On page 97, it should be imperative to underscore the significance of Commission Regulation (EU) 2023/2482, which amended Regulation (EC) No 1907/2006 to align the sunset date for DEHP in medical devices with the transitional periods specified in the Medical Device Regulation (MDR). This regulatory amendment allows for the continued usage of DEHP until 2030, demonstrating a harmonisation with the principle of meticulous risk assessment. Originally slated for May 2025, the sunset date for DEHP has been extended to July 1, 2030, under Regulations (EU) 2017/745 and (EU) 2017/746. This is especially important for blood bag sets as it allows the development, regulatory and validation of new materials and storage solutions in blood establishments throughout Europe.	This comment is addressed above. Please see the answer to comments #7 and #14.
17.	Blood Transfusion Association (BTA)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	Page 96, lines 7 to 9 should this be a direct quote it should be written in the italic style and between commas (“.”) to avoid confusion.	The sentence was modified, and it is not a direct citation anymore, therefore commas (“.”) and italics are not needed.
18.	Blood Transfusion Association (BTA)	A. UPDATE of the GUIDELINES on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	"Page 8, line 36, “Indeed, the call for information also revealed that the guidelines were also applied for other listed CMR/ED substances as indicated in Annex I Chapter II Section 10.4.4, notably cobalt (Co).” This comment should be expanded to suggest that this guidance document benefit risk assessment approach should be used for other substances of high concern. “This guidance document benefit risk assessment approach should be used for other substances of high concern.” "	Please see the answer to comment #9. These guidelines are drafted based on the MDR (EU 2017/745) Annex I, Chapter II art 10.4.3. and are therefore limited to the justification for the use of CMR/ED phthalates. SCHEER has acknowledged, already in the guidelines adopted and published in 2019, that the approach as described for phthalates also might be applicable for justification of the use of other CMR/ED substances. The MDR also indicates the possibility of drafting similar guidelines for other substances as indicated in art 10.4.4. Indeed, some submissions to the call for information on the use of the guidelines published in 2019 indicated its use for other CMR/ED substances, notably cobalt.
19.	Blood Transfusion	Annex 9: Health hazards of CMR/ED phthalate alternatives	Page 88, line 1, For Table 9.1, there is one edit we suggest making. TOTM is listed as having “liver toxicity and reproductive effects” in the “Critical toxicological endpoint	Thanks for highlighting this. The SCHEER agrees and the Table has been amended accordingly (please see the answer to comment #11).

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	Association (BTA)		for NOAEL derivation" column but the "Developmental and/or Reproductive Toxicity" column says "no up to 1000 mg/kg bw/day in rats". The referenced CPSC 2018c, Bernauer and Fromme 2022 support the statement that TOTM does not have reproductive toxicity up to 1000 mg/kg. So, we suggest "liver toxicity and reproductive effects" should be changed to "liver toxicity" alone.	
20.	Blood Transfusion Association (BTA)	Annex 6: Use of phthalates in medical devices	1. Page 69, lines 6, 2. 25, 26 and 3. 35, to enhance clarity, it is suggested that the term "blood bag sets" be utilised. This adjustment captures the true representation including apheresis sets as well as whole blood collection and processing sets.	1. The SCHEER agrees and has modified the sentence: *"Besides being used as plasticiser in a multitude of polyvinyl chloride (PVC) based consumer products, phthalates are also abundantly used in polyvinyl chloride (PVC) medical devices such as blood bag sets, bags storing liquids for intravenous administration, nutrition pockets, tubing, catheters, respiratory masks or disposable gloves (Luis et al., 2021; Šimunović et al., 2022)."* 2. The SCHEER disagrees since the term "blood bags" was used here when referring specifically to the storage of red blood cell concentrates. 3. The SCHEER agrees that here "bags" can be replaced by "bag sets".
