Results of the public consultation on SCHEER's Guidelines on the benefit-risk assessment of CMR/ED phthalates used in medical devices

A public consultation on these Guidelines was opened on the website of the non-food scientific committees from 18 March to 29 April 2019.

Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

A total of 197 submissions from 19 contributors (providing 378 comments and additional references) provided input to different chapters and subchapters of the document.

The vast majority of comments came from industry and were requesting clarifications.

Each submission was carefully considered by the SCHEER and the scientific opinion has been revised to take account of relevant comments.
The literature has been accordingly updated with relevant publications.

The SCHEER expresses its thanks to all contributors for their comments and for the literature references provided during the public consultation.

The table below shows all comments received on different chapters of these Guidelines and SCHEER's response to them. It is also indicated in red if the comment resulted in a change of the Guidelines.

Comments received during the public consultation on the SCHEER's Guidelines on the benefit-risk assessment of CMR/ED phthalates used in medical devices

No	Name of individual/organisation	Table of contents	Please indicate the line numbers of the text on which you comment, if appropriate (Submission)	SCHEER's response **Changes in text are indicated in red.**
1	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany		The guideline is phrased broad enough to meet requirements of different medical devices for use on several routes of exposure. For the evaluation of alternatives information regarding drug/device interactions and suitability of the alternative to sterilization should be provided.	SCHEER agrees. The alternative has to fulfil all functionalities now associated with DEHP. So, this would also include possibilities for sterilisation. Text added that also "other functionalities" like sterilisation should be covered by the alternative. In this comparison also additional issues not directly related to the functionality and performance of the alternative itself, like technical possibilities, sterilisation effects and interactions with infusion liquids, are important for the application of the alternative and the comparison with the CMR/ED phthalates, and thus should be considered. (chapter 5, step 8 –> i.e. preliminary version = page 20 after line 40) See comment #15 for references.

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2	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 9, line 2-4: “Although quite a number of alternative substances were available for DEHP, serious data gaps were observed regarding hazard identification and exposure estimation for some of them (Bui et al., 2016, SCENIHR 2016).” Suggest to add after line 4 a reference to the updated chapters of the EU Pharmacopoeia: 4 additional plasticizers (DINCH, BTHC, TOTM and DEHT) used in medical devices in Europe have recently been included in the updated chapters of the European Pharmacopoeia.	SCHEER agrees. Text added Page 9 Lines 2-4, For example, four additional plasticisers for PVC (BTHC, DEHT, DINCH, and TOTM) used in medical devices have recently been included in the updated chapters of the European Pharmacopoeia (Council of Europe, EDQM 2018). and Page 24 line 9 Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM) however, this may not be the case for other alternatives identified.
3	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 9, line 2-4: “Although quite a number of alternative substances were available for DEHP, serious data gaps were observed regarding hazard identification and exposure estimation for some of them (Bui et al., 2016, SCENIHR 2016).” Suggest to add after line 4 a reference to the updated chapters of the EU Pharmacopoeia: 4 additional plasticizers (DINCH, BTHC, TOTM and DEHT) used in medical devices in Europe have recently been included in the updated chapters of the European Pharmacopoeia.	See answer to above comment number 2.

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4	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 14, line 8-9: EFSA grouping Please note that this is still a draft and the scientific basis for the EFSA approach is currently under scrutiny.	SCHEER disagrees. Page 14 Lines 8-9: The draft issue is already indicated in the text by the word “proposed”. Text added for clarification. Some risk assessment data regarding the combination of phthalates are available, as EFSA has recently proposed a Group TDI for some of them, having a similar Mode Of Action (MOA) in vivo (EFSA 2019, see Annex 5). Information on assessment of combined exposures to phthalates can be found for example at the report by the National Research Council Committee on the Health Risk of Phthalates (2008) and the ECHA website on the restriction of four phthalates (https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180d73895) and EFSA guidance on cumulative exposure (EFSA, 2019) (https://doi.org/10.2903/j.efsa.2019.5634) (Chapter 3)
			Page 15, lines 43-47: “considered safe exposure levels” Please add that the DNELs, DMELs, ADIs or TDIs/TWIs should be reflect the appropriate route of exposure. TWI = Tolerable weekly exposure? Should be added to the list of abbreviations.	SCHEER agrees. Page 15 Lines 43-47. TDI added. And text added. TWI added to abbreviations. TWI Tolerable Weekly Intake As such data are often obtained in rat

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			Please add TDI (tolerable daily intake) as the guidelines are intended to cover phthalates. Please take note that the male programming window for reproductive toxic phthalates comprises only some some days in the rat, i.e. GD 15.5-19.5 (Welsh et al., 2008, reference is attached). The rat NOAEL is the basis for the TDI, therefore, therefore a TDI instead of a TWI is preferred.	studies, the use of the TDI seems more appropriate in view of the critical effect window for androgenic reproductive toxicity in rats has been reported to be a few days (Welsh et al., 2008). In addition, patients may be exposed to medical devices only for a limited period of time. (Chapter 3, step 3)

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5	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 19, lines 14-21: risk characterization Please add TDI (line 19) Suggest to add that DNELs, DMELs or safe dose levels on the relevant route of exposure should be applied. Page 19, lines 30-34: Suggest to consider use of route specific NOAELs and modify this chapter, e.g. to: …., the assessment could refer to these derived figures for the relevant route of exposure. For the intravenous route a safe dose level should preferably be deduced from this route of exposure as for phthalates, the first pass effect plays a major role, as for those plasticizers, where a NOAEL for the intravenous route from a repeat dose toxicity study is available, the NOAEL i.v. is higher than the NOAEL on the oral route.	 SCHEER agrees SCHEER agrees Partially accepted. Text added to Page 18 Line 43 and Page 19 Line 34. P18L43. Hazards should preferably be evaluated by a relevant exposure route for the intended use of the medical device. (chapter 4, step 7) However, in general the toxicity data are not obtained using exposure routes similar to med dev exposure. P19L33. Data on the relevant exposure route of the medical device application (e.g. intravenously) are preferred (see also Table 1A, EN ISO 10993-1).

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6	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 22, line 31: Should be modified to: The table should be adapted depending on the number of criteria evaluated… Page 23, Table 1, 3rd – 4th row: For relevant route of exposure Page 23, line 10: Suggest to modify to: In this evaluation, the full toxicological profile of the potential alternatives shall be taken into account. Lines 6 – 19, general comment: the criteria are not very clearly defined, however, this gives enough room for the medical device producer to deal with the specific scenarios.	SCHEER agrees. Can replaced by "should". SCHEER agrees. Added: Leaching from medical device for relevant conditions e.g. media, temperature, etc (mg per hour/day) ..for relevant route of exposure.. (Chapter 6, Table 1) Text added. So, the full toxicological profile of the potential alternatives shall be taken into account. (chapter 6, under Table 1) (Ref. to chapter 2 explaining steps + Figure 1 + chapter 4 step 5). No comment.

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7	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 24, lines 8-15: Availability of alternatives This chapter should be critically evaluated as the main alternative plasticizers in discussion here, i.e. DINCH, BTHC, TOTM and DEHT are high production volume chemicals that easily can serve the volume needed for medical applications.	SCHEER agrees. Text adapted: Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM) however, this may not be the case for other alternatives identified. (chapter 6)
8	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 24, lines 8-15: Availability of alternatives This chapter should be critically evaluated as the main alternative plasticizers in discussion here, i.e. DINCH, BTHC, TOTM and DEHT are high production volume chemicals that easily can serve the volume needed for medical applications. Page 24, lines 25-42: 7.1. Material benefit Suggest to delete the BTHC example as Simmchen et al. 2012 listed several further plasticizers and if you mention BTHC, then consequently you also should mention the unpleasant smell and the higher hemolysis rate when compared to DEHP or DINCH. Page 24, Lines 36-42: Agree that for platelet storage DEHP has been replaced but as a matter of fact today with BTHC, DINCH and TOTM.	See above answer to comment number 7. SCHEER agrees. Text modified. A number of alternatives were evaluated as alternative for DEHP in blood bags (Simmchen *et al.,* 2012, SCHENIR 2016,) (chapter 7.1) Text modified. For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen et al. 2012, Prowse *et al*. 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags

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				(Prowse et al. 2014). See also comment #53.
9	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 30, lines 18-20: While SCHEER claims missing data for alternatives to DEHP, where are the data for DEHP based devices. When testing alternative plasticizers, we realize that DEHP data are not robust enough as analytical methods used decades ago were not sensitive enough or are even completely missing.	SCHEER agrees. But these Guidelines describe a methodology, so actual data are not mentioned.

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10	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 32, lines 30…. Please add the missing references: Bui (2016) Simmchen (2012) Mariana (2016) Katsikantami (2016)	SCHEER agrees. References added.
11	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 33, line 33: adverse health effects of phthalates in humans? If that would be the case, then e.g. DEHP would have to be classified as Repro Cat 1A according to CLP (Regulation (EU) No 1272/2008). As DEHP is classified as Repro Cat 1B, the human evidence for adverse effects is ambiguous. Especially, as there are no adverse testicular effects seen with the marmoset. The literature cited (Mariana, 2016 and Katsikantami, 2016) are not supporting this statement. Both are dealing with correlations or associations, both are referring to epidemiology, i.e. should be critically discussed in the appropriate context.	SCHEER disagrees. Text indicates indeed “correlations” not with scientifically demonstrated causality. This was also discussed in the RAC/SEAC background document on the restrictions of the four phthalates (ECHA)

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12	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 42, line 28: DINCH, chemical name must be corrected: 1,2-cylohexanedicarboxylic acid, diisononyl ester Page 43, line 28: add missing abbreviation TWI = tolerable weekly intake	SCHEER agrees. Name corrected. TWI added. Also added. TEHTM Tri(2-ethyl hexyl)trimellitate also TOTM Trioctyltrimellitate TOTM Trioctyltrimellitate also TEHTM Tri(2-ethyl hexyl)trimellitate

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13	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com, Germany	1. Introduction	Page 47, lines 3 – 19: References to EU Regulations should be corrected and unified Page 48, lines 2 – 18: Please note that for DINP (FCM 728) and DIDP (FCM 729), group restriction (26), i.e. SML(T) = 9 mg/ kg food applies additionally to group restriction (32), i.e. SML(T) = 60 mg/kg food. Page 48, line 20: Needs to be corrected to: Furthermore, for all the plasticizers listed in Reg (EU) No 10/2011, Table 2 lists group restriction (32), i.e. SML(T) = 60 mg/kg food (overall migration limit value). The current sentence listing phthalates together with DINCH does only present half of the truth and seems not to be appropriate. Page 48, line 29, table 1, entry for DEHP. As the reference is the candidate list, please add listing as ED for human health and the environment (both with reference to REACH, article 57(f) This is the exact entry on the candidate list for DEHP, available from the ECHA website: https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e1807d8dc8	SCHEER agrees. P47 L3-19. Done. SCHEER agrees. This is indicated in the text within brackets after DINP and DIDP (cumulative with DINP) (cumulative with DIDP). SCHEER agrees. P48 L20 text modified. Furthermore, for certain e plasticisers listed in Regulation (EU) 10/2011, including a number of phthalates applies a group restriction (Group restriction number 32), that is, the sum of these substances must not exceed an SML of 60 mg/kg foodstuff. (above Table 1) P48L29. This is a general classification Specific identification of art 57(f) is not needed. Text added below the table for clarification with referral to REACH: “published in accordance with Article 59(10) of the REACH Regulation”. (below Table 1)

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14	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Page 51, line 25: Please correct the CAS registry number of DINCH to: CAS 166412-78-8	SCHEER agrees. CAS number corrected into: 166412-78-8.
15	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,Germany	1. Introduction	Drug/Device interactions should be mentioned somewhere. Literature to be added would be e.g. Soloum H Al et al., Int J Pharm 496, 2015, 664–675 Tortolano L et al., J Appl Polymer Sci, 2018, 46649(1-8); DOI: 10.1002/app.46649 Treleano A. et al., Int J Pharm 369, 2009, 30–37 Regarding technical suitability for alternatives, sterilization needs to be considered. Literature to be added: Burgos N et al., Polymer Degrad Stabil 94, 2009, 1473–1478 Crespo JE et al., J Appl Polymer Sci, 2007, 1215–1220	SCHEER agrees. Page 18 Line 6. Text added to address other aspects of functionality. Also other aspects related to performance of the alternatives need to be considered like material processing conditions (Crespo et al., 2007), material quality after sterilisation (Burgos and Jiménez 2009), and possible interaction with drugs in therapeutic infusion systems (Treleano et al., 2009, Salloum et al., 2015, Tortolano et al., 2018). (Chapter 4, step 6) And Page 20 Line 41. See comment number 1. In this comparison also additional issues not directly related to the functionality and performance of the alternative itself, like technical possibilities, sterilisation effects and interactions with infusion liquids, are important for the application of the alternative and the comparison with the CMR/ED phthalates, and thus should be considered.

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16	Dr. Otter,Rainer,BASF SE,rainer.otter@basf.com,	1. Introduction	Page 15, lines 43-47: “considered safe exposure levels” Please add that the DNELs, DMELs, ADIs or TDIs/TWIs should be reflect the appropriate route of exposure. TWI = Tolerable weekly exposure? Should be added to the list of abbreviations. Please add TDI (tolerable daily intake) as the guidelines are intended to cover phthalates. Please take note that the male programming window for reproductive toxic phthalates comprises only some some days in the rat, i.e. GD 15.5-19.5 (Welsh et al., 2008, reference is attached). The rat NOAEL is the basis for the TDI, therefore, therefore a TDI instead of a TWI is preferred. not upload possible due to file size restriction! Please find here the reference for the male programming window: Michelle Welsh, … , Lee B. Smith, Richard M. Sharpe J Clin Invest. 2008;118(4):1479-1490. https://doi.org/10.1172/JCI34241	Comment addressed under #4 including addition of reference Welsh *et al.* 2008.

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17	van den Burg,Peter,European Blood Alliance (EBA),p.vandenburg@europeanbloodalliance.eu,Netherlands	1. Introduction	The comments refer in general to the passages regarding patients and clinics; 1) The exposition to phthalates is described in relation to patients. However, the focus on patients does not give a good representation of all exposed recipients. Blood products for clinical care, e.g. plasma, platelets or stem cells, are collected from donors via aphaeresis. The systems used to perform the aphaeresis may contain phthalates. Since the principle of aphaeresis is that blood is returned to the donor, the donor is consequently, exposed to phthalates contained within the device, especially with platelet aphaeresis. Although the exposition to donors is low for each donation, the exposition is often frequent, can be 25 donations per year, for many years. We therefore suggest including donor exposure in the risk assessments. 2) Outcomes of benefit-risk assessments are dependent on the target population. With respect to clinical care, there is an indication for treatment that may justify a certain level of risk that may be outweighed by the benefits of treatment. In contrast, donors are in general healthy individuals who are, on a voluntary basis, donating substances of human origin without an indication for treatment. This therefore has another impact on the outcome of the benefit-risk assessment compared to patients. 3) The risk of the exposition to phthalates depends on the recipients. With regard to recipients of blood products, different vulnerable groups can be defined such as transfusions intra-uterine, to neonates and very young children or frequently transfused recipients (e.g. patients with hemoglobinopathies). Specific risk reduction measures, to be included in the risk assessments, may be considered for these high-risk populations. 4) The level of phthalate in the transfused blood product may vary	SCHEER agrees. Text added to reflect donor exposure. Page 15 Line 12. Text modified to consider frequents use including donors. Consider repeated use scenarios (e.g. dialysis, apheresis donation, chronic treatment) and different population groups. (Chapter 3, step 3) Page 18 Line 23. ... person groups (e.g. including patients, donors, users). (Chapter 4, step 7) Also added text: Page 12 Line 11. ....professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines. When the word “patient” is used in these Guidelines, this includes professional

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			dependent on the specific manufacture process of the blood component, and this may use multiple containers from different manufacturers, e.g. a pooled platelet component may be stored in a bag that is free from DEHP however the primary collections of whole blood may have been collected into systems containing DEHP.	users and other persons exposed to the medical device as well. (Scope) Page 18 Line 25. For each subgroup a different level of risk may be accepted based on the potential benefit of the medical device for that particular group. (Chapter 4, step 7)

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18	van den Burg,Peter,European Blood Alliance (EBA),p.vandenburg@europeanbloodalliance.eu,Netherlands	1. Introduction	This comment refers to the involved stakeholders and experts in the field; Although the use of phthalates is primarily the responsibility of the manufacturer of the medical devices, the users (e.g. blood establishments and clinicians) have much experience and knowledge with respect to functionality, performance and biocompatibility. We therefore promote collaboration in the benefit-risk-assessment of phthalates between manufacturers of medical devices, blood establishments and clinical users. The European Blood Alliance (EBA) could assist in this process and through collaboration act as a representative of many blood establishments in Europe.	Comment noted. However, it is not the task of SCHEER to promote any stakeholder in this area. Cooperation between the various stakeholders has to be established by the stakeholders themselves.

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19	van den Burg,Peter,European Blood Alliance (EBA),p.vandenburg@europeanbloodalliance.eu,Netherlands	1. Introduction	The comments refer in general to the references to patients and clinics; 1) The exposition to phthalates is described in relation to patients. However, the focus on patients does not give a good representation of all exposed recipients. Blood products for clinical care, e.g. plasma, platelets or stem cells, are collected from donors via aphaeresis. The systems used to perform the aphaeresis may contain phthalates. Since the principle of aphaeresis is that blood is returned to the donor, the donor is consequently, exposed to phthalates contained within the device, especially with platelet aphaeresis. Although the exposition to donors is low for each donation, the exposition is often frequent, can be 25 donations per year, for many years. We therefore suggest including donor exposure in the risk assessments. 2) Outcomes of benefit-risk assessments are dependent on the target population. With respect to clinical care, there is an indication for treatment that may justify a certain level of risk that may be outweighed by the benefits of treatment. In contrast, donors are in general healthy individuals who are, on a voluntary basis, donating substances of human origin without an indication for treatment. This therefore has another impact on the outcome of the benefit-risk assessment compared to patients. 3) The risk of the exposition to phthalates depends on the recipients. With regard to recipients of blood products, different vulnerable groups can be defined such as transfusions intra-uterine, to neonates and very young children or frequently transfused recipients (e.g. patients with hemoglobinopathies). Specific risk reduction measures, to be included in the risk assessments, may be considered for these high-risk populations.	SCHEER agrees. See answer to comment 17. Also added text: Page 12 Line 11. ....professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines. When the word “patient” is used in these Guidelines, this includes professional users and other persons exposed to the medical device as well. (Scope)

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			4) The level of phthalate in the transfused blood product may vary dependent on the specific manufacture process of the blood component, and this may use multiple containers from different manufacturers, e.g. a pooled platelet component may be stored in a bag that is free from DEHP however the primary collections of whole blood may have been collected into systems containing DEHP. Due to unstable internet connections these comments could be send twice.	

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20	Oran,Giulia,Institut Straumann AG,giulia.oran@straumann.com,Other	1. Introduction	Line 6-9: No indication is given on how to estimate combination of phthalates. A medical device can be made of different materials which have a different exposure to the human body and/or are invasive. For example a part of an instrument which contains one or more phathalates but does not come into contact with the patient (for example the handle of a drill) does qualify for assessment? Line 11-14: Often raw materials are supplied to manufacturers of medical devices by external suppliers. The composition of the raw materials (for example polymers) is not disclosed by the source on confidentiality grounds. On request, some suppliers are willing to provide safety data sheets. But these only state the hazard classification and not the composition of the raw material. The hazard classification contains hazard statements according to CLP and conversion to CMR Categories 1A and 1B is not trivial. Even more complicated is to demand assessment for ED as procedure for ED identification is new and pertains other regulatory framework not known to the raw material suppliers or the medical device manufacturers. Suppliers of raw materials are often only distributors and have to rely for the classification on the original manufacturers. Suppliers of polymers/plastic serve different industry sectors and are not committed to retrieve information if (like often is) medical device manufacturers are not their main clients. The problem of identification of potential CMR and ED will be even more prominent for the more general guidance on CMR/ED substances as required in the regulation if medical device manufacturers are not provided with a list of hazardous substances and relative chemical name but are requested to extrapolate only partial information from the biocompatibility assessment according to ISO 10993 series. Finally it is desiderable to be provided with a clear method for calculating the 0.1% w/w treshold quantity and scenarios for te nature of contact (transient/accidental/permanent) of the hazardous substance with the human body.	Yes, all parts of a medical devices need to be assessed by the MDR. For such a handle of a drill the RA may be relatively simple. The SCHEER agrees with the comment. However, these aspects cannot be addressed in these Guidelines. It is already covered by the Annex II of the MDR. According to EN ISO 10993-18 (currently under revision, FDIS published in 2019, final publication expected in 2019/2020) the chemical components of a medical device needs to be identified and documented in the dossier.

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21	Napierska,Dorota,Health Care without Harm Europe,dorota.napierska@hcwh.org,Belgium	1. Introduction	. Page 15, lines 12-13: "The combined exposure to multiple phthalates shall also be considered when present in medical device". The entire Chapter 3 seems to focus on a single medical device and exposures resulting from its use. The combined exposure to multiple medical devices (and therefore potentially to phthalates present in those devices) should also be considered, at least for certain vulnerable patients groups such neonates / children that are exposed during intense care to multiple invasive medical procedures and therefore to multiple medical devices simultaneously, sequentially, or intermittently (Demirel et al. Hidden toxicity in neonatal intensive care units: phthalate exposure in very low birth weight infants. J Clin Res Pediatr Endocrinol. 2016; Malarvannan et al. Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units. J. Hazard Mater. 2019). Also, in the report from a Committee at the National Academy of Sciences in the US, the authors make a strong case for considering the risk resulting from exposure to multiple phthalates from multiple sources. In fact, they also make the case that chemicals that impact a common endpoint should be considered in the aggregate even if they have different mechanisms of action. (National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press - FILE SIZE ABOVE 1 MB therefore not uploaded here). Only when combined exposure to phthalates from multiple medical devices will be considered, the estimation of the potential exposure to phthalates of various patient groups will be based on worst-case scenario and relevant. . Page 15, lines 14-15: Please clarify how the results of the "biomonitoring programs" should / could be used in the context of the BRA. Do "biomonitoring programs" refer to the clinical monitoring? . Page 15, lines 27-30: "Where a DNEL and/or a DMEL have already been derived in the context of other EU legislations, the analysis could refer to these derived figures without referring to detailed assessment how these	SCHEER disagrees. It will not be possible for a manufacturers to estimate the phthalate exposure from other MDs. This also depends on the choices made in the hospitals for treatment of patients. Page 15, lines 14-15: Biomonitoring could be both clinical and in the general population. Text added for clarification. .....in the general population and more specifically during medical treatment.(Chapter 3, step 3) Page 15 Line 30. Text added.

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			data have been derived (e.g. under REACH legislation, Food Contact Material legislation)". Some caution is recommended here: a DNEL and/or a DMEL derived under REACH legislation is not necessarily derived considering the most sensitive endocrine disruption endpoints, and the most up-to-date scientific evidence. Current EU regulations (except the assessment of biocidal and crop protection active substances/products) extensively rely on evaluation of chemical-induced adverse apical responses but not on endocrine Mode of Action. Therefore, not only figures derived in the context of other EU legislations, but also relevant up-to-date scientific evidence (based upon a systematic literature review) and up-to-date risk assessment methodology for all relevant toxicological endpoints, should be considered. For example, the recent report from Danish Centre on Endocrine Disrupters (Report on Interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk? Danish Centre on Endocrine Disrupters 2019) clearly illustrates that the use of the different approaches leads to marked differences in the external DEHP dose value considered as a safe or low risk level for humans, i.e. the values range from 0.004 to 50 µg/kg. As such this illustrates that the DNEL of 50 µg/kg bw/d applied for DEHP in the EU risk assessment is not too cautious. . Page 15, line 35: Incorrect internet address (as it provides link to Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures). Please replace by: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311	However, as some of these data may have been derived in the past, relevant up-to-date scientific evidence (based upon a systematic literature review) and up-to-date risk assessment methodology for all relevant toxicological endpoints needs to be considered. (Chapter 3, step 3) Referral to EFSA/ECHA document website corrected.

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22	Napierska,Dorota,Health Care Without Harm Europe,dorota.napierska@hcwh.org,Belgium	1. Introduction	. Page 15, lines 43-47: Regarding "Exposure levels that are considered safe", especially in vulnerable patients group, we support the approach proposed in the recent report from Danish Centre on Endocrine Disrupters (Report on Interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk? Danish Centre on Endocrine Disrupters 2019), i.e. additional safety / uncertainty factor to protect the most vulnerable patients. This is because 1) the adverse effects of endocrine disrupters can be much greater when exposed during sensitive periods (in utero, as a newborn or during puberty) - the additional uncertainty factor will ensure better protection during these sensitive periods, and 2) the current test methods for endocrine disrupting effects are not considered sufficiently sensitive. Moreover, it should be considered that patients / individuals receiving medical treatment through medical devices leaching CMR/ED phthalates are often ill or injured, what possibly compromises their detoxification systems. For example, several clinical observations point out that possible interaction during dialysis between BPA/DEHP and a kidney disease–specific abnormal electrophysiological (EP) substrate in patients with end-stage renal disease, may increase risk of sudden cardiac death (Tereshchenko and Posnack. Does plastic chemical exposure contribute to sudden death of patients on dialysis? Heart Rhythm. 2019 - FILE SIZE ABOVE 1 MB therefore not uploaded here). . Page 16, line 3: Following the text in lines 1-3 "The risks can also be described by calculation….SCCS Notes of Guidance – SCCS/1602/18)", the following sentence should be added: "Perform this evaluation for every patient group for which the device is intended to be used" (as has also been done in "Assessment of the risk of identified potential alternatives", under "Description of risk (risk characterization)" Page 19, lines 27-28). Moreover, after a Margin of Safety for a single device is calculated, it must then be considered in the context of exposures of every patient group from multiple sources. . Page 16, lines 5-8: "Determine and describe in which situation the risk can be acceptable for the use of the CMR/ED phthalate in the medical device. Describe …. (Chapter I of MDR). Here the emphasis continues to be on the risk associated with the use of a single medical device. Risks associated with exposure to phthalates from a	SCHEER agrees. Page 15 Lines 43-47 text added. Specifically for ED effects additional assessment factors might be considered as proposed recently (Hass et al., 2019). (Chapter 3, step 3) Page 16 Line 3. Text added. Perform this evaluation for every group (patients/donors) for which the device is intended to be used. (Chapter 3, step 3) SCHEER disagrees. Comment by itself is correct, but the Guidelines are dealing with a justification for the use of a CMR/ED phthalate applied in one single device.

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			single device should be assessed in the real-world context of exposures from multiple devices and sources.	

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23	Napierska,Dorota,Health Care Without Harm Europe,dorota.napierska@hcwh.org,Belgium	1. Introduction	. Page 16, lines 15-16: Regarding a scientific debate on “no-effect level”: as long as this debate is ongoing and we cannot ascertained with confidence a safe threshold, we support the conclusion of Danish researchers from Danish Centre on Endocrine Disrupters (2019). They emphasize in their recent report (already mentioned in two comments above) that is possible that there is no tolerable exposure limit to the various endocrine disrupters. The researchers therefore recommend that risk assessments use a non-threshold approach as default when evaluating endocrine disruptors. Moreover, the report from a Committee at the National Academy of Sciences in the US on phthalates (National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press) makes clear that there may be no threshold because of background/cumulative exposures, and the subsequent report “Science and Decisions: Advancing Risk Assessment” says: “Noncancer effects do not necessarily have a threshold, or low dose non-linearity. Background exposures and underlying disease processes contribute to population background risk and can lead to linearity at the population doses of concern.” (National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press - FILE SIZE ABOVE 1 MB therefore not uploaded here). We would like therefore once more emphasize that the concept of a threshold for DEHP exposure from a single device should be discarded simply because patients are typically exposed to DEHP from multiple sources and devices.	SCHEER acknowledges the comment. The Guidelines are intended for evaluation of alternatives and/or justification of use of CMR/ED phthalates in a single medical device. Furthermore, the RA is for the specific CMR/ED risk of using this single device. The recent Danish report is cited now on Page 15 Line 47. See comment 22. Specifically for ED effects additional assessment factors might be considered as proposed recently (Hass *et al.,* 2019). (Chapter 3, step 3)

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24	Napierska,Dorota,Health Care Without Harm Europe,dorota.napierska@hcwh.org,Belgium	1. Introduction	. Page 16, lines 38-40: Regarding "Inventory of possible alternatives" (that must contain all available information on substances, materials, designs and/or medical treatments, including alternative medical devices available on the market), the guidelines lack recommendations for sources to identify those alternatives and collect required information. It is also not clear how notified bodies and competent authorities can verify completeness and correctness of this part of the BRA. For example, one of the information sources on the plasticisers and alternatives to DEHP in medical devices could be the European Pharmacopoeia. Most importantly, the revamped MDR's EUDAMED database with improved functionalities (currently under development) should be the source of the information on alternatives that are already in use (applied in the medical devices available on the market, e.g. existing DEHP-free and PVC-free and devices). It should be possible to search within the EUDAMED database for devices within the same category of use, and this might act as a starting point for identifying medical devices that provide alternative substances / materials /designs.	The Guidelines indicate (give guidance) what should be done for the evaluations of the alternatives. It is outside the scope of the Guidelines to present for every possibility a list of potential alternative. This evaluation should be performed by a specialist (or a team of specialists) knowing what the potential alternatives could be. Page 16 Line 40. Footnote added for information. Information source for alternatives might be the European Pharmacopoeia. (chapter 4, step 4) The EUDAMED database does not contain this type of information and accessibility is restricted.

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25	Napierska,Dorota,Health Care Without Harm Europe,dorota.napierska@hcwh.org,Belgium	10. Conclusions	Page 36, lines 6-11: As specified in the mandate, “In order to ensure the appropriateness of this guidance the Scientific Committee should inter alia involve at the appropriate level the notified bodies active in the field of medical devices, or other relevant stakeholders such as Competent Authorities, professional and patient associations, industry associations”. However, it is not clear if this requirement has been fulfilled by the SCHEER. On Page 3 of Preliminary Guidelines document, External experts and Experts from EU Agencies that were consulted / contributed to this opinion are listed. None of the notified bodies active in the field of medical devices, or other relevant stakeholders such as Competent Authorities, professional and patient associations, industry associations are mentioned. In our opinion, at least the notified bodies and Competent Authorities should be involved before finalization of this document, in order to ensure the appropriateness of this guidance.	SCHEER prepared these Guidelines independently. Comments and consultation of the Competent Authorities and Notified Bodies were obtained during the Stakeholder meetings and the public consultation.
26	de Korte,Dirk,Sanquin Blood Supply,d.dekorte@sanquin.nl,Netherlands	10. Conclusions	This is an overall comment on the Guidelines, not on specific chapters/sections, including a reference to our earlier comment in the stakeholders consultation round for ECHA.	Thank you for the comments.