21.	Blood Transfusion Association (BTA)	Annex 4: CMR and/or ED substances	Page 64, lines 13 to 23, regarding DEHP (Di(2-ethylhexyl) phthalate) likely pertains to its acknowledgement by the Commission as a toxic substance, particularly in the context of its use in medical devices. The Commission's acknowledgement of DEHP's hazardous nature underscores the importance of addressing its use in medical devices. Despite recognising its toxicity, the Commission has allowed its continued use in medical devices until 2030. This decision likely stems from the practical challenges associated with phasing out DEHP completely from medical devices, such as the need for suitable alternative materials and ensuring the safety and efficacy of replacement products. From a scientific perspective, it is crucial to weigh the risks associated with	The text below has been added to Annex V, and reference to Annex 5 is made in Annex X (please see the answer to comment #7): Commission Regulation (EU) 2021/2045 (amending Annex XIV of REACH (Regulation (EC) No 1907/2006) extended the scope of the use of several phthalates including DEHP in the EU. Since this modification of entry n°4 of the REACH authorisation list to include DEHP's endocrine-disrupting (ED) properties, the use, previously exempted from the REACH authorisation, will be subject to an authorisation requirement. Originally, the use of DEHP was subject to authorisation requirements after May 2025, but the new Regulation (EU) 2023/2482, issued in November 2023, postpones this deadline. This

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			DEHP exposure against the necessity of its use in medical devices. While DEHP has known adverse effects, the benefits of using medical devices containing DEHP, such as preserving adequate blood and blood components during storage, must also be considered.	amendment aligns with the extended transitional periods for medical device regulations (EU) 2017/745 (MDR) reflecting the need for a gradual shift to DEHP-free medical devices. Under the new Regulation (EU) 2023/2482, users of DEHP in medical devices will no longer be able to use DEHP from July 2030, unless they apply for authorisation before January 2029. After 2030, that authorisation process will be necessary in addition to the current requirements in the MDR that requires for the use of DEHP above 0.1% in a medical device a justification and comparison with potential alternatives for which the revised guidelines can be used. This regulatory change aims to ensure public health and patient safety standards while addressing the risks of shortages, the limited capacity of notified bodies and the challenges industry faces in transitioning to DEHP-free alternatives.
22.	Blood Transfusion Association (BTA)	8.1. Material benefit	Page 37, lines 26-27, the impact of use of plasticisers on the flexibility of PVC is highlighted for e.g. intubation devices. Anyway, for completeness, it is suggested to mention also other significant functionalities of plasticised PVC, e.g. for pump tube of apheresis sets, where the PVC characteristics is a critical requirement affecting cell separation procedure and where lack of studies prolong the effective replacement of DEHP.	The SCHEER disagrees, examples provided are not meant to be exhaustive.
23.	Blood Transfusion Association (BTA)	8.1. Material benefit	1. "Page 37, regarding the terminology used, it is noted that the term ""blood bags"" is employed in lines 27 2. and 32. To enhance clarity, it is suggested that the term ""blood bag sets"" be utilised. This adjustment captures the true representation including apheresis sets as well as whole blood collection and processing sets. 3. Furthermore, attention is drawn to the statement made from line 35 to line 37 regarding the replacement of Di(2-ethylhexyl) phthalate (DEHP) in medical devices. While it is	1. The SCHEER agrees that “blood bag materials” can be replaced by “blood bag set materials” in line 27 (see also the answers above to comments #20 and below to comments #39 and #42). 2. The SCHEER agrees that clarity can be improved. The sentence was modified to clearly state that Annex 10 reports recent progress on the use of alternative plasticisers to DEHP for RBC storage: “*A number of alternatives were evaluated as alternative for DEHP during RBC storage and some of these are already in use (see Annex 10).”* 3. The recent amendments in the regulation regarding the exemption of the use of several phthalates in medical devices for authorisation according to the REACH (REGULATION (EC) No

Line	Affiliation	Section	Comment	SCHEER response
			stated that DEHP has been fully replaced (except blood bag sets – see below), it is applicable to acknowledge recent regulatory amendment by the European Commission. Commission Regulation (EU) 2023/2482 amended Regulation (EC) No 1907/2006 to align the sunset date for DEHP in medical devices with the transitional periods specified in the Medical Device Regulation (MDR). Originally slated for May 2025, the sunset date for DEHP has been extended to July 1, 2030, within the scope of Regulations (EU) 2017/745 and (EU) 2017/746. This regulatory adjustment acknowledges the challenges faced by manufacturers, particularly regarding blood bag sets. Proven substitutes for DEHP are yet to be fully validated for blood bag sets, as acknowledged in Annex 10. Thus, the statement indicating full replacement of DEHP requires clarification, given the evolving regulatory landscape and ongoing research efforts by both blood establishments and industry. 4. Additionally, the transition from risk class II to risk class III for blood bag sets containing anticoagulant solutions, according to MDR 2017/745 (Annex VIII, rule 14), underscores the efforts necessary to fully validate any material changes in contact with solutions. This includes thorough scrutiny by the drug authority."	1907/2006) is indicated in Annex 5. A specific reference to Annex 5 is now included in Annex 10. Please see the answer to comment #21 Regarding lines 35 to 37, the sentence mentioned is meant specifically for bags devoted to platelet storage. The sentence was modified: *"For this reason, DEHP, although still present in connecting tubes and ports of blood bag sets, has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) in platelet storage bags (Simmchen et al., 2012; Prowse et al., 2014)."* 4.SCHEER agrees with the comment that for any material change in a medical device, a proper analysis needs to be performed. When substantial changes are introduced in a medical device, these changes (in terms of material properties and safety) also need to be included in a (benefit) risk assessment. The medical device as a whole, including material changes, needs to comply with the essential requirements as presented in the MDR (EU 2017/745).