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27	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	10. Conclusions	1. The Guidelines do not specify that the requirement for benefit-risk assessment is limited to those devices, parts or materials described in MDR Annex I Section 10.4.1.: "Devices, or those parts thereof or those materials used therein that: — are invasive and come into direct contact with the human body, — (re)administer medicines, body liquids or other substances, including gases, to/from the body, or — transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body." The Guidelines suggest that the benefit-risk assessment is always performed at the level of the device, whereas the assessment may be limited to those parts or materials of the device that fulfil the criteria described in Section 10.4.1. We believe that the Guidelines should mention clearly that, in line with the MDR legal text, benefit-risk assessment is only required for these specified devices/components, and not for other contact/surface materials. This needs to be addressed throughout the document. 2. Benefit-risk assessment (BRA) is a general methodology not specific to phthalates and guidelines already exist: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM506679.pdf (see also CER MEDDEV guidance). Overall, the size of the document could be reduced by cross-referencing already existing methodologies rather than describing them again (e.g. toxicological risk assessment appears to be a guideline describing a methodology which already exists elsewhere (ISO 10993 etc.). In turn, the BRA for phthalates may not be different than a BRA for other hazardous substances regulated under the MDR. In the current version of the Guidelines, there does not appear to be further information coming from references to phthalates, and such information provided on phthalates (e.g., within the Annexes) does not seem to support a BRA specific to phthalates. In the event that the Guidelines would apply to all CMR/ED captured under MDR Annex I Section 10.4., it is all the more essential that the points included are fully considered and acknowledged by SCHEER, considering the far-reaching consequences of the scope of the Guidelines as we understand it.	SCHEER agrees. 1. Annex I Section 10.4.1 is now explicitly mentioned in the scope of the Guidelines. Text added: These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1. They do not provide information….(chapter 1 scope) See also comment #58, #59 #90 According to the MDR benefit risk determination has to be performed for every device irrespective whether it contains a CMR/ED substance. 2. SCHEER agrees. The BRA is part of the justification needed to use a CMR/ED phthalate in a medical device. The Guidelines describe a methodology for justification by applying a comparison of the BRA for the used CMR/ED phthalate versus an alternative.

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			3. The Guidelines are not linear with respect to Figure 1 (p. 13). This makes the written body confusing to follow. The Guidelines would increase in clarity and actionability if the different steps of the BRA would be incorporated in a decision tree type of structure. The current layout of the Guidelines reduces the possibility to shorten/simplify the assessment. Following a risk-based methodology, it would seem logical and proportional to take full account of risk factors, such as characteristics pertaining to the risk class of the device as well as cases where patient exposure may not be relevant e.g. gaseous administration versus very low vapour pressure of the used phthalate, very small contact area, low extraction rate. In general, the level of detail and the extent of the BRA should depend/take into account the relevance of exposure, known risks for the patient and the hazards of alternative substances (e.g. avoiding regrettable substitution or extensive assessments of non-existing exposure).	3. As mentioned in the comment, many of these factors are already known (or should be known by an applicant for marketing a device). The Guidelines therefore do not extensively describe details on phthalate hazards/risk assessment. It provides a procedure to follow for justification of continued or new use of a CMR/ED phthalate. The BRA evaluation can be limited (shortened) at level 2 when discussing the (lack of) functionality of the alternatives. Data on use, function and risk of the phthalate should already be available within the risk assessment dossier of the medical device itself.

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28	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	10. Conclusions	4. P. 2 (line 43-45): "Therefore, manufacturers are encouraged to produce (semi)quantitative data on the use of alternatives for CMR/ED phthalates in medical devices." (see also conclusion section) We would like the Guidelines to recognise that in some cases, data from scientific literature could be used, hence new data would not always have to be “produced”. Could this sentence refer to “assessment” or “identification” of (existing) data instead (e.g. allow a manufacturer to present a review of scientific data available in the literature and combine this with own exposure data). 5. P. 2 (line 47) (see also conclusion section: p. 30, line 22): “Pending on new scientific evidence, it is recommended to evaluate the use and usefulness of these Guidelines after an experience period of three years.” We would like to get clarification why the review period of the Guidelines has been set at 3 years. MDR Annex I Section 10.4.3. specifies that the Guidelines should be reviewed at least every 5 years or when deemed appropriate based on the latest scientific evidence. No argumentation is provided in the Guidelines in terms of what scientific evidence would require an update already after 3 years.	4. This specific paragraph addresses the methodology of the BRA itself for which information on the many existing methodologies is presented in Annex 7. It should be possible to use existing information to do the risk assessment also for the alternatives. Whether new data need to be generated would be an interpretation of the legislation in the MDR. 5. SCHEER is asking for sharing experience on the use and usefulness of the Guidelines and not for a revision. In order to make a clear distinction with the regular BRA update text has been added on Page 30 in the conclusion referring to the regular BRA update. As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, an update of the BRA of the medical device may be needed. The BRA of the CMR/ED phthalate should be updated when new scientific information becomes available on alternatives for the use of phthalates, when new Guidelines are released, or as the "overall" benefit-risk determination of the medical device is updated,

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29	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	10. Conclusions	6.We would like the Guidelines to clearly call out the overall purpose, and that is to enable manufacturers and Notified Bodies to approve the inclusion of a CMR/ED in medical devices (enable appropriate risk assessment). While assuring customers and regulators that appropriate due diligence has been conducted, it should not become an obstacle to placing innovative medical devices on the market.	SCHEER believes these Guidelines provide sufficient guidance to guarantee a proper evaluation of CMR/ED phthalates versus possible alternatives. This is specifically addressed in the scope of the Guidelines.

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30	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	10. Conclusions	7. Throughout the Guidelines, “performance” is mentioned, but it is unclear whether this refers to clinical performance or product performance, which are defined differently in the Guidelines.	7. The referral is dependent on the context in which the word “performance” is used. It can indicate both functional performance and clinical performance. But in the end clinical performance would be the definitive parameter for approval or rejection of an alternative, when compared to the use of a CMR/ED phthalate.
			8. In several places, the Guidelines mention the evaluation of hazard or “risk in terms of hazards”. Risk = hazard x exposure; i.e., risk is expressed in terms of hazard and exposure. The value of evaluating hazard, especially in the context of safety risk, is unclear; e.g.: An alternative may have a different hazard than a CMR/ED, but the exposure to both may be non-existent resulting in no risk. In this case, hazard x exposure (value equals zero) = no risk, and the consideration of hazard alone would not seem to be relevant. The MDR is a risk-based regulation, and exposure is specifically mentioned in Annex I Section 10.4.2. (a) which confirms that, as is customary under product legislation, the evaluation of safety per the Regulation is done based on risk rather than hazard. Our understanding is that the hazard assessment is performed under the CLP, REACH or BPR legislation under which the CMR/ED substances are identified, after which a risk analysis is carried out specific to the use of these hazardous substances in a medical device – where exposure (i.e. risk) is the key element to consider.	8. SCHEER deleted “in terms of hazards” (Abstract + text).
			9. P. 9 (line 23-25) (see also p. 11, line 10): “For such a justification several steps need to be considered including the possible use of alternative substances, materials, designs, and medical treatments.” Alternative medical treatments are not part of the analysis of alternatives as specified in MDR Annex I, Chapter II, Section 10.4.2. (substances, materials and design). Secondly, it is not clear how medical treatment is defined as part of these Guidelines. Clarification is requested for any reference to "medical	9. Medical treatments was seen as a possible alternative as indicated in the MDR (Annex I, 10.4.3).

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			treatment" throughout the Guidelines.	
			10. P. 9 (line 33): We would like the Guidelines to allow for the possibility of having industry-wide justifications for medical devices with similar intended use, such as blood bag sets. Where manufacturers can show that their devices fall within the parameters defined in the industry scenario, they should be allowed to leverage joint industry justifications (where these exist).	10. It is up to the manufacturers to demonstrate the safety of a product according to the MDR.
			11. Pages 10 – 12 appear to be redundant with pages 14 – 21, which discuss the steps in more detail. It is recommended that pages 10 – 12 be deleted and pages 14 – 21 provide the sole explanation of Figure 1.	11. SCHEER disagrees. Pages 10-12 give a short introduction, overview and explanation of the approach whereas pages 14-21 give more detailed information.
			12. P. 10: Assessment of the used phthalate (use scenario), Step 3 – this is essentially the description of a four-step risk assessment. We suggest providing the traditional references for a toxicological risk assessment, e.g. — NAS. 1994. Science and Judgment in Risk Assessment. National Academy of Science. National Academy Press, Washington, D.C. — NRC. 1983. Risk Assessment in the Federal government: Managing the Process. National Research Council. National Academy Press, Washington, D.C.	12. SCHEER agrees. The schedule as presented is essentially the RA paradigm as proposed by NAS in 1994. There is no need to add references to the RA schedule as this is well known.
			13. P. 10 (line 35): Is it "patient" or "patient and user" exposure? Page 11, line 25 refers to patient or user exposure. Page 12, line 11 specifies that a similar approach is required for professional users, and as part of the introduction on page 7, line 22-23, reference is made to the general requirement that the device should be safe for users and patients. However, throughout the document there is a lot of focus on patients. The text should be consistent and, in our opinion, focus on patient exposure. If professional users are mentioned, it should be specified that exposure levels are different for these users (surgeons/nurses) than for patients.	13. The focus is on patients in general. But as commented as well also non patients might be exposed (users/donors). See comment #17, #19. Added: In view of the importance of this aspect this text is now included in the Scope of the Guidelines.

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				When the word “patient” is used in these Guidelines, this includes professional users and other persons exposed to the medical device as well. (Chapter 2, after step 10)

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31	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment		Page 10-12 provide a general description and introduction to the framework. So, detailed information is not provided. This is done in pages 14-21. All comments regarding page 10-12 will be addressed in page 14-21.
			14. P. 10: Step 3b: “Identification of biocompatibility, general toxicological and specific CMR/ED hazards associated with the phthalate” – If enough data from literature are available for a phthalate such as DEHP, would a summary of the literature on general toxicological and specific CMR/ED hazards associated with the phthalate suffice?	14. Yes, as this is common practice at the moment. The acceptance depends on the quality of the data, as indicated in the MDR.
			15. P. 11: Step 3c: “Determination of the maximum tolerable/acceptable exposure for the patient, based on pre-clinical and clinical information (if available).” – The substances referenced in Annex I Sections 10.4.1. (a) and 10.4.1. (b) are regulated due to evidence of their toxicity, which is documented in studies within the scientific literature, therefore we believe that the best source of data to derive TEs (tolerable exposure) would come from the scientific literature, not pre-clinical (e.g., biocompatibility) or clinical data.	15. Scientific literature is not excluded so it can be a source of information. More explanation is provided in Step3 presented on Page 14.
			16. P. 11: Step 4c: The need to evaluate benefit-risk assessments of alternative medical treatments against a potentially hazardous substance in a device does not always seem meaningful. The fact that a particular medical treatment exists is because the benefit for it has been shown to outweigh the risk and that, in spite of the availability of alternative treatments, the clinician may decide to use it for reasons that have nothing to do with the presence of a potentially hazardous substance. For example, a clinician may choose to perform cardiac surgery on a patient to replace a heart valve because he/she determined that a trans-catheter approach is not appropriate due to complex patient anatomy. The prospect of using a cardiopulmonary bypass circuit with tubing containing DEHP does not	16. The BRA and justification needs to be provided by the manufacturer of a device. A clinician is always by her/himself responsible for the chosen treatment.

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			figure into this decision at all. Comparing benefit-risk assessments of alternative medical treatments is an “apples to oranges” comparison. We suggest avoiding a “one-fits-all” type approach.	
			17. P. 11: Step 5: We would like the Guidelines to state clearly that economic feasibility and availability (such as single-sourced material) are relevant inclusion/exclusion criteria for possible alternatives. If an alternative is not commercially available, that should count as a justification for not being able to switch to the alternative.	17. The issue of availability is presented on Page 17 Step 5 text is added. In addition, analysis of availability and technical feasibility might affect choices for alternatives as well. (Chapter 4, step 5)
			18. P. 11 (line 19): The functionality/performance of the alternative shall be comparable to the extent that there would be no clinically significant difference in performance of the device (see page 10, line 8: where does the assessment stop?) Technical feasibility, availability, and socio-economic factors (page 17, line 25-28) are also important.	18. This is mentioned in Page 17 Lines 25-28. If potential alternatives can be identified, a shortlist of the potential alternatives can be established for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, availability (e.g. sufficient availability or accessible to the manufacturer), and technical performance. (step 5) In step 6 now a tiered approach is detailed: The evaluation of the identified potential relevant alternatives can be done in a tiered way to avoid full assessments for each candidate alternative. For example, based on the outcome of the functionality evaluation, the choice of the potential

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				relevant candidates might be reconsidered and some might be discarded before performing the risk assessment (see Step 7).
			19. P. 11 (line 21): We suggest adding: "Based on the outcome of the functionality and performance evaluation, the alternative(s) may be discarded and no further assessment is required."	19. This is addressed on Page 17 Lines 41-43. Text moved .
			20. P. 11: Step 7: No data (or very limited data) for the relevant route of exposure available for an alternative would make it not possible to determine the appropriate risk assessment of the alternative. Is the manufacturer expected to produce such data for alternatives where years of research in the scientific community has failed to do so? Also, how does one handle the assessment of an alternative substance that contains DEHP as impurity because of structural similarity?	20. This is addressed in step 7 Page 18. Added (step 7): In the event that the risk assessment of a potential relevant alternative cannot be performed due to lack of information, documentation should be presented on the actions undertaken to obtain information to characterise the risk, including the outcome (for example, QSAR /read across could be performed). (before chapter 5)

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32	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	21. P. 11: Step 8: Comparison of functionality and performance of the CMR/ED phthalate as used in the medical device with that of potential alternatives: If the alternatives are substance substitution or material replacements, would this comparison be only at the substances/material level since no finished devices made of alternatives are available? If there is no published comparison data of function and performance of CMR/ED material versus alternatives, is the manufacturer expected to conduct the comparative function and performance studies?	21. Yes, the alternatives should be evaluated individually. Explained in Step 8 Page 20.
			22. P. 12: Step 9: If no leachable and/or toxicity data are available for alternatives, this would automatically place the alternatives at higher risk than CMR/ED containing devices?	22. Not necessarily. But some data might be generated depending on the level of functionality of the alternative substance. See Step 9 Page 21. Some kind of RA is necessary. No data does not mean no risk. For example, QSAR /read across data should be possible.
			23. P. 12: Step 10: “Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential alternatives.” – Should this step compare only the “benefit” since the “risk” was compared in step 9?	23. In step 10 SCHEER used the conclusion of step 9 and compared this with the benefit of both uses. Step 10 includes the overall conclusion.
			24. What is meant by professional user? Please define this. [Several references throughout, including p. 12, line 11; dermal and inhalation exposure mentioned (p. 46), assume healthcare worker.]	24/25. The person handling/applying the medical device. Also defined in the MDR.
			25. P. 12 (line 10-11): “Where appropriate, a similar approach shall be used for the justification of the presence of CMR/ED phthalate in medical devices to evaluate the risk for professional users” – How does one factor the evaluation for professional users into the overall justification since professional user exposure route and duration could be different from patient exposure route and duration, and the benefit-risk for the	25. Comment correct. But this should be described and documented. And indeed in general exposure would be limited compared to patient groups.