24.	Blood Transfusion Association (BTA)	2. Methods	"On page 16, line 3, table 3 the alternative plasticizers are listed. We have created a new table below with relevant critical factors based on work done by Spectrum Plastics that can impact whether a plasticizer can be used in a finished good. While there has been work on the use of the alternative plasticizers, there is not one that meets all the requirements in the Table below and can replace DEHP as a commercially available product to date. The ranking goes from 1 to 7, 1 being best and 7 being worst. See the table attached.	The SCHEER thanks the BTA for providing this information. However, these guidelines describe a process for the justification for continued use of CMR/ED phthalates in medical devices and a process for comparing phthalates with potential available alternatives substances. The comparison between the various available alternative substances is out of the scope of the guidelines and not included in the mandate of SCHEER to revise the guidelines. The SCHEER is aware of the amount of information and data on DEHP, and the SCHEER recognises that sometimes less data is

Line	Affiliation	Section	Comment	SCHEER response
			* Actual migration will vary based upon polymer composition or other material ^DEHP has been evaluated for all of the ISO 10993-1 relevant endpoints, chemical characterization and toxicological risk assessment. To date, there is limited available literature on the full biocompatibility testing of finish goods that have the other plasticizers as part of the material composition. Therefore, the other plasticizers are ranked 3 as more testing is needed to quantify the leachables and extractables and biological endpoints. "	available for the alternatives. See the SCHEER Opinion DEHP (2015). Each manufacturer has to perform an evaluation of the use of CMR/ED phthalates in its medical device, for which these guidelines can be used. Also, for any possible alternatives, a risk assessment and/or benefit risk assessment has to be performed Therefore, the SCHEER disagrees with the inclusion of a comparative table. In the end, the outcome of the (benefit) risk assessment determines the use or non-use of any constituent of a medical device including phthalates or their alternatives.
25.	Blood Transfusion Association (BTA)	2. Methods	Page 16, Table 3, line 3 Literature search terms should also include the chemical compound that result from the degradation or break down of the alternative substance. (For example, MEHP is a metabolite of DEHP. The BTA suspects that publications that are exploring clinical implications of the transition to non-DEHP may discuss or mention the chemical compounds that are affecting the patient (ie metabolites), which may or may not be the original compound introduced into the blood bag material by the manufacturer).	The SCHEER agrees. Therefore, in the literature search performed by the SCHEER, the search terms are applied in title, abstract, key words and, when accessible, text fields of the publications within the respective literature databases. This procedure ensures that any metabolite of the phthalates considered in the Opinion is also covered by the literature search, as it can be expected that publications related to MEHP, for example, also have the search term DEHP within title or abstract or key words or text fields.
26.	European Plasticisers (a sector group of Cefic)	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	1. "Page 96 Line 37: Please note that Morishita et al. (2017) reports only hemolysis rates for the plasticiser mixtures DINCH+DOTH or DL9+DOTH. 2. Page 97 Line 27: Please include Lagerberg et al. (2015), relating to DINCH based blood bags and lack of increased hemolysis, particularly highlighting “With alternative ASs like PAGGS-M, AS-3, or PAGGG-M, the absence of DEHP had no effect on hemolysis. We believe that this reference should be	1.The SCHEER disagrees, Morishita *et al.*, 2017 does report hemolysis rates for DEHP, DINCH+DOTH and DL9TH+DOTH. The study of Morishita *et al.* 2017 is discussed in Annex 10. 2. The SCHEER agrees and included a paragraph summarising the Lagerberg study in Annex 10. Text added: “*For red blood cells stored in DINCH bags in the storage solution SAGM, end of storage hemolysis was increased in DINCH when*

Line	Affiliation	Section	Comment	SCHEER response
			included as it shows that hemolysis is as low as with DEHP bags when using 2nd generation additive solutions. Full reference: Johan W. Lagerberg, Eric Gouwerok, Richard Vlaar, Mya Go, Dirk de Korte (2015). In vitro evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethylhexyl) phthalate–plasticized materials, Transfusion vol 55 (3), 522 – 531. https://doi.org/10.1111/trf.12870 "	*compared to DEHP but remained below the European limit of 0.8%. (Lagerberg et al., 2015). This study also showed that two second generation storage solutions (phosphate–adenine–glucose–guanosine–saline–mannitol (PAGGSM) and AS-3) or an experimental storage solution (phosphate–adenine–glucose–guanosine–gluconate–mannitol PAGGGM) reduced hemolysis associated with the usage of DINCH-PVC bags to a level similar to DEHP bags/SAGM solution*." Reference added: Lagerberg JW, Gouwerok E, Vlaar R, Go M, de Korte D. (2015). *In vitro* evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethylhexyl)phthalate–plasticized materials. Transfusion 55: 522-531.
27.	European Plasticisers (a sector group of Cefic)	Annex 9: Health hazards of CMR/ED phthalate alternatives	"Page 87 1. Table 9.1 - DINCH: In the combined chronic and carcinogenicity study with DINCH, thyroid hyperplasia and thyroid adenoma occurred. This means that chronic oral DINCH exposure did not result in carcinoma but in benign tumours (adenoma) for which the human relevance is subject to debate. Therefore, in our view it is not suitable to write 'positive' under the Carcinogenicity column. We noted the asterisk "*" was given but its placement on the subsequent page (page 88) may case it to be overlooked Additionally we suggest adding the official EFSA opinion (2006) as a reference: Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to the 12th list of substances for food contact materials. (The EFSA Journal (2006) 395 to 401, p. 7 of 21. https://doi.org/10.2903/j.efsa.2006.395) 2. Page 89i Table 9.1 Lines 8-15 for DINP: Please add the following key publication showing the difference between DBP (Di(n-butyl) phthalate) and DINP with respect to ED activity:	1. The reference to the EFSA (2006) Opinion on DINCH for use in food contact materials is already included in Table 9.1, and, in fact, the outcome of studies evaluated by EFSA (2006) are reported in that Table. The SCHEER disagrees with including any change in the Table, since the correct information is cited in the Table and in the (*) note, which is part of the Table itself. 2.The paper was already cited in the text of Annex 9 of the guidelines and there is therefore no need to include it in Table 9.1.

Line	Affiliation	Section	Comment	SCHEER response
			Sander van den Driesche, Serena Shoker, Fiona Inglis, Christine Palermo, Angelika Langsch, Rainer Otter (2020), Systematic comparison of the male reproductive tract in fetal and adult Wistar rats exposed to DBP and DINP in utero during the masculinisation programming window. Toxicology Letters, Volume 335, 37-50 (https://doi.org/10.1016/j.toxlet.2020.10.006) 3.Page 89 – Please add the page number in the guideline document. 4. Page 90 Table 9.2: We do not understand the relevance of referring to COMGHA mentioned in Regulation (EU) No 10/2011. If this one should be mentioned in this table, we wonder why not all other plasticisers listed in the said Regulation. Furthermore, the IUPAC name for the substance is missing: 1,3-bis(acetyloxy)propan-2-yl 12-(carboxyoxy)octadecanoate; 2,3-bis(acetyloxy)propyl 12-(acetyloxy)octadecenoate (https://echa.europa.eu/registration-dossier/-/registered-dossier/2571/1/1) 5.We suggest adding FCM numbers all the approved substances in the EU. 6..Page 94 Lines 40-43: Please update the reference to reflect the revised 2015 SCENIHR opinion (February 2016) (https://health.ec.europa.eu/document/download/d17de743-1077-4654-81a7-b4148667f20c_en?filename=scenihr_o_047.pdf). "	3.The page number has been added. 4. The reference to Regulation (EU) No 10/2011. has been deleted and the IUPAC name added to Table 9.2. 5. The SCHEER considers adding FCM numbers not relevant for these guidelines. 6.The link to the website of the SCENIHR and the SCHEER references has been added to the references.
28.	European Plasticisers (a sector group of Cefic)	Annex 5: Regulatory context on CMR and/or ED phthalates	1. "Page 65 Line 2: To avoid any misunderstanding of the hazard properties of phthalates among the readers, we suggest modifying the title from 'Regulatory context on CMR and/or ED phthalates' to 'Regulatory context on ortho-phthalates classified for toxicity to reproduction and/or ED'.	1.The SCHEER disagrees with changing the title of Annex 5. In the guidelines in general the word phthalates is used. The specific indication of ortho-phthalates is presented separately in the Introduction. The wording is the same as used in the mandate from the Commission.

Line	Affiliation	Section	Comment	SCHEER response
			2. Page 70 Lines 35-38: The request for an appropriate benefit-risk analysis for the alternatives is scientifically justified. Please note that currently DEHP may be used in medical applications where for most of the exposure scenarios either risk/unacceptable risk must be concluded, or relevant exposure data are even missing. "	2.The SCHEER agrees with the comment. For all constituents of a medical device, the risk has to be evaluated, and when indicated, a benefit risk assessment may be performed. This also applies to any possible alternative that may be used as substitute for DEHP or any other CMR/ED phthalate.