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			professional user is often very different from benefit-risk for the patient?	
			26. P. 12 (line 18): We suggest adding "Revisions of the BRA are only required at the time of re-certification of the medical device or when the Guidelines are updated."	26. SCHEER disagrees. This is a matter of regulation and not the task of SCHEER.
			27. P. 13: Suggestion to also include a decision flow for when the alternatives may be discarded before performing the risk assessment step. Clarification is needed with regard to this flowchart that in some cases it is not possible/necessary to perform the next steps. This is suggested on page 17, line 15-19 but should be emphasised for the different steps (suggest decision tree type structure instead of circular flowchart).	27. As mentioned this is indicated on Page 17 Lines 15-19 as explanation. This does not fit in the short description/explanation of the framework.

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33	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	28. P. 14 (line 26): Is it expected that the biological evaluation of a medical device according to ISO-10993-1 shall be included in step 2? This is not applicable in step 2 but rather part of step 3. 29. What would be helpful in the Guidelines is recommendations on methodology for going from 0.1% w/w in the article to an appropriate design of an extractable study based on the type of device – to mimic better what a patient would receive. So a way to evaluate true exposure to the raw material composition. Examples of this would also be welcome. 30. Throughout the Guidelines, clarification as to what 'acceptable risk' means is needed; e.g.: "Determine and describe in which situation the risk can be acceptable for the use of the CMR/ED phthalate in the medical device." Can acceptable risk be defined as: — 10-6 – 10-4 risk for non-threshold carcinogens — Margin-of-safety > 1 — Hazard index < 1. The Guidelines also refer to REACH terminology (DNELs – Derived No-Effect Level – and RCR – Risk Characterisation Ratio). Is there a preference for a specific value?	28. Reference to EN ISO 10993-1 is included for information on exposure frames for the RA to be performed in the following steps.. Reference to the ISO series is added to Step 3 Page 14/15. Inserted Page 15 Line 18. EN ISO 10993-1 provides information on hazard endpoints to be considered depending on the exposure and use category of a medical device, whereas allowable limits can be determined according to EN ISO 10993-17.. (step 3) 29. SCHEER agrees. Comment correct. However, this is outside the scope of the Guidelines. They provide a framework for the justification of the use of a CMR/ED phthalate. Chemical composition and chemistry evaluation can be found in EN ISO 10993-18. It is currently under revision. FDIS is just published. 30. This is outside the scope of the Guidelines. Acceptable risk should be determined and justified by the manufacturer, as it is for all medical devices. Acceptable risk also differs relative to the benefit of a medical device.

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			31. P. 14: The extensive definition of "vulnerable groups" covers the complete population (children, women/men in reproductive age, elderly etc.). Can this be limited?	31. According to SCHEER, vulnerable groups should be identified and this cannot a priori be limited.
			32. P. 14 (line 7-9): The Guidelines state that justification is required for each use of CMR/ED phthalates and their combination. Could clarification be provided on when a combined assessment would be required (e.g. for the same toxicological endpoint)? MedTech Europe's understanding is that, in line with the MDR text, the justification would have to be for an individual substance. Only where several substances in the same device are in scope of MDR Section 10.4.1. and have the same adverse effect (identical hazard with the same mode of action), a cumulative assessment could be required.	32. This is included in the introduction of chapter 3.
			33. P. 14 (line 7-9): Reference is made to EFSA and food contact materials. The reference values for use of phthalates in food contact materials and articles with respect to migration limits may not necessarily apply to medical devices, which have a different risk profile. The specified migration limits for the individual CMR/ED and group restriction for materials (Annex V, page 48 line 20-22) could be interpreted that such limits also apply for medical devices, which was not the intended scope of EFSA. We therefore suggest deleting this reference.	33. SCHEER disagrees. This reference is included as information. It is not the suggestion that the same values apply to medical devices. But the values can be used as they provide information on a TDI. Text modified for clarification. Some risk assessment data regarding the combination of phthalates are available, as EFSA has recently proposed a Group TDI for some of them, having a similar Mode Of Action (MOA) in vivo (EFSA 2019, see Annex 5). Information on assessment of combined exposures to phthalates can be found for example at the report by the National Research Council Committee on the Health Risk of Phthalates (2008) and the ECHA report

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				on restrictions of four phthalates (August 2017)(https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180d73895) and EFSA guidance on cumulative exposure (EFSA, 2019 https://doi.org/10.2903/j.efsa.2019.5634).(chapter 3)
			34. P. 15 (line 1-4): “Provide information, preferably based on data from direct measurement or, when not available, an estimation based on worst-case scenario or from scientific literature, on the release of the CMR/ED phthalate from the medical device when used in various clinical modalities.” – This contradicts step 3a.	34. SCHEER disagrees. 3a asks for patient exposure. Page 15 Line 7-9 Describes the release from a device. Patient exposure is directly related to the release of the phthalates from a device.
			35. P. 15 (line 4-7): “For data generation, analytical contact conditions for the evaluation of leaching of substances from medical devices, should consider for example temperature, contact duration and frequency, polarity of contact liquids, flow rates, contact surface, and volume of contact liquids.” – reference ISO 10993-1, -12, and -18 (and perhaps USP <661>). An extractables and leachables analysis without chemical identification (assuming all reported mass is the hazardous substance of interest) is also a possible approach.	35. References to ISO and USP included. ... (EN ISO 10993-1, EN ISO 10993-12, EN ISO 10993-18, USP 661).
			36. P. 15 (line 11) (see also p. 18, line 31): "Dialyzers" are no adequate example for frequently used phthalate-containing devices: Dialyzers are single-use disposables and do mostly not contain PVC and phthalates like DEHP.	36. SCHEER disagrees. Even if dialysers are single use, there use is repeated in time. Text modified for clarification. See comment 17.

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				Consider repeated use scenarios (e.g. dialysis, apheresis donation, chronic treatment) and different population groups. (Chapter 3, step 3)

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34	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	37. P. 15 (line 14-15): The utility of biomonitoring data for the justification of a CMR/ED is unclear. “[D]ata from biomonitoring programs may become available that could also provide information on exposure levels of phthalates.” “For some of the phthalates already human biomonitoring assessment values, namely Biomonitoring equivalents (BE) or human biomonitoring (HBM) values, have been derived – these are concentrations of biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since the basic assumption is an equilibrium between external exposure and internal burden (Angerer et al. 2011, Apel et al. 2017).” Biomonitoring data provides body burden values for specific chemicals; in most cases, the source of the exposure (e.g., a manufacturing site) is known. Where should this biomonitoring data come from? How can we ensure that the BE values mentioned above are from relevant sources (i.e., the medical device of interest) and not from other, non-relevant sources (exposome)?	37. As the exposure to EDs by medical devices can be increased this information was added. Text is modified for further clarification.: ...phthalates in the general population and more specifically during medical treatment. (step 3)
			38. P. 15 (line 33-35): “The ED property of the phthalate can be described according to the recently published EFSA/ECHA guidance document (https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311). This includes impacts on fertility, birth defects (e.g., cryptorchidism, hypospadias), developmental effects, and other effects associated with the CMR/ED phthalates.” This is of interest, because endocrine disruptors are not totally clearly defined. In the reference, there is no mentioning of “endocrine disruptor.” Conclusion is that ED must be included in the CMR group. Furthermore, only one paragraph exists on reproductive toxicity and no references were immediately found for “cryptorchidism” or “hypospadias”.	38. Identification of ED substances is described in Annex I 10.4.1 of the MDR. This information is in the EFSA/ECHA Guidance and has been added to the Annex 4. Page 44 Line 32. Cryptorchidism or hypospadias are common reproductive toxicity outcomes so for this context it was considered that a reference would not be needed here.
			39. P. 15 (line 40-43): “In case of non-threshold effects (e.g. in the case of genotoxic carcinogens or for substances acting via an ED-mediated MoA), such a dose descriptor could be a T25 value or the benchmark dose associated with a 10% response (BMD10) (ECHA, 2012).” A BMD10 or a T25 are deemed sufficient to obtain a safety exposure level in case of non-	39. Text modified:T25 and BMD10 added as possible PoD. Starting points (points of departure, PoD) for exposure levels that are considered

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			threshold effects, as it is the case for many ED substances. It is less conservative than the use of NOAEL. Should adapted uncertainty factors be applied?	safe could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD) for threshold substances. For non-threshold substances, a T25 value or the benchmark dose associated with a 10% response (BMD10) could be used. From these PoDs, acceptable exposure values can be derived such as “Derived No-Effect Level ” (DNEL), “Derived Minimum Effect Level” (DMEL) or intakes over lifetime without presenting an appreciable risk to health (ADI or TDI/TWI or TE). As such data are often obtained in rat studies, the use of the TDI seems more appropriate in view of the critical effect window for androgenic reproductive toxicity in rats has been reported to be a few days (Welsh et al., 2008). In addition, patients may be exposed to medical devices only for a limited period of time. EN ISO 10993-17:2002 calculates for medical devices a Tolerable Exposure (TE), which is based on a product of the tolerable intake, the body mass and the utilization factor. When necessary, acceptable exposure levels can be derived by dividing the point of departure for risk assessment by appropriate assessment or uncertainty factors. Text on consideration for possible adaptation of assessment factors is added based on comment 22: Page 15 Lines 43-47 text added.

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			40. P. 15 (line 46-47): “When necessary, they can be derived by dividing the point of departure for risk assessment by appropriate assessment or uncertainty factors.” – They can be derived by dividing the point of departure for risk. Moreover, it could be clearer to give a generic name to the PoD after derivation by appropriate uncertainty factors. 41. P. 16 (line 1-3): “The risks can also be described by calculation of the Margin of 1 Safety (MoS), which is the ratio between the lowest PoD and the expected exposure (worst case scenario) and comparison with a reference MoS (see SCCS Notes of Guidance – SCCS/1602/18).” – Suggestion: replace the sentence by "the MOS is the ratio between the most appropriate derived PoD and the expected exposure (WC scenario)". If the PoD is derived with uncertainty factors (as specified in the previous section), it would not be useful to compare to calculated MOS with a reference MOS. 42. P. 16 (line 10-12): “[D]iscuss any other potential hazards associated with the composition of the device.” – Is this a discussion of endpoints other than CMR that are addressed via ISO 10993 biocompatibility testing? If so, why because these endpoints have nothing to do with the potential of experiencing CMR/ED effects (i.e., CMR/ED risk). No value is added because the device has passed all pertinent biocompatibility testing. This is redundant with page 15, lines 17-26.	Specifically for ED effects additional assessment factors might be considered as proposed recently (Hass et al., 2019). 40. See answer to item 39 above. Text added for possible adaptation of assessment factors is added based on Comment #22. 41. The PoD to which safety/uncertainty factors can be applied and the MoS are two different things. Using a PoD one can apply various safety/uncertainty factors to obtain a (relative) safe exposure level. The MoS is usually applied with a safety/uncertainty factor of 100. 42. SCHEER agrees. This text is addressing other non CMR/ED endpoints to be determined by the 10993 series of standards. It would be no good for a patient if there is a considerable reduction in CMR/ED hazard risk, while another hazard (and associated risk) like liver toxicity would be more serious. So, overall the alternative must show a reduced risk profile. The text is a warning not to focus only on CMR/ED while neglecting biocompatibility results. Text added to refer to EN ISO: (e.g. by using the EN ISO 10993 series of standards). (Chapter 3 step 3)

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35	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	43. P. 16: “Note: It should be realised that for some genotoxic carcinogens a no effect level does not exist.” – but acceptable risk levels do exist. “Similarly, a scientific debate is ongoing about whether this also applies to ED activity.” – but the MDR is accepting that the presence of less than 0.1% w/w is associated with a no effect level (acceptable). Is the recommendation to apply a T25 value or a BMD10 as dose descriptor? 44. P. 16 (line 18-19): “The assessment of the risk should be accompanied by an estimation of the impact of uncertainties in the described outcomes (see section 9).” – Can this be an explanation of the uncertainty factors used in the toxicological risk assessment?	43. The NOTE is added to make the reader aware that there is an ongoing scientific debate. The recent Danish report suggest that there is no threshold and a non monotonic dose response (NMDR). While the EFSA/ECHA Guidance on Endocrine Disrupting activity leaves the conclusion open. The 0.1% is determined by the legislation in the MDR. The use of T25 and BMD10 is already addressed in the text on page 15. 44. The intention is to indicate how confident the risk assessor is in the final RA.

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36	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	45. The non-use/alternate materials/devices/medical procedure cases are going to be very difficult to prepare in a thorough manner. A number of issues: — “there may be difficulties in comparing the risks of a substances, e.g. a phthalate, and the risks of a technical alternative such as medical design or medical treatment…” [p. 21, 3rd paragraph] This is a very challenging request, complicated further with contradictory instructions/guidance further along (p. 21 lines 21-22, clear description may be adequate) (lines 38-46, need statistical comparisons). — Can amount of data required on alternatives be available without actual testing? (no literature available & no prototyping conducted) — Demands to provide alternative substances (e.g. replacement plasticiser – non phthalate), alternative materials (different class of flexible material), alternative medical practices/devices/ procedure require full cross-functional team to prepare and review (medical affairs, CPDT, legal, R&D, operations, marketing). It also requires knowledge of medical practice/socio-economic factors/analysis in EU member countries. — Request to include statistical approaches and uncertainty analysis may be impossible when much of the analysis may be based on expert judgement and heavily reliant on assumptions. — Note that current CMR/ED phthalate substances and materials are exhaustively studied and new alternative substances and materials are likely to be less studied and have potentially limited histories of safe use. This limitation in information would be part of the risk profile for the new substances.	45. SCHEER is aware of the difficulty to compare with each other different approaches using substances, materials, designs and medical treatments. However, the MDR requires a justification of CMR/ED phthalate use in a medical device. This includes an effort to look for alternatives. The Guidelines offers a methodology to provide a justification by using a framework/approach. The most likely alternatives would be substances and/or materials in terms of functionality. Also in the DEHP 2015 Opinion of the SCENIHR already the presence of extensive toxicological information on DEHP and the scarce information on some alternative substances was noted by SCENIHR.
			46. Several statements throughout the Guidelines suggest that ‘prototype’ devices made with the alternative would be required to complete the BRA, e.g.: “The functionality and performance of the alternative shall be comparable to the extent that there would be no clinically significant difference in the performance of the device... Considerations of functionality and performance shall be based on proper scientific justification.” “[T]here is a considerable lack of data for potential alternatives to be used in medical devices. Therefore, manufacturers are encouraged to produce quantitative data on the use of alternatives for CMR/ED phthalates in medical devices.” These statements suggest that the medical device industry should make ‘prototype’ devices to understand leaching (exposure), biocompatibility, functionality, and (clinical/product)	46. This is not the task of the SCHEER to decide how the data is being obtained. Some testing of an alternative as a plasticiser in a material would be part of usual R&D. However, most alternatives are already identified in the literature, so justification might be based on a thorough systematic literature search.

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			performance of the device constructed with the alternative in comparison to the device with the CMR/ED substance. MedTech Europe would like to challenge this and asks for the Guidelines to specify that prototyping will not be mandatory.	

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37	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	47. It appears that the Guidelines want industry to justify the presence of a CMR/ED substance based on an endpoint (e.g., most sensitive) that is different than endpoints for CMR/ED. This would be the most stringent risk assessment method, potentially driving down the allowable safety levels. Can clarification be provided? “Describe hazards associated with the CMR/ED phthalate by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity…such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest observed-adverse-effect-levels (LOAEL)...” Data present in the biocompatibility evaluation of the device (e.g., risk assessment and/or in vivo testing) meets this request, but for some devices, may not speak to the risk of CMR/ED effect occurring. If the exposure is above that considered safe for the most sensitive endpoint, yet the device passed in vivo testing for that endpoint, an evaluation of whether the exposure elicits a CMR/ED effect may still be warranted. Furthermore, if the safety evaluation of a CMR/ED containing device is based on endpoints other than CMR/ED, why are CMR/EDs not being regulated on whether the device containing them passed biocompatibility testing? 48. Throughout the preliminary Guidelines, the possibility that the risk of using a CMR/ED substance and the risk of using an alternative could be equivalent does not appear to be acknowledged; e.g.: “The justification for the use of CMR/ED substances in a medical device with a presence above 0.1% w/w shall be based on… an argumentation why possible alternatives are appropriate or inappropriate…” “However, for it to be suitable, the potential alternative must represent a reduction in the overall risks to human health…” This may be due to the absence of risk classification within the Guidelines. Can risk be classified into categories (negligible, low, medium, high), (e.g., comparable to control banding system under EU Occupational Safety & Health legislation)? If so, the CMR/ED and the alternative may have identical risks (e.g., negligible). In this case, can the conclusion be that the risk is equivalent and, in turn, there is no change to the risk?	47. Not really. The Guidelines want the Industry to use the most sensitive endpoint, which might or might not be the ED activity. The comment on Regulation in relation to the biocompatibility testing is outside the remit of the SCHEER. The biocompatibility testing demonstrates the potential hazards that should be weighed against the benefit of using the device. If the biocompatibility shows no hazard, this may indicates a safe device. If a suitable alternative is identified, the CMR/ED substance may not be used above 0.1% w/w. (MDR Annex I, 10.4) 48. In view of the answer above with an equal activity/functionality/performance/risk of the phthalate and the alternative the MDR requires that the CMR/ED substance is not used above 0.1% w/w in the device or parts thereof. (MDR Annex I, 10.4).

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			49. P. 16 (line 31-35): “Instead of using PVC with a phthalate as plasticiser, or replacing the phthalate also other materials such as natural or synthetic polymers can be used. The application of biodegradable polymers is of increasing importance for implantable medical devices. Typical representatives of such biodegradable polymers are poly-L-lactide (PLA), polyglycolic acid (PGA), polyhydroxybutyrate (PHB) and polycaprolactone (PCL).” Suggest deleting. This text seems to suggest specific alternatives to be used. The purpose of the Guidelines is to provide guidance on the justification and BRA. Since this guidance has been mandated, any suggestions to alternative substances, materials, designs could be seen as endorsement that one of these options should be pursued which could impede an objective BRA and justification.	49. SCHEER agrees. Page 16 Lines 31-35 are deleted.(chapter 4, 2nd paragraph) Also comment #61.
			50. P. 16 (line 32-35): Relevance of given examples for substitution of phthalates is unclear. Are named polymers considered to be feasible alternatives for PVC? Is / Why is biodegradability of these alternative polymers a relevant property?	50. See above. Text is now deleted.
			51. P. 16 (line 41-43): “A description of the alternative scenario (CMR/ED phthalate "non-use scenario”) needs to be presented including identification of alternative substances, materials, designs or medical treatment, e.g. by including consideration of all available information…” – Can a limit or specific boundaries be provided for this information request?	51. No limitation can be given. The Guidelines gives a methodology of the justification on the use of CMR/ED phthalate. It depends on the substance/material/device. The inventory should be a general overview of which in a later phase the most likely candidates can be selected for further analysis. It could be foreseen that for some medical devices the inventory would be the same as the alternatives evaluated.

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38	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	52. P. 17 (line 21-23): Suggest adding: “The chemical safety assessment shall be done after assessment of the functionality and performance. Based on the outcome of the functionality and performance evaluation, the alternative(s) may be discarded and no further risk assessment is required.”	52. SCHEER agrees. Text added, but slightly modified. …and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance. (Chapter 4 step 5) See also comment #60.
			53. P. 17 (line 25): Replace "Finally, a short list of the potential alternatives can be chosen…" by "If potential alternatives can be identified, ..." This is to limit the list of potential alternatives, if available. The Guidelines seems to assume that there are always alternatives available, which may not be the case for certain applications.	53. SCHEER agrees. Text adapted. If potential alternatives can be identified, a shortlist of the potential alternatives can be established for further detailed assessment ...
			54. P. 17: Economic feasibility is mentioned (at least once) as relevant aspect of "availability" (for the manufacturer) and "risks" for patient (socio-economic impact; affordability for the society/healthcare systems). This aspect should be emphasised (e.g. p.24).	54. Although availability is covered by the Guidelines, the economic aspects are not. Annex I of the MDR covers safety and performance aspects of medical devices only. Economic aspects are not considered.
			55. P. 18 (line 20): We suggest adding before this sentence: "If an appropriate alternative was identified under Steps 1-6, a risk assessment..."	55. SCHEER agrees and it has been added : If an appropriate alternative was identified under Steps 1-6, a risk assessment of the potential relevant alternative substance/material used in the medical device or designs or medical treatments should be performed.(chapter 4, step 7)

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			56. P. 19 (line 10-12): Can clarification be given on what other hazards are to be considered? It is not very clear if the Guidelines aim to provide justification on the continued use of phthalates based on a BRA related only to CMR/ED activity of phthalates or related to all the biological endpoints listed in the 10993-1 standard. In the former case, hazards others than CMR/ED could be considered as part of the EN ISO 14971 risk management activities and would not necessarily be in scope of the Guidelines.	56. For the phthalate the risk assessment cannot be limited to the evaluation by this Guidelines. Similar to other components of a medical device a complete risk assessment needs to be performed. The other hazards are the "usual" hazards that might be indeed be evaluated according to EN ISO 14971 and the EN ISO 10993 series. For clarification the text is modified: These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series. See also Table 1.
			57. P. 19 (line 10-12): "[P]otential alternative (substances, materials, designs or medical treatments) would also have other hazards than those of the CMR/ED activity. These other hazards should be discussed." – This should be a risk-based discussion, and therefore hazard does not matter outside the context of exposure (i.e., risk = hazard x exposure).	57. SCHEER Agrees. See 56.
			58. P. 19 (line 16): What is meant by "realistic worst-case scenario"? "3a. Determination of the patient exposure based on realistic worst-case3 use scenario in the intended use." Can a variety of options for analysing exposure be provided in the Guidelines (e.g., the option to evaluate true exposure), for example — Exposure assessment under realistic simulated-use scenarios (see ISO 10993-12). — Extractables & leachables analysis (ISO 10993-18) or a non-volatile residue test (USP <661>) for accurate exposure information.	58. This is explained by Footnote #3 on page 10. Text is modified for clarification. Realistic worst case is the situation where the exposure is estimated using from a range of factors (i.e. duration, amount, exposure controls), where applicable, the ones that would be expected to lead to maximum amount of exposure (e.g. exposure might be assessed under realistic simulated-use scenarios by EN

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				ISO 10993-12 and EN ISO 10993-18 or a non volatile residue test (USP <661>)). The realistic worst case does not include deliberate misuse. (EU Biocides Regulation 528/2012).
			59. P. 19 (line 41-42): “Consider any known adverse events associated with the operation of the device using the phthalate, and whether the potential alternatives might affect these adverse events. These considerations can be based upon a systematic literature review.” – How can a literature review speak to the safety of the device containing the alternative if that specific device has never been made? What is the purpose of this consideration?	59.Many alternatives have already been discussed or suggested in the literature. The purpose of this consideration is to indicate that pilot production or trial of a new biomaterial might not be needed.
			60. P. 20 (line 8-9): Allow for the possibility of a shared literature review assessment on DEHP for devices with similar intended use. This would allow for a BRA from one manufacturer to be used by other manufacturers.	60. This is up to the manufacturer(s) or the industry to decide. The Guidelines do not prescribe how to do this, just that it has to be done.
			61. P. 20 (line 14-15): “The assessment of the risk should be accompanied by an estimation of the uncertainties in the described outcomes (e.g. confidence interval, standard deviation).” – If estimates are made and no actual quantitative data on the alternative exists, how can CI/Std Dev be determined?	61. Text modified for clarification. This is further elaborated in Section 9. The assessment of the risk should be accompanied by an estimation of the uncertainties in the described outcomes which might be quantitative (e.g. confidence interval, standard deviation) or qualitative (see section 9). (end of Chapter 4)

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39	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	62. The Guidelines do not consider the possibility that the use of the CMR/ED substance presents no-to-negligible risk, thereby precluding the need to assess the benefit of the device with the CMR/ED and/or the device constructed with the alternative. “[A]cceptability of any risk is evaluated in relation to the benefit of the use of the medical device” For such a justification several steps need to be considered including the possible use of alternative substances, materials…” If there is no-to-negligible risk associated with the use of a CMR/ED substance present in a device above 0.1% (w/w), the benefit will always outweigh the risk. If the safety of using the CMR/ED can be proven (i.e., no-to-negligible risk exists), the assessment of any potential alternatives would not yield any meaningful results – as the risk profile of the device would not significantly be altered. We therefore suggest that the BRA process outlined in the Guidelines incorporate a decision tree type of structure, to facilitate and allow to discontinue the assessment where further steps are not relevant, based on a defined quantitative risk threshold/margin of safety. 63. P. 21 (line 8-9): “There may be difficulties in comparing the risks of a substance e.g. a phthalate, and the risks of a technical alternative such as medical design or medical treatment.” – Is it requested that a margin-of-safety comparison for all biological endpoints including CMR/ED be conducted?	62. SCHEER disagrees. Even if the phthalate does not pose a risk the regulation (including the MDR) requires when possible the replacement of some phthalates based on the Commission decision to designate these as substances of very high concern (SVHC). As is also included in Annex I, 10.4.1 a and b of the MDR. So, this is a regulatory obligation.(see 48 above) 63. This paragraph is intended as explanation as it may not be possible to determine for some alternatives a MoS. It is for the manufacturer to decide how the risks will be compared. In the overall risk assessment. The Guidelines do not replace the general risk assessment that has to be performed. It is intended to provide an addendum to the risk assessment for justification of the use of a CMR/ED phthalate.

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40	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	64. P. 22: “Benefit-risk ratio” seems to imply that a number will be provided. Could this be clarified?	64. SCHEER agrees that a ratio indicates a figure showing a relationship between two outcomes. However, for a benefit description this may not always be possible. This is addressed in section 8 Page 26. Text modified on Page 26 for clarification. However, it should be underlined that for medical devices the quantitative determination of a benefit-risk ratio may be rather difficult to provide and expressed in a figure. In such cases a qualitative approach of weighing the benefit based on expert judgement might be used.
			65. P. 22-23: Table 1 – “Functionality/performance and clinical benefit/performance” – A prototype device would never be in the field and therefore performance/clinical data would not exist. This category is purely speculative for the alternative. “Concentration (% w/w)” – concentration is independent of exposure. This value is not meaningful with respect to assessing safety.	65. SCHEER disagrees. A prototype material as component of a medical device may be prepared to evaluate chemical compatibility between an alternative and the main material (PVC or other material). As indicated there is already literature available on many possible alternative plasticisers for phthalates. In addition, the total presence in a material of all components needs to be evaluated, as part of the chemical composition. Based on content and leakage properties an estimation may be made for the potential exposure.
			66. P. 23 (line 2): The example table would only need to be completed for material/parts/devices that contain CMR/ED phthalates above 0.1% w/w. Such comparison table is not required for those equal or below the 0.1% w/w threshold since those do not require justification nor BRA.	66. SCHEER agrees. That is also indicated by the text. % now added for clarification. This Table shall be completed for every component of the medical device that

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				contains CMR/ED phthalate(s) above the 0.1% w/w level. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated.
			67. P. 23 (line 15-17): Suggest deleting: "In contrast, a slight clinically insignificant loss in functionality might be acceptable if there is a large benefit to be gained in terms of reduced or even absence of toxicity." The BRA is more than a comparison of clinical benefit and reduced toxicity. It is also dependent on functionality and exposure levels, leaching properties, feasibility etc. Moreover, it is unclear what is meant by 'large benefit' and 'absence of toxicity'. Can this be clarified? Should 'absence of toxicity' be 'absence of risk'? If the use of the CMR/ED substance is considered safe (< agreed threshold), how 'large' should the benefit be to favour the alternative? What is a 'slight clinically insignificant loss in functionality'? i.e., how 'slight' should the 'loss of functionality' be to favour the alternative? Can quantitative definitions be provided for this statement?	67. SCHEER disagrees to delete this example. This is an example how weighing of benefit versus risk might be done. It is for the manufacturer to give a description on these issues. Text modified for clarification. In contrast, a minor loss in medical functionality might be acceptable if there is a large reduction or even absence of toxicity.
			68. P. 24 (line 8-15): Feasibility, availability and benefits also include economic aspects: the overall cost of the alternatives should not hamper availability and affordability of required medical devices/treatments.	68. Text added on availability of alternatives as examples. See also comment # 38 no 54. Although not the main subject of these Guidelines, it should be realised that availability might be a limitation for the introduction of an alternative substance/material. Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM), however, this may not be for other alternatives identified. The lack of the availability of a potential

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				alternative for a medical device might result in the conclusion that replacement is not feasible and that the use of a phthalate with CMR and/or ED property continues in order to keep the availability of the device for patients. The issue of availability is also addressed #t 31 no 17. Text added: In addition, analysis of availability and technical feasibility might affect choices for alternatives as well. (Chapter 4, step 5)

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41	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	69.P. 24 (line 19-21): “These Guidelines do not provide information for the benefit-risk assessment of the use of a medical device itself but are limited to the evaluation of potential alternatives to the use of CMR 1A or 1B and/or ED phthalates in a medical device.” – How can functionality/performance be evaluated without use? This appears to be a contradictory statement to other content within the Guidelines. It would not be possible to perform the BRA of the alternative substance without use per the request for functionality/performance data on the alternative substance.	69. This assumes that the performance of the device is presented in the overall dossier itself. Regarding the alternative the main focus is on the change in material and functionality. Text added. The benefit-risk analysis and risk management is regulated by the MDR in Annex II, Section 5. These Guidelines do not provide information for the benefit-risk assessment of the use of a medical device itself but are limited to the evaluation of potential alternatives to the use of CMR 1A or 1B and/or ED phthalates in a medical device. The evaluation of the overall benefit-risk assessment of a medical device is presented in other documents (e.g. MEDDEV 2.7/1 rev4, ISO 14971).