29.	European Plasticisers (a sector group of Cefic)	Annex 4: CMR and/or ED substances	"Page 62 Lines 24 to 25: We suggest changing the weblink mentioned in the guideline to the official ECHA weblink: https://echa.europa.eu/information-on-chemicals/cl-inventory-database" Weblink mentioned in Opinion not include here. Weblink present in Excell table #33	The SCHEER thanks you for your comment. The link has been changed to the suggested ECHA website. For more clarity, the text referring to the ECHA website has been modified: "*Documents on the classification and labelling are publicly available, and information on the C&L Inventory to search for notified and registered substances is given here*:"
30.	European Plasticisers (a sector group of Cefic)	B. REFERENCES	Page 47: Please add DOI for Klei et al. (2022); https://doi.org/10.1111/vox.13384	Weblinks are only provided for references to official documents and not for all publications. For the references to published scientific papers, the DOI is not indicated in the guidelines.
31.	European Plasticisers (a sector group of Cefic)	11. Conclusions	"Page 43 Line 5/6: Please note that specific ortho-phthalates are classified and accordingly labelled based on their toxicological profiles (such as toxicity by reproduction and also ED). However, we find that the wording used in the guideline may be misleading, as ortho-phthalates are not identified as genotoxic/mutagenic or carcinogenic. For some of them peroxisome proliferation leads to liver tumours, but based on the mode of action, these ortho-phthalates are not classified or labelled as carcinogenic according to CLP rules."	The SCHEER cites the classification CMR/ED as the regulatory identified group. CMR/ED is the group identification for phthalates with possible effects that could be either carcinogenic, mutagenic, reprotoxic or show endocrine-disrupting activity. This CMR/ED group identification does not mean that the identified phthalate produces all of these effects. When one effect is demonstrated *(e.g.* endocrine disruption), the substance belongs to the CMR/ED group. The classification is based on the regulatory designation of the substance according to Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP regulation.
32.	European Plasticisers (a sector group of Cefic)	6. Assessment of most relevant alternative substances, materials,	"Page 32 Line 27 and several other locations: We see the naming of 'CMR/ED phthalate', and recommend referring to the exact substance name to avoid any ambiguity. In this particular	Only CMR/ED phthalates are included in the mandate (general terminology) and not any specific phthalate.

Line	Affiliation	Section	Comment	SCHEER response
		designs or medical treatments	case on Line 27, we recommend that DEHP should be mentioned."	The SCHEER disagrees. Only CMR/ED phthalates are included in the mandate (general terminology) and not any specific phthalate. Also, in the MDR ((EU) 2017/745, specifically a justification needs to be presented for the presence of CMR and/or endocrine-disrupting substances in general (Annex I, Chapter II art 10.4.2. Whereas in Annex I, Chapter II art 10.4.3 specifically guidelines on phthalates are mentioned.
33.	European Plasticisers (a sector group of Cefic)	5. Assessment of possible alternative substances, materials, designs or medical treatments	"Page 31 Line 21: TDI values derived by EFSA refer to the oral route of exposure. Please note that medical applications may use the intravenous route of exposure. Please also note that the NOAELs on the oral and the intravenous route may differ significantly. For example, for DEHP, the NOAEL oral is 5 mg/kg bw/day (Wolfe et al., 2003 TRC Study No7244-200 NTP-RACB-98-004-) while on the intravenous route the NOAEL is 60 mg/kg bw/day (Cammack et al., 2003; DOI: 10.1080/10915810305098)."	The SCHEER agrees and indeed considerations about the possibility of performing a route-to-route extrapolation were already included in the text (Step 3- Risk characterisation). Further clarifications have been added to make the concept clearer in the description provided for Step 3 and 7: *"Identify an adequate point of departure (PoD) for risk assessment, meaning that it should be representative of the route and duration of exposure for the specific medical device under evaluation."*
34.	European Plasticisers (a sector group of Cefic)	1. Introduction	1. "Page 12: Line 11 to 12: We suggest the following correction: from 'A typical concentration of Bis(2-ethylhexyl) phthalate (DEHP; CAS 117-81-7) in 11 plasticised polyvinyl chloride (PVC) can be around 30%' to 'A typical concentration of Bis(2-ethylhexyl) phthalate (DEHP; CAS 117-81-7) in 11 plasticised polyvinyl chloride (PVC) can be around 40 %' (please see European Pharmacopoeia 11th ED, chapter 3.3.3.) 2.Line 15: We suggest the following correction: from 'Classification, Labelling and Packaging (CLP) regulation (EC 1272/2008 'to 'Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008'	1. The reference to EU Pharmacopeia 11th ed., 2022 was added, and the range of DEHP used was indicated as 30-40 %. 2.According to the guidance on EU legal sources (directives, decisions and regulations): - In-text citations need to include 'The type of legislation (EC or EU*) its number/year)' - Reference list needs to include 'Legislation name - including the type of legislation (EC or EU*) its number/year (Official Journal issue)' * In 2009, the EC (European Community) was renamed the EU (European Union) <u>Examples</u>:

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				In-text citation: "Taking account of the new hazard classes and criteria for classification, labelling and packaging of substances introduced by Commission Delegated Regulation (EU) 2023/707 of 19 December 2022, reference to endocrine disruptors for human health, of Category 1, should be specified in 10.4.1., point (b) of Annex I of Regulation (EU) 2017/745 in light of the relevance of that hazard class to the type of substances in medical devices." Reference list: Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117 5.5.2017).
			3.Line 19: Please add 'specific' before 'Phthalates' to emphasise that this line refers only about phthalates classified as reprotoxicity 1B. There are plenty of ortho-phthalates which are not toxic to reproduction, and we are concerned that the original draft wording in this guideline could cause misunderstanding among the readers. Line 20: We suggest the following correction: from 'Classification, Labelling and Packaging (CLP) regulation (EC 1272/2008)' to 'Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008' Lines 21/22/27: We suggest the following correction: from 'REACH Regulation (EC) 1907/2006' to 'REACH Regulation (EC) No 1907/2006' Line 33: Please add reference for the revised 2015 SCENIHR opinion (February 2016): https://health.ec.europa.eu/document/download/d17de743-1077-4654-81a7-b4148667f20c_en?filename=scenihr_o_047.pdf	3.The SCHEER disagrees. Text inline 19 indicates "*Phthalates currently classified as reproductive toxicants…*". It is very clear from the text that only a specific group of phthalates is indicated and not all phthalates.
			4.Page 13 Line 10: We suggest the following correction: from 'REACH (Regulation (EC) 1907/2006' to 'REACH Regulation (EC) No 1907/2006' Line 10 to 11: We suggest the following correction: from 'the Biocides Regulation (Regulation (EC) 528/2012)' to 'the	4. All references to any EU or EC regulation are now corrected in the text as presented in the published regulation. So, the presence or absence of No depends on the wording of the publication. See examples presented above.

Line	Affiliation	Section	Comment	SCHEER response
			Biocidal Products Regulation (Regulation (EC) No 528/2012)' Line 13: We suggest the following correction: 'the Commission Delegated Regulation (EU) 2023/707' to ' the Commission Delegated Regulation (EU) No 2023/707' Among the lines, there is consistency between the reference to the legal text reference (with No and without No). We recommend unifying the description into either way. "	
35.	MedTech Europe	ACKNOWLEDGMENTS	Please find attached MedTech Europe's paper summarizing the comments submitted to the present consultation on the individual chapters of this draft revised report as well.	The SCHEER thanks MedTech Europe for their comments, which have been included in this Table.
36.	MedTech Europe AISBL	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	1. "General comment: Annex 10 reports on recent progress in the use of alternative plasticizers to DEHP for red blood cell storage. DEHP replacement is still under replacement efforts (in this application as well), however, will still take time, as per the extended REACH Sunset Date. 2. Lines 6 & 16: Suggest using the term ""blood bag sets"" instead of ""blood bags"" to capture the true representation including apheresis sets as well as whole blood collection and processing sets. 3. Lines 35-36: MedTech Europe agrees with the author's conclusion that PAGGSM reduced hemolysis in non-DEHP systems compared to other red blood cell storage solution. However, MedTech Europe does not agree with their conclusion that PAGGSM had a similar membrane stabilizing effect as DEHP. The mechanism of action is different and the publication does not support that conclusion. MedTech Europe recommends a rewording of this conclusion. Proposed rewording: ""Interestingly, both studies showed that RBC storage in PAGGSM additive solution was associated with lower end-of-storage hemolysis, compared to other storage solutions that are in routine use today (ie SAGM, AS-1). This improvement may at least in part compensate for the increase in end of storage hemolysis that results from the removal of DEHP,	1. Please see the SCHEER answers to comments #3and #12. Information on the regulatory changes regarding the postponement of the sunset date for DEHP are now included in Annex 5, which is referred to in Annex 10. 2. Please see the SCHEER answers to comments #9 and #11. Where appropriate, "blood bags" has been changed to "blood bag sets" 3. Please see the SCHEER answer to comment #8.

Line	Affiliation	Section	Comment	SCHEER response
			which has been shown to incorporate into and stabilize the RBC membrane."	
37.	MedTech Europe AISBL	Annex 9: Health hazards of CMR/ED phthalate alternatives	Annex 9 provides a brief compilation of toxicological information for several phthalates, DEHP and its alternatives DEHT, DEHT and TOTM. DEHP is a substance used in multiple medical device applications and currently subject to REACH Authorisation efforts by MedTech Europe members.	The SCHEER thanks you for this comment.