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42	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	70.P. 24 (line 25-42): Suggest deleting or rewriting this text: It is suggestive of alternatives to be used for certain medical devices while the purpose of the Guidelines is to focus on the justification and BRA. The referenced articles do not provide scientific evidence for maintaining functionality or performance. Examples on page 24, line 33-35 suggest alternatives with performance of RBC containers at 40°C (typo) up to 35 days while performance varies depending on the procedure and additive solution used. According to the German "Richtlinie Hämotherapie 2017", RBCs can be stored from 28 up to 49 days at 4°C. Performance may vary depending on the conditions but generally RBCs are stored in SAG-m solution up to 42 days at 4°C. The proposed example is showing inferior performance or functionality than what is generally accepted, however is presented as an acceptable alternative. Similar for platelets, the referenced article is not quoted correctly (e.g. page 24, line 40). The original article states: "potentially allows the storage ..." while the Guidelines state it more as a certainty "This allows the storage of ..." We propose that no reference is made to potential alternatives in the Guidelines. If the purpose is to provide some examples of material benefits, reference could be made to examples such as finetuning of tubing flexibility for certain applications, the stabilising effects of DEHP on RBCs, resistance to heat or chemical as part of sterilisation processes, need for permeability of gases. These properties are not necessarily specific to CMR/ED but could also be considered for the alternative materials as part of the BRA's.	70. SCHEER agrees partially. Other comments specifically ask for inclusion of examples, including mentioning alternative substances. The aspects of using DEHP as plasticiser were previously extensively discussed in the 2015 Update of the DEHP Opinion published in early in 2016. Text modified and text added. Page 24 line 25. A number of alternatives were evaluated as alternative for DEHP in blood bags (Simmchen et al., 2012, SCHENIR 2016). Page 24 line 38. For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen et al. 2012, Prowse et al. 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags (Prowse et al. 2014). This potentially will allow the storage of platelet concentrates for up to 7 days, if measures to prevent bacterial contamination can be safely implemented.

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43	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	71.P. 25 (line 27-33): We suggest adding to this list: "improved product quality".	71. SCHEER agrees. Text added. improved product quality/clinical performance…

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44	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	72. Uncertainty Analysis is one of the longer sections of the draft Guidelines. As much of the analysis could be based on expert judgment and assumptions using literature data, can clarification be provided on the request to include statistical approaches and uncertainty analysis?	72. SHEER. This section is provided for some clarification for the user of the Guidelines. Page 29 Lines 4-7 give some additional explanation on statistical analysis with reference to EN ISO 14971. “In situations where sufficient data are available, a quantitative categorisation of 4 probability levels is preferred. If this is not possible, the manufacturer should give a 5 qualitative description. A good qualitative description is preferable to an inaccurate 6 quantitative description (EN ISO 14971).”
			73. Uncertainty analysis & probability score – If not enough data is available for overall uncertainty analysis (some part assessment is quantitative, and some part is not), would overall uncertainty analysis and probability score be qualitative? Could the Guidelines provide examples of uncertainty analysis and probability score as applied to the specific use of a phthalate in a medical device?	73. SCHEER cannot give examples as the task of SCHEER was the drafting of the Guidelines, not to perform the BRA including an uncertainty analysis and probability itself. The Guidelines contain suggestions how this can be done in Table 2 and the references.
			74. P. 27 (line 11): No standard is available to determine leaching of DEHP from devices; this is currently part of a New Work Item Proposal for an international standard. So even measurement of how DEHP is released from PVC medical devices has not (yet) been standardised.	74. ISO 10993-18 on characterisation of is under revision. However, the FDIS is just published in 2019. The final publication is expected in 2019/2020. (ISO/FDIS 10993-18 Biological evaluation of medical devices -- Part 18: Chemical characterization of medical device materials within a risk management process)

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			75. P. 28 (line 31 and 36): What is meant by “non-standard uncertainties”?	75. Text from EFSA. This is necessary in all assessments except those 30 standardised assessments where no non-standard uncertainties are identified. Text modified for clarification. This is necessary in all assessments except those standardised assessments where only standard uncertainties are identified (e.g. inter-and intra-species uncertainty factors). Required for all assessments, but extremely brief in standardised assessments where only standard uncertainties are identified.

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45	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	76.P. 33 (line 29-31): “The interaction of phthalates with the polymers they are embedded in is weak, so they may be released from the plastic product into the environment and into the human body if the product is in contact with it” – This is polymer dependent, but more importantly is dependent on other factors such as solubility. The release of a lipophilic phthalates (or any substance for that matter) would be minute if the surrounding media was polar. This sentence appears to suggest that phthalate release from a plastic product and subsequent exposure will always occur due to “weak” chemical interactions.	76. SCHEER disagrees. The text clearly states “may” which is indeed dependent on the environment in which the medical device with the phthalate is used. This text is part of the mandate as published and cannot be amended by SCHEER.

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46	Buijs,Nathalie,MedTech Europe,n.buijs@medtecheurope.org,Belgium	2. Framework for Benefit-Risk Assessment	77. It should be clarified that BRA is equivalent in meaning to benefit-risk determination, which appears in Annex 3 (Definitions).	77. SCHEER Agrees. The MDR in Annex I, Point 10.4.3 states benefit risk assessment, so in the Guidelines benefit risk assessment is used. Text added page 9 line 18. Other descriptions for BRA may be "benefit risk analysis" or "benefit risk determination" as defined in the MDR. As Annex I Section 10.4.3 indicates a benefit risk assessment this terminology is used in these Guidelines.
			78. Glossary: Please add missing acronyms such as MDD, MDR, CLP.	78. SCHEER. MDD, MDR and CLP are already included in the glossary.
			79. P. 44 (line 3-5): Wording of the following sentence need to be corrected: "CMR substances are substances identified and classified as carcinogenic, mutagenic or toxic for reproduction of different categories based on the intrinsic toxic properties of a substance or a mixture whereof categories 1A and 1B apply to these Guidelines." We suggest deleting "or a mixture" since this chapter refers to substances only. Moreover, the described process is limited to harmonised classification according to the CLP Regulation.	79. SCHEER agrees. The word mixture is not needed here and is deleted.
			80. P. 46 (line 22-39): Information missing that medical devices are currently exempted or fully out of scope of these regulations/restrictions.	80. SCHEER disagrees. This is already specifically mentioned on page 47 lines 3-9 indicating other specific regulations in which phthalates are mentioned..

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47	Laursen,Lene,Medicoindustrien,ll@medicoindustrien.dk,Denmark	2. Framework for Benefit-Risk Assessment	Scope: We ask for at a clear demarcation – the scope of this guideline is phthalates, not 'substances', this is clear and this is the mandate given to SCHEER by the Commission. So we propose that p. 9 line 16-17 be deleted at this point as in the future the Commisson will mandate a specific guideline for other substances, see MDR annex I, 10.4.4.	SCHEER disagrees. The comment is correct that these Guidelines are drafted based on the MDR Annex I, 10.4.3 intended for phthalates, however, there is no reason why the same principles could not be applied to other substances.

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48	No agreement to disclose personal data	2. Framework for Benefit-Risk Assessment	- Page 9, lines 11-17: This Guideline and the European Pharmacopeia mention alternative plasticizers for DEHP. However, as already stated in this Guidelines, there is a considerable lack of data for long term experiences on health risks for these alternative plasticizers. As it stands today these alternatives are not well studied what makes the assessment of risks and benefits at this point in time difficult. Decision making can currently not be based in solid facts. In results the justification for use of either DEHP or an alternative cannot be based on facts. - This Guideline is supposed to support relevant stake holders of the Medical Device Industry, such as manufactures, notified bodies and regulatory bodies for the justification of the use of phthalates with potentially CMR or ED effects. We have to point out that risk evaluation on CMR or ED are a complex and challenging scientific topic and that requires know how and personnel with the appropriate skill set. This expertise does not necessarily exist today amongst these stakeholders.	SCHEER disagrees. For any substances used also according to the current regulation a risk assessment has to be performed. These Guidelines are specifically drafted for alternatives for phthalates. Indeed for some possible alternatives limited information is available as already demonstrated in the Updated 2015 DEHP Opinion of the SCENIHR. However, also for some alternatives sufficient information was provided to perform a risk assessment. Regarding know how, each risk assessment has to be performed by a knowledgeable person. This is also stated in the MDR, EN ISO 14971 for risk management and the EN ISO 10993 series of standards for hazard identification.

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49	No agreement to disclose personal data	2. Framework for Benefit-Risk Assessment	- Page 10, line 21ff: The method of the described BRA is very scientific based and even though proper planning was applied the process is too sophisticate to follow. We do therefor, as a general comment, ask to simplify and combine steps to allow a better usable striped down version. - Methodology: Combine Step 9 and 10 in one single step to clarify the methodology and to avoid duplication. It is unclear why the risks of use must be compared to alternative scenarios in Step 9 and again in Step 10.	SCHEER disagrees. Step 1 -10 are a short summing up of steps to be performed. Further explanation and some examples are provided in section 3. Step 9 is a comparison of the risks, whereas Step 10 is an overall comparison with input of Step 9 and includes the benefit. This separation was included for a clear distinction between the risk and benefit comparison.
50	Kolb,Stefan,Fresenius Kabi Deutschland GmbH,stefan.kolb@fresenius-kabi.com,Germany	2. Framework for Benefit-Risk Assessment	- Page 15, lines 12-13: The combined exposure to multiple phthalates shall be considered when present in medical devices. A blood bag manufacturer can only assess the phthalate exposure of the blood bag system he is producing. A manufacture is not in the position to overlook the use of multiple phthalates for a patient in a hospital that does receive a blood transfusion as treatment are not standard and vary from hospital to hospital and from country to country. For this reason, the assessment has to be limited to the phthalates used during manufacturing of a blood bag systems.	(*addressed already see step 3 chapter 3)* SCHEER agrees. Therefore the shall is replaced by “also needs to be”. This as a awareness raising issues. The combined exposure to different phthalates also needs to be considered when present in a medical device. See also comment 21 which specifically asks for exposure assessment based on multiple medical devices used. Comment #60, also refers to difficulty of determining exposure to multiple devices especially if devices of different manufacturers are used.

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51	Laursen,Lene,Medicoindustrien,ll@medicoindustrien.dk,Denmark	2. Framework for Benefit-Risk Assessment	Regarding step 4: We envisage problems relating to the handling of intellectual Properties Rights when a manufacturer has an obligation to asses alternative substances, materials, design or medical treatments. P. 16, line 39: We propose to add 'such as' substances, materials, designs or medical treatments. This to ensure that the manufacturer decides which substances, materials are relevant and relating to patient safety of his product. Regarding step 5: P. 17: We propose that the manufacturer be granted the discretion to scope the liste of possible alternatives to the relevant alternatives only.	Step 4. SCHEER partially agrees. IPR needs to be solved by the interested parties. It is not for SCHEER to solve such problems if they arise. P16 Line 39. SCHEER agrees. Text modified. Prepare a list of possible alternatives (such as substances, materials, designs or medical treatments). Step 5 P17. SCHEER agrees. That is also the intention of Step 5 to limit the evaluation of alternatives relevant for the specific device of a manufacturer. It is therefore recommended to select a number of potential relevant alternatives.

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52	Kolb,Stefan,Fresenius Kabi Deutschland GmbH,stefan.kolb@fresenius-kabi.com,Germany	2. Framework for Benefit-Risk Assessment	- Page 23, line 2: To assess the exposure of DEHP that is used in a blood bag system the leaching of the PVC material into the blood component is the bases. The amount of leaching DEHP is a summative effect of all components, e.g. foil, tubes, Y-pieces, used in the blood bag systems. This does determine the patient exposure. It is therefore not reasonable or useful to determine the exposure per DEHP component used in the blood bag system, instead the basis is the blood bag system as a complete set.	SCHEER agrees. However, comment #50 specifically asks for a single component analysis. Text modified. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated.
53	Kolb,Stefan,Fresenius Kabi Deutschland GmbH,stefan.kolb@fresenius-kabi.com,Germany	2. Framework for Benefit-Risk Assessment	- Page 24, line 34: The temperature for the storage capability must be indicated with 4°C. 40°C is not correct. - Page 24, lines 36-42: The information given here is scientifically outdated. In the meantime there are better performing alternatives than TEHTM available for the storage of platelet concentrates, like butyryl tri-n-hexyl citrate or short BTHC. (Commercially available blood storage containers, Prowse et al., Vox Sanguinis, (2014) 106, 1–13)	SCHEER agrees. Typo is corrected. P24 Lines 36-42. Text modified to reflect comment. Page 24 line 38. For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen et al. 2012, Prowse et al. 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags (Prowse et al. 2014). This potentially will allow See also comment 8 and 42.

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54	Laursen,Lene,Medicoindustrien,ll@medicoindustrien.dk,Denmark	2. Framework for Benefit-Risk Assessment	Relating to step 7, page 19, line 45-46: The assessment of potential alternatives in step 7: Here it is a demand, that this step be carried out for each possible alternative substance and or material identified as a likely replacement for the CMR/ED designated phthaleate. In step 5 – 6 the manufacturer has to evaluate why possible substances/materials are appropriate or inappropriate, so why does the manufacturer in step 7 have to perform this exercise for all possible alternatives? We propose to change the wording in p. 19, line 45 to 'relevant' alternative substance and/or materials in stead of 'each possible' alternative substance. Also: You cannot do this for all alternatives, since there might be lack of data.	SCHEER agrees. The intention is that a manufacturer starts with an inventory (step 4), makes a selection of relevant alternatives (step 5) and then performs an evaluation (steps 6 and 7). In steps 6 and 5 the word relevant has been added based on comment #51 above. Step 5 P17. It is therefore recommended to select a number of potential relevant alternatives. Also added to title of step 6 and 7. Step 6: Description of identified potential relevant alternative(s) and conclusion on their technical feasibility. Step 7: Assessment of the risk of identified potential relevant alternatives P18 line 20. If an appropriate alternative was identified under Steps 1-6, a risk assessment of the potential relevant alternative substance/material used in the medical device or designs or medical treatments should be performed. In terms of lack of data, this should be documented.

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55	No agreement to disclose personal data	2. Framework for Benefit-Risk Assessment	-Page 27, Line 1ff - Methodology: The fact that an uncertainty analysis has to be performed as a final step of the BRA does already indicate that too little facts are known for the use of alternative phthalates. It is indicational for the general dilemma that the use of DEHP is presumed to be a risk, but on the other hand we are confronted with a lack of data for the risks of these alternatives. Furthermore, the technique of this analysis is described to be complex and complicated. Performing such an analysis is not necessarily established amongst the stake holders today. In conclusion, the usability is questionable, and the value of the outcome of the uncertainty analysis is not clear. It might be better to eliminate this step at this stage and consider it for future update of the Guideline once more data become available.	SCHEER disagrees to delete this step at this moment. There is a potential to perform a uncertainty analysis as per EFSA guidance taking into account differences in data availability.

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56	No agreement to disclose personal data	3. Assessment of the presence of phthalates in a medical device	-Page 51, lines 23-27: The details about potential alternatives to DEHP are incomplete. In 2017, the European Pharmacopoeia Commission identified four plasticizers as alternatives for DEHP (cyclohexane 1,2-dicarboxylic acid, diisononyl ester; butyryl tri-n-hexyl citrate; tris(2-ethylhexyl) trimellitate; bis(2-ethylhexyl) terephthalate), these should be added to the list. However, none of these alternatives have shown the beneficial effect of stabilize red blood cell membranes for the full storage period of 42/49 days, and are thus not fully covering the intended use.	SCHEER agrees. butyryl tri-n-hexyl citrate (BTHC, CAS 102818-95-1) added. However, text indicates “are being proposed” so there is no suggestion that these alternatives are indeed full replacements of DEHP. Today, other plasticisers such as Di-isononyl cyclohexanoate (DINCH, CAS 1166412-78-8), Tri-2-ethylhexyl trimellitate (TEHTM, CAS 3319-31-1), butyryl tri-n-hexyl citrate (BTHC, CAS 102818-95-1) and Dioctyl Terephthalate (DOTP, CAS 6422-86-2) are being proposed in medical applications such as medical tubing and blood bags
57	Laursen,Lene,Medicoindustrien,ll@medicoindustrien.dk,Denmark	3. Assessment of the presence of phthalates in a medical device	Generel proposal: If SCHEER would provide for an example of a BRA it would be very usefull for manufacturers of medical devices.	SCHEER agrees. However, SCENIHR has already performed an extensive evaluation of DEHP and a number of alternatives (SCENIHR Opinion 2016). A full evaluation is outside the scope of the cuurent mandate for SCHEER.

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58	Schaaf,Sebastian,BSN medical GmbH,sebastian.schaaf@essity.com,Germany	3. Assessment of the presence of phthalates in a medical device	Regarding the scope (lines 6 to 13): MDR Annex I chapter II point 10.4.1 clearly limits its application to certain types of medical devices or parts thereof ("are invasive and come into direct contact with the human body, (re)administer medicines, body liquids or other substances, including gases, to/from the body, or transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body,"). Accordingly, the MDR excludes certain types of medical devices (basically all direct contacting non-invasive devices) from the obligations on CMR and ED substances. We assume that this applies to the guideline in development as well. However, the draft mentions disposable gloves as an example of a medical device containing phthalates (annex 6 line 5), which is clearly a product which is not included according to MDR Annex I chapter II point 10.4.1. In addition, it is not clearly mentioned in the scope that this guideline is not applicable to all medical devices, but only to certain types of devices. Please amend the scope by adding a clear statement on the applicability of this guideline and remove the incorrect example from annex 6.	SCHEER agrees. Text added to P6 line 20. Annex I Section 10.4.1 is now explicitly mentioned in the scope of the Guidelines. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1 of the MDR. See also comment #27, #59 Annex 6 line5. The listing of medical gloves is here an example of the widespread use of phthalates and has no relation to Annex I 10.4.3 and the Guidelines. It is provided as general information.

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59	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 6, line 16: According to Annex I, Chapter II, par.10.4 of the MDR, the justification of the presence of CMR 1A or 1B and/or ED phthalates above 0,1% w/w concern “Devices, or those parts thereof or those materials used therein that: — are invasive and come into direct contact with the human body, — (re)administer medicines, body liquids or other substances, including gases, to/from the body, or — transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body” The current guidelines do not make this distinction and only refer to ‘medical devices’ which, as such, includes all materials and all medical devices. There is therefore an inconsistency throughout the text between the general reference to medical devices and the scope of the mandate, which is specific to the abovementioned medical devices, parts and materials. We would welcome more clarity on the categories of medical devices to which the guidelines will apply and how those specifics will be taken into account.	SCHEER agrees. Text added to scope. See also comment #27, #58. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1 of the MDR.

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60	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 9, Line 24-25: Annex I, Chapter II, point 10.4.2 of the MDR (Substances, materials and design) provides that the justification shall be based upon “an analysis of possible alternative substances, materials or designs”. There is no reference to an analysis of alternative medical treatments. If such an analysis is expected as part of the implementation of the guidelines: • a definition of “medical treatments” should be provided; • it should be kept in mind that in the course of a medical treatment the use of multiple similar medical devices from different manufacturers is not unusual (especially for neonate use or certain therapeutic indications). In such cases, it is difficult to assess the overall phthalate exposure resulting from the treatment. Page 9, Line 33: The benefit-risk assessment shall take into account the intended purpose and context of the use of the device. Against this background, if a justification is already available for a medical device with	SCHEER disagrees. MDR Annex I, 10.4.3 specifically also mentions “medical treatment” as possible alternative to include in the Guidelines for phthalates. It is outside the scope to present a specific definition of a medical treatment. Medical treatment is a common understanding. Some medical devices comprise a whole system (e.g. infusion systems). In these cases the overall exposure can be evaluated. See comment #21 asking for multiple device, #50 for single devices. Text modified. The combined exposure to different CMR/ED phthalates also needs to be considered when present in a medical device. P9 line 33. Added text to P9 line 15 to indicate this issue.

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			similar intended use, the existing justification should be used as a reference.	A justification for the use of a CMR/ED phthalate can also be based on an already available justification relating to a medical device for which equivalence with the device in question can be demonstrated according to the MDR Annex XIV Section 3. The existing justification can be used as a reference, and should be provided.
			Page 10, Line 16: In order to ensure that the misuse of medical devices does not fall under the scope of the guidelines, it should be clarified that “A number of aspects need to be considered for the justification of the presence of a phthalate […] in a medical device as intended to be used". This clarification should be made throughout the document.	P10 line 16 Text modified. A number of aspects need to be considered for the justification of the presence of a phthalate classified as CMR category 1A or 1B and/or identified as ED (i.e. content > 0.1% on w/w) in a medical device, or parts thereof or those materials used therein, as intended to be used.
			Page 10, Line 34: It is not clear whether the guidelines focus on "patient" or "patient and user" exposure. While Page 11, line 25 refers to “patient or user exposure” and page 12, line 11 indicates that a similar approach is required for “professional users”, the rest of the document is mainly focused on patient exposure. The guidelines should focus on patient exposure as user exposure (such as operators/nurses) is extremely difficult to assess since the practices and level of exposure may differ depending on hospitals and hospital departments. Focusing on user exposure would also lead to a risk-only assessment considering that patients are the primary beneficiaries of the treatment.	P10 line 34. SCHEER disagrees. According to the MDR also users should not be harmed by a medical devices. In addition, there may be non patients (e.g. donors) on who the device is applied. The Guidelines mention mainly patients as the most likely highest exposure group but also identifies users and donor as possible risk groups. This is indicated at Page 12 line 11-12 which now states. In addition to patients, the same

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				approach shall be used for the justification of the presence of CMR/ED phthalate in medical devices to evaluate the risk for professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect the following has been also included in the scope Page 6 line 26. When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. See comments #17, #19, #30.
			Page 11, Line 13-15: The following sentence should be added to the paragraph on the identification of the candidates for assessment as potential alternatives (step 5): "No further assessment will be required for the possible alternatives for which a justification for exclusion has been provided." In addition, the benefits of the current material/substance/design should be taken into account as part of the evaluation of potential alternatives. If the identified benefits are lower with the alternative substance, the said substance should be discarded. In order to keep consistency with page 17, line 25-28, we further suggest including the following sentence: “The short list of the potential alternatives can be chosen for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, economic feasibility, availability and technical performance.”	P11 line 13-15. Page 11 is a short summing-up of the various steps. Further explanation is presented below the Figure 1. SCHEER agrees. Text with similar meaning has been added to P17 line 23 according to comment #38. …and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance. (Chapter 4 step 5)

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			Page 13: The previous comments should be reflected in the flowchart (Figure 1 page 13).	If the benefit of the current device are better than an alternative can be discarded. This would be the outcome of Table 1 on page 22. P13. The Figure has been modified based on various comments received.

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61	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 14, Line 7-9: The legal framework used in the food sector should not be used as a reference for Medical Devices as substance migration limits (SML) may differ for medical devices. The specifics of medical devices should always be considered in the development on the guidelines. This comment also applies to Annex 5.	P14 line 7-9. SCHEER disagrees. A number of aspects of food contact materials can be relevant for medical device materials as well. The EFSA group TDI values are dealing with the toxicological evaluation and risk assessment of phthalates. These data are also relevant for the risk assessment of medical devices. Annex 5 provides general background information on legislation of phthalates.
			Page 15, Line 13-14: Reference is made to Annex 6 for considering the combined exposure to multiple phthalates. However, Annex 6 addresses the use of phthalates in different subgroups, not the combined exposure. Assessing the overall phthalate exposure would further require access to data on the use of phthalates in other medical devices that could be used as part of the same medical treatment. In the case of blood bags that are supplied to blood establishments, manufacturers will not be in a position to determine exposure as such exposure depends on how the final product (blood or pharmaceutical product) is processed and used in a medical treatment, which varies from one country to another. Manufacturers will only be able to consider the exposure related to their own medical device(s), from a manufacturing standpoint, and not the combined exposure to substances in multiple medical devices used as part of a medical treatment.	P15 line 13-14. SCHEER agrees. Text modified based on comment #21 and #50. Reference to Annex 6 modified. The combined exposure to different phthalates also needs to be considered when present in a medical device. See also comment 21 which specifically asks for exposure assessment based on multiple medical devices used. More details on the use of phthalates in medical devices are presented in Annex 6.
			Page 14, Line 24-26: As stated in the guidelines, “ISO 10993-1 provides information on use type in terms of exposure potential”. However, this section relates to step 2 on the use and function of the phthalates in the medical device. The reference to ISO 10993-1 would rather fit in step 3 on the assessment of the risks of the CMR/ED phthalate.	P14 line 24-26 SCHEER agrees. Text on EN ISO 10993-1 moved to step 3. Page 14 line 36.

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62	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 16, Line 31-35: The assessment of possible alternatives includes an inventory of possible alternatives (step 4) and the identification of the candidates for assessment (step 5). As such, the guidelines should not include a list of specific alternative substances. Lines 34-35 should therefore be deleted as the list of alternatives could be interpreted as providing directions to manufacturers for assessing potential alternatives.	P16 line 31-35. SCHEER agrees. Text on alternative material is removed. See comment #37
			Page 17, Line 25: Considering that in certain cases alternatives may not be available, we suggest adapting the wording throughout the text to refer to the "potential alternative, when available"	P17 line 25. SCHEER agrees. Text modified. If potential alternatives can be identified, a shortlist of the potential alternatives can be established for further detailed assessment...
			Page 18, Line 20: In line with the previous comment, we suggest the following wording: "If an appropriate alternative was identified under Steps 1-6, a risk assessment..."	P18 line 20. SCHEER agrees. Text modified. Comment #54. If an appropriate alternative was identified under Steps 1-6, a risk assessment of the potential relevant alternative substance/material used in the medical device or designs or medical treatments should be performed.
			Page 19, Line 10-12: The guidelines are intended to provide a framework for the BRA of the presence of phthalates in medical devices. The consideration of any other hazards would be considered as part of the EN ISO 14971 risk management activities and would therefore not fall within the scope of the guidelines unless further guidance is provided on these hazards other than those of the CMR/ED activity.	P19 line 10-12. SCHEER agrees. Text modified. Comment #38. These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series. See also Table 1.

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63	Volle,Aurelio,French Blood Establishment ,aurelio.volle@efs.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 6 - Lines 18-19 Original : They are intended to be used by the relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies. They are intended to be used by the relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies. The liability of performing the benefit-risk assessment must not fall on Blood Establishments. The benefit-risk assessment must be carried by relevant stakeholders such as manufacturers, notified bodies and regulatory bodies but not by Blood Establishments. Suggestion : They are intended to be used by the relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies. The liability of performing the benefit-risk assessment must not fall on Blood Establishments. Explanation : The benefit-risk assessment must be carried by relevant stakeholders such as manufacturers, notified bodies and regulatory bodies but not by Blood Establishments.	P16 Line 18-19. SCHEER answer. Users like Blood Establishments are not indicated in the text. The Guidelines present examples of relevant stakeholders. Exclusion of certain users of medical devices is not included. It is not deemed necessary to include end users. The risk assessment is a task of the manufacturer of a medical device.

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64	SIRDEY,THIERRY,ANSM,thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 7 - line numbers: 33-34 Comments :ISO 10993-1 is not a series of endpoints but 10993-1 ask for strategy and programme for the biological evaluation of the medical device. Annex A (10993-1) gives the general evaluation tests that should be considered for each device and duration category. Proposed change: Add : "According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. In annexe A", a series of endpoints is indicated from which a selection can be made for the biological evaluation of a medical device.	P7 line 33-34. SCHEER agrees Text modified. According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. In Annex A of EN ISO 10993-1, a series of endpoints .....

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65	Volle,Aurelio,French Blood Establishment,aurelio.volle@efs.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	* Page 10 lines 34-35 Original text : 3a. Determination of the patient exposure based on realistic worst-case use scenario in the intended use. Suggestion : 3a. Determination of the patient and donor exposure based on realistic worst-case use scenario in the intended use. *Page 11 lines 1-2 Original text : 3c. Determination of the maximum tolerable/acceptable exposure for the patient, based on pre-clinical and clinical information (if available). Suggestion : 3c. Determination of the maximum tolerable/acceptable exposure for the patient and the donor, based on pre-clinical and clinical information (if available).	P10 line 34-35 SCHEER disagrees. This is not addressed in the short description of the steps to be done. Text on donor (non patient) risk is addressed on page 12 line 11 together with possible risk for users. Text modified. See also comment #17. .....professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines. When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. P11 line 1-2. SCHEER disagrees. Text on donor (non patient) risk is addressed on page 12 line 11 together with possible risk for users. See also comment #17. .....professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of

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			Explanation: the exposition to phthalates is only described in relation to patients. However, the focus on patients does not give a relevant representation of all exposed recipients. Blood products for clinical care, e.g. plasma, platelets or stem cells, are collected from donors via aphaeresis. The systems used to perform the aphaeresis may contain phthalates. Since the principle of aphaeresis is that blood is returned to the donor, the donor might consequently be, exposed to phthalates contained within the device. It is therefore necessary to take them in consideration too.	the Guidelines. When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well.

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66	SIRDEY,Thierry,ANSM, thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 8 - line 3 : Comments : The standards deals also with other endpoints. In Table A.1, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities. Proposed change : Add : "immunotoxicity and organ-specific toxicities" endpoints Page 8 : Lines 29-30 : Comments : To our knowledge there isn't any phthalates in 10th ATP. Moreover, there are different ATP for different phthalates: for examples dihexylphtalate (cas no. 84-75-3) was classified as a Repr.1B in October 2013 (5th ATP / Regulation 944/2013). So we are wondering which phthalates is concerned in this sentence. An up to date list could be useful for stakeholders. Proposed change : Precision on the list of phthalates and relevant ATP could be added for better understanding for stakeholders in annexe 5, for example. Page 9 - lines 7-10 : Comments : The ED-properties are described as scientific evidence of probable serious effects to human health identified in the sense of article 57(f) of REACH (Regulation (EC) No. 1907/2006), But the definition of ED for medical device is not clearly given in this article. There is another citation to Biocides Regulation (No. 9 528/2012), but we are wondering which is the link with medical device regulation. Proposed change : Add: Is it possible to add a more precise reference to endocrine disruptor definition? Page 9 : Lines 16-17: Comments : The sentence "The approach of these Guidelines may also be used for a BRA of other CMR/ED substances	P8 line 3. SCHEER partially agrees. For immunotoxicity and organ specific toxicities there are no dedicated standards. So, text added to emphasize these specific toxicities as well. Additionally immunotoxicity and organ-specific toxicities need to be considered, if appropriate. P8 line 29-30. SCHEER agrees. Several phthalates are indicated in the 10th ATP. As there is also a referral to the restriction list the reference to the 10th ATP is deleted to avoid confusion. P9 line 7-10. The MDR indicates in Annex I point 10.4.1 sub b that the use of ED substances is not allowed above 0.1% (w/w). If used above this 0.1 % a justification is needed that can be determined according to these Guidelines. Further information is provided in Annex 4 as indicated on Page 8 line 17. The MDR itself does not provide a definition of an ED substance. The link is in the text that limits the use of CMR/ED substances. P9 line 16-17. SCHEER disagrees. However, the view of SCHEER is that

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			present in medical devices" extends the scope of these guidelines. Netherlesless, the title of the guideline does not mention other substances. Proposed change : Add : Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties "and other susbtances (CMR/ED)"	indeed the approach as outlined in these Guidelines can also be applied to other CMR/ED substances. Title and content of these Guidelines are restricted to Annex I point 10.4.3 as presented in the mandate (see Annex 1).