38.	MedTech Europe AISBL	Annex 8: Exposure identified for currently used alternatives	Annex 8 accurately depicts industry efforts regarding e.g. the exposure identified for currently used alternatives: it notes that progress has been made on the replacement of DEHP by other phthalates and/or alternative substances in various applications and it clearly mentions other admitted phthalates like DEHT, DEHA, and TOTM.	The SCHEER agrees.
39.	MedTech Europe AISBL	Annex 6: Use of phthalates in medical devices	Lines 6, 25, 26 & 35: Suggest using the term “blood bag sets” instead of “blood bags” to capture the true representation including apheresis sets as well as whole blood collection and processing sets.	Please see the SCHEER answer to comments #16 and #32-2.
40.	MedTech Europe AISBL	Annex 4: CMR and/or ED substances	General comments on CMR and/or ED: Categorization of Endocrine-Disruptor (ED) substances: the guidance on how to assign substances as EDs (meaning known or presumed endocrine disruptors, Category 1 ED, and suspected endocrine disruptors, Category 2 ED) and to designate different ED categories is still under development. Also, the ED categorization is also not yet included in the Medical Device Coordination Group (MDCG) endorsed documents or other EU Guidance documents on medical devices. MedTech Europe would like to understand when the industry might expect insights on these categorization efforts.	In March 2023, the European Commission published Delegated Regulation 2023/707 establishing new hazard classes in the CLP Regulation on classification, labelling and packaging of substances, and determining the criteria for the classification of endocrine disrupting substances (EDs), persistent, bioaccumulative and toxic (PBTs) and persistent, mobile and toxic (PMTs). The new CLP entered into force in April 2023. The new classifications will apply for industry from 1 May 2025 for new substances and from 1 November 2026 for substances that have already been on the EU market. For mixtures, separate transition times apply from **1 May 2026** for new mixtures and from **1 May 2028** for existing mixtures. ECHA, in cooperation with EFSA, is preparing an update of the Guidance on the Application of the CLP criteria to include guidance on the new hazard classes. Following consultations with stakeholders, the updated guidance is planned to be published by the end of 2024. Until then, the following guidance can be used for endocrine disruptors: EFSA/ECHA Guidance for the identification of

Line	Affiliation	Section	Comment	SCHEER response
				endocrine disruptors in the context of Regulations (EU) No 528/2012 and EC No 1107/2009 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311 With regard to medical devices, the Commission proposal COM(2023)783 amending Regulation (EU) 2017/745 (MDR) was published in December 2023. The proposal contains an amendment of the MDR to update the references to the new classification for Endocrine Disruptors (EDs). Endocrine disruptors for human health, of Category 1, should be specified in the MDR.
41.	MedTech Europe AISBL	10. Uncertainty analysis	"We would like to raise 3 points on this section in general: 1. Uncertainty in the biological difference among individuals: a part of uncertainty factors guided in Sections 4 and 5 on toxicological risk characterization, consistent with current practice. 2. Uncertainty in the analytical chemistry laboratories variability (or analytical evaluation of constituent) described in ISO 10993-18: consistent with current practice. 3. Uncertainty in the diagnostic tools and clinical information: both are part of clinical investigation but may be lacking and could need to be addressed further."	The SCHEER thanks you for the comment. These issues are addressed in chapter 10.
42.	MedTech Europe AISBL	8.1. Material benefit	Lines 27 & 32: Suggest using the term "blood bag sets" instead of "blood bags" to capture the true representation including apheresis sets as well as whole blood collection and processing sets.	Please see the answers to comments #23, #36, and #39).
43.	MedTech Europe AISBL	8. Benefit assessment	Per these guidelines, the contents of the benefit-risk assessment to be conducted by a medical device manufacturer seem to be in line with the contents of some of MedTech Europe members' documents prepared in the context of the DEHP REACH Authorisation.	The SCHEER thanks you for the comment.
44.	MedTech Europe AISBL	5. Assessment of possible alternative substances, materials, designs or medical treatments	Relevant for sections 5 & 6 in general regarding alternatives: Speaks about risk, based on acute accumulated exposure, but we have no long-term knowledge of the accumulated exposure of the alternatives to DEHP. It will be important to clarify the parameters we	The SCHEER is aware that for some alternatives, long term effects are not yet known, while for others, long-term effects have already been described (see Table 9.1 in the guidelines). The (B)RA for the alternatives should follow the rules as indicated in the MDR. One method to comply with the safety assessment as

Line	Affiliation	Section	Comment	SCHEER response
			need to collect from the alternatives in the future to identify an unexpected risk and gave the time to react to it.	indicated in the MDR, could be the use of ISO 10993 series of standards dedicated to the safety evaluation of medical devices.
45.	MedTech Europe AISBL	2. Methods	Line number 3: Literature search terms should also include the chemical compound that result from the degradation or break down of the alternative substance. (For example, MEHP is a metabolite of DEHP. Publications that are exploring clinical implications of the transition to non-DEHP may discuss or mention the chemical compounds that are affecting the patient (ie metabolites), which may or may not be the original compound introduced into the blood bag material by the manufacturer).	Please see the answers to comment #25.
46.	MedTech Europe AISBL	1. Introduction	Lines 28-30: Should not make reference to “on which the device is used”, should instead focus on the reasonably foreseeable use and the potential exposure to any individuals whether patient, healthcare professional or otherwise.	For each medical device, the (B)RA is based on the exposure resulting from the intended use of the device. This also includes the various patient groups for which the device is intended.
47.	MedTech Europe AISBL	A. UPDATE of the GUIDELINES on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Line numbers 25-27: Should make reference to the “reasonably foreseeable use” of the device when discussing potential exposure to patients, healthcare professionals or other persons.	Please see the answer to comment #46.
48.	MedTech Europe AISBL	Main changes in the first UPDATE of the guidelines	"Line number 16: Going from potential relevant to most relevant is a good change; helps industry focus on the scope. Line number 26: MedTech Europe would advise against ISO 10993-18 being listed under step 1 - if the hazardous substance isn’t released that does not mean it is not present in the material at an acceptable level. MedTech Europe members’ experience demonstrates that it would be more suited for ISO 10993-18 to be referenced for the TRA (e.g., exposure assessment) in the MoC justification. This may otherwise lead to confusion that was experienced in the early stages of EU MDR implementation. MoCs are content and biocompatibility is exposure."	The SCHEER thanks you for the comment. The SCHEER disagrees. Step 1 is identification of the constituent, whereas the exposure, including potential release from the medical device, is part of the RA.

Line	Affiliation	Section	Comment	SCHEER response
49.	DIAGEN Bic.	Main changes in the first UPDATE of the guidelines	"Hello dear official, Regarding the SCHEER benefit-risk analysis, you only focused on MDR. Can the relevant substances be added to the SCHEER benefit-risk analysis within the scope of the IVD Regulation? Companies within the scope of IVDR will be very pleased with your work. Kind regards"	The mandate of the SCHEER is limited to the justification of the use of CMR/ED phthalates in medical devices. However, it is indicated in the guidelines that a similar approach may be used for justification of the use of other CMR/ED substances.
50.	MACO PHARMA	Annex 10: Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage	"In order to complete this Annex 10, we propose some modifications. 1.in line 11 add longer storage duration of red blood cells (RBC) In addition, leached DEHP incorporates in the red blood cell membrane and has a stabilising effect, which helps to maintain cell integrity, reducing hemolysis and thus permitting longer storage duration of red blood cells (RBC) (Horowitz et al., 1985; 11 Rock et al., 1984) 2.And after the § “on the plasticiser alternatives for DEHP did not show a negative impact on the end of storage ATP level, suggesting that red cell metabolism is not negatively impacted by DEHP removal (Morishita et al., 2017; Larsson et al., 2021; Graminske et al., 2018; Vermeulen et al., 2022),” to add these sentences: “In addition, an in vitro study comparing the migration of DINCH, DEHT and DEHP into blood products showed that patients transfused with blood products using PVC-DEHT or PVC-DINCH blood bags are less exposed to plasticizers than using PVC-DEHP bags with a ranging exposure reduction from 38.9% to 87.3%, due to lower leachability into blood components (Thelliez et al., 2023).” The corresponding reference is: Thelliez A, Sumian C, Chazard E, Reichenberg S, Lecoeur M, Decaudin B. Migration of di(2-ethylhexyl) phthalate, diisononylcyclohexane-1,2-dicarboxylate and di(2-ethylhexyl) terephthalate from transfusion medical devices in labile blood products: A comparative study. Vox Sang 2023;118: 533-42."	1.The SCHEER agrees and has modified the sentence as follows: *“In addition, leached DEHP incorporates in the red blood cell membrane and has a stabilising effect, which helps to maintain cell integrity, reducing haemolysis and thus permitting longer storage duration of red blood cell concentrates (Horowitz et al., 1985; Rock et al., 1984).”* 2.The SCHEER disagrees. The reference of Thelliez *et al*., 2023 is cited in Annex 8 section 8.1” Leaching and extractable properties”. In this section it was already stated that when using PVC blood bags plasticised with DINCH and/or DEHT, there was less leaching of these plasticisers n compared to blood bags plasticised with DEHP, resulting in a reduced exposure of patients to these plasticisers. It should be noted that the amount of leaching is only one parameter that determines the exposure dose. The safety also depends on the hazards associated with the substances. Annex 10 mainly addresses the issue of the effect of various alternatives on blood cell storage.