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67	Volle,Aurelio,French Blood Establishment,aurelio.volle@efs.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	* Page 14, line 35 Original text : This should separately include the vulnerable groups. Suggestion : This should separately include the vulnerable groups such as neonatology and pediatrics. Explanation : The risk of the exposition to phthalates depends on the recipients. With regard to recipients of blood products, different vulnerable groups can be defined such as transfusions intra-uterine, to neonates and very young children or frequently transfused recipients (e.g. patients with hemoglobinopathies). Specific risk reduction measures, to be included in the risk assessments, may be considered for these high-risk populations. * Page 15, lines 12-13 Original text: Consider multiple use scenarios (e.g. frequent use of a dialyzer, various types of possible contact) and different population groups. Suggestion: Consider multiple use scenarios (e.g. frequent use of a dialyzer, apheresis devices or various types of possible contact) and different population groups. Explanation: The exposition to phthalates is only described in relation to patients. However, the focus on patients does not give a relevant representation of all exposed recipients. Blood products for clinical care, e.g. plasma, platelets or stem cells, are collected from donors via aphaeresis. The systems used to perform the aphaeresis may contain	P14 line 35. SCHEER diasagrees. Vulnerable groups are specifically presented in Footnote 6 on page 14. So, the group is sufficiently identified. P15 line 12-13. SCHEER agrees and modified the text. Consider repeated use scenarios (e.g. dialysis, apheresis donation, chronic treatment) and different population groups.

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			phthalates. Since the principle of aphaeresis is that blood is returned to the donor, the donor might consequently be, exposed to phthalates contained within the device. It is therefore necessary to take them in consideration too.	

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68	Volle,Aurelio,French Blood Establishment,aurelio.volle@efs.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 22, lines 26-27 Original text : This should include consideration and discussion of possible high risk groups such as children or pregnant or breastfeeding women, and other patient groups considered particularly vulnerable to such substances and/or materials. Suggestion : none: EFS strongly supports this wording. Explanation : the risk of the exposition to phthalates depends on the recipients. With regard to recipients of blood products, different vulnerable groups can be defined such as transfusions intra-uterine, to neonates and very young children or frequently transfused recipients (e.g. patients with hemoglobinopathies). Specific risk reduction measures, to be included in the risk assessments, may be considered for these high-risk populations.	Thank you for this agreement.

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69	SIRDEY,Thierry,ANSM, thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 11 - lines 17-18 Comments : Hazard and biocompatibvility is quote on step 7, but it seems relevant to add hazard prior to step 7. Indeed Step 6 is dedicated to description of identified potential alternative(s) and hazard . Proposed change : Add in figure 1 : " 6 a . Description of the hazard, including CMR/ED hazards","6b". Functionality, performance (4), "6c". Benefit and use (7) Page 11 - lines 27-30 : Comments : If hazard and exposure are not available, it will be difficult to assess the risk for the altrenatives, so "where avalilable" and "if avaliable" leads to uncertainty. Delete for the point 7b : where available, Delete for the7c. :if available. Page 13 - Comments : In order to clarify titles "use scenario" and "non-use scenario" in the decision tree, the goals of the two scenari in th assessment may be clarified. Proposed change : Add a definition for "use scenario" and "non-use	P11 line 17-18. SCHEER disagrees. First an inventory is made on possible alternatives. For selected alternatives the functionality can be assessed. If this is insufficient such alternative can be discarded and exposure/hazard do not need to be further evaluated. This is now added as explanation on Page 17 line 23 in Step 5. Information/data on functionality (e.g. level of flexibility in tubes) as well as performance and/or chemical safety assessment (e.g. hazard profile) may be used for rejection of the less likely alternatives (see below) and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance. P11 line 27-30. SCHEER disagrees. All depends on availability. This is also indicated in other areas of the Guidelines Even when or if not available these items should be considered. P13*)* SCHEER agrees. Use and non-use replaced by CMR/ED phthalate scenario AND non CMR/ED phthalate scenario

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			scenario" Page 13- figure 1 : Comments : - step 1 refers to "Use scenario" and it is not easy to understand the methodology if text block "step 1" remains in the middle of the figure.-> move text block "step 1" on the left side. - step 8 -10 : for the final analysis, do we have to consider each step one after the other, or are they independent. Putting them at the same level could be more relevant if there isn't any sequence of steps?-> Putting step 8 - step 9 - step 10, at the same level, could be more relevant if there isn't any sequence of steps.	P13 Figure 1. SCHEER disagrees. Step 1 is really the starting point. Phthalates might be the first (best?) option. After considering this the Guidelines can be used to evaluate a possible relevant alternative. Figure 1 Step 8-9-10. These are subsequent steps. After each step a possibility for rejection of an alternative is possible e.g. step 8 lack of functionality, step 9 more toxic, step 10 reduced benefit.

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70	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 6, line 16: According to Annex I of the MDR, the presence of CMR 1A or 1B and/or ED phthalates above 0.1% w/w shall be justified with regard to "Devices, or those parts thereof or those materials used therein that: - are invasive and come into direct contact with the human body, - (re)administer medicines, body liquids or other substances, including gases, to/from the body, or - transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body" However, the current guidelines do refer to "medical devices" and it includes as such all medical devices and materials. Therefore, it is needed to resolve this inconsistency within the text and to make it clear to which categories of medical devices the guidelines will apply.	P6 line 16. SCHEER agrees. The following text is added. P6 line 20. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1. of the MDR. They do not provide information for the BRA of the use of a medical device itself.

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71	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 22, line 1: The guidelines do not take into account that international standards exist for blood bag sets (ISO 3826-1 on containers for the collection of human blood and blood components). These standards set a limit of 15mg/100mL of extractable DEHP in blood bag sets. This DEHP limit should therefore be considered as a justification for the continued use of DEHP in blood bag sets. Page 23, Line 2: It should be clarified that the table should only be completed for materials/parts/devices that contain CMR/ED phthalates above 0.1% w/w. In addition, those parts of the medical device that: - are not in direct contact with the human body, - do not (re)administer medicines, body liquids or other substances, including gases, to/from the body, - do not transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body should not be considered as they do not contribute to the patient exposure to the substance (e.g. needle protection device, tubing clamp). Some factors such as leachability in blood bag sets are determined on the overall set and not on the individual components. To determine the overall exposure of DEHP in a blood bag set, the leaching of DEHP should be considered at a set level rather than at a component level as the addition of exposure by each individual component does not equal the overall	P22 line 1. SCHEER disagrees. These Guidelines are not intended to specifically consider blood bags only. The MDR supersedes any ISO standard. The figure of 15 mg/100mL is now included in Annex 6 for information on page 51 line 22. A maximum limit of extractable DEHP of 15 mg/100 mL for flexible PVC containing DEHP is indicated in EN ISO 3826-1 on containers for the collection of human blood and blood components. P23 line 2. SCHEER agrees. This is also indicated by the word component the text: Text modified for clarification. See comment #40 This Table shall be completed for every component of the medical device that contains CMR/ED phthalate(s) above 0.1% w/w level. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated. For specific groups of devices it is now referred to the MDR in the Scope. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1.of the MDR.

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			exposure of a blood bag set. Page 23, Line 15-17: Lines 15 to 17 ("In contrast, a slight clinically insignificant loss in functionality might be acceptable if there is a large benefit to be gained in terms of reduced or even absence of toxicity") should be deleted. Current biocompatibility testing of medical devices is performed to show medical devices are safe and not toxic. The BRA is more than a comparison of clinical benefits and reduced risk of exposure to the CMR and ED phthalate. Page 24, Line 8-15: Those lines should be deleted. As stated in the text, it is not the main subject of these guidelines.	P23 line 15-17. SCHEER disagrees. This comparison of risks and benefit is specific for these Guidelines. The text is an example how a weighing might be performed. P24 line 8-15. SCHEER disagrees. The text indicates that there may be other issues that can affect the replacement of a phthalate when considering certain alternatives (e.g.availability). The text has been modified based on comment #40. Although not the main subject of these Guidelines, it should be realised availability might be a limitation for the introduction of an alternative substance/material. Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM), however, this may not be for other alternatives identified.

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72	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 24, Line 25-42: We would propose that no reference is made to potential alternatives in this section. If the purpose is to provide some examples of material benefits, reference could be made to examples such as the finetuning of tubing flexibility for certain applications, stabilizing effects of DEHP on RBCs, resistance to heat or chemical as part of sterilization processes, or need for permeability of gases. These properties are not necessarily specific to CMR/ED but could also be considered for the alternative materials as part of the BRA's.	P24 line 25-42. SCHEER disagrees. Text modified. See comment #8. A number of alternatives were evaluated as alternative for DEHP in blood bags (Simmchen et al., 2012, SCHENIR 2016,) For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen et al. 2012, Prowse *et al*. 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags (Prowse et al. 2014).
73	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 25, Line 27-33: We suggest adding to this list: "improved product quality"	P25 Line 27-33. SCHEER agrees. Text added.

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74	SIRDEY,Thierry,ANSM, thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 14 - lines 6-9 Comments : Reference to MOA approach for for the combinaison of phthalates is quoted but it is difficult to understand how to use and for which pourpose, this kind of approach. Add : MOA approach for the combinaison of phthalates has to be developed as we don't know exactly how to use this information for the justification. Page 14 - lines 1;10 : Comments : Footnote n°5 is not enough clear; We understand that "step 1" is the first step of "Use scenario". A new title, added at this level, could assist in the understanding, Add :an intermediate title : "Use scenario" on line 10 Page 15 - lines : 1;17;39 : Comments : In order to make the reading easier, for risk assessment Add: subtitle : Exposure (l1) - Hazard (l17) risk characterisation is already highlighted (l39) Page 16 : Lines 3 : In order to make the reading easier, add the context with the type of regulation because it refers to cosmetic regulation : 1223/2009. SCCS Note of Guidance for the testing of cosmetic ingredients and their safety evaluation – SCCS/1602/18 Page 16 Lines 14-16 : The note for substances without threshold (genotoxic carcinogens and PE) arise a problem for risk assessment without suggesting solutions for risk assessment. However, in line 41-43-page 18, in the chapter (=chapter4 : Assessment of possible alternative substances, materials, designs or medical) the use of a dose descriptor T25 is advised.. Add guidance for risk assessment of substances without threshold, or add the reference to dose descriptor (T25).	P14 line 6-9. SCHEER disagrees. Text refers to EFSA proposal for a group TDI. No activity regarding a MOA is proposed. P14 line 1-10. SCHEER disagrees. Footnote gives clear explanation on possible continued use of phthalate. P15 line 1-17-39. SCHEER agrees. Subheadings added. P15 line 17 added. Exposure estimation P15 line 37 added. Hazard identification P16 line 14-16. Explanation on risk assessment for threshold and non-threshold responses is included on Page 15 line 41-47. See comment #34.

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75	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 9, Line 24-25: Annex I of the MDR (Chapter II point 10.4) indicates that the justification shall be based upon “an analysis of possible alternative substances, materials or designs”. A reference to an analysis of alternative medical treatments has not been provided. To perform such an analysis as part of the implementation of the guidelines, a definition of “medical treatments” should be provided. In addition, during a medical treatment, multiple similar medical devices from different manufacturers might be used which makes it difficult to assess the overall phthalate exposure resulting from the treatment. Page 10, Line 16: The misuse of medical devices should not fall under the scope of the guidelines. To ensure this it is necessary to clarify that “A number of aspects need to be considered for the justification of the presence of a phthalate […] in a medical device as intended to be used". This clarification should be made throughout the document. Page 10, Line 34: While Page 11, line 25 refers to “patient or user exposure” and page 12, line 11 indicates that a similar approach is required for “professional users”, the rest of the document is mainly focused on patient exposure. So, it is unclear whether the guidelines focus on "patient" or "patient and user" exposure. It is extremely difficult to evaluate user exposure due to the fact that the practices and level of exposure may differ depending on hospitals and hospital departments, therefore the guidelines should only focus on patient exposure which would lead to assessing of both risk and benefit of the treatment.	P9 line 24-25 See comment#30. Medical treatments was seen as a possible alternative as indicated in the MDR (Annex I, 10.4.3). P10 line 16. SCHEER agrees. Intended use is indicated on P10 line 35, and in footnote 3. In several steps the intended use is emphasized. This should be sufficient information for the reader. .... in a medical device as intended to be used. P10 line 34. SCHEER disagrees. The document does focus on patients mainly, buy also gives a clear indication that also other persons that may be exposed (users, donors) should be considered. Text modified on P12 lin10. .....evaluate the risk for professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines.

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			Page 11, Line 13-15: On the identification of the candidates for assessment as potential alternatives (step 5), the following sentence should be added to the paragraph: "No further assessment will be required for the possible alternatives for which a justification for exclusion has been provided." Furthermore, the benefits of the current material/substance/design should be taken into account and in case the identified benefits are lower with the alternative substance, the said substance should be cast-off. In addition, we propose to include the following sentence in order to keep consistency with page 17, line 25-28: “The short list of the potential alternatives can be chosen for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, economic feasibility, availability and technical performance.” The previous comments should also be reflected in the flowchart (Figure 1 page 13)	When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. P11 line 13-15. SCHEER agrees. However, on page 11 a short listing of the steps is presented. Further explanation is presented on page 14 and onwards. Text regarding this is presented on Page 17 line 23 as further explanation of Step 5. Text modified. ....alternatives (see below) and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance.

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76	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 26, Line 19-20: The guidelines refer to elements of guidance and additional information available in other documents. It is not clear whether manufacturers are expected to look at these documents for additional guidance for the BRA of medical devices. The paragraph creates confusion on how to approach and implement the BRA methodology.	SCHEER disagrees. As the BRA itself can be performed by various methodologies the reader is referred to other more comprehensive documents for information. The Guidelines provide a framework for evaluating CMR/ED phthalates and/or possible alternatives. A full review of BRA methodologies is outside the scope of these Guidelines.
77	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 27, Line 11: The guidelines mention a significant number of sources of uncertainty without specifying which of these sources of uncertainty should be considered as part of the BRA. Specific guidance would be welcome as authorities and reviewers would not necessarily have the relevant expertise on all the suggested methodologies/sources of uncertainty. The uncertainty analysis would also be very challenging for some substances like DEHP for which there is no common methodology to assess how much of the substance would leach from a medical device. Having to perform an uncertainty analysis would undermine the value of the BRA analysis.	SCHEER agrees but as for the BRA methodologies an extensive review of the uncertainty analysis is outside the scope of these Guidelines. The Guidelines refer to documents more specifically dealing with uncertainties (e.g. EFSA Guidance EFSA 2018a and 2018b). For determination of leachables the Guidelines refer to ISO 10993-12 and ISO 10993-18. Text is added on page 15 line 7.

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78	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 30, Line 19-20: The sentence "Therefore, manufacturers are encouraged to produce quantitative data on the use of alternatives for CMR/ED phthalates in medical devices" should be deleted as recommendations for the production of data are not in the scope of the Committee's mandate.	P30 line 19-20. SCHEER disagrees. Also in the DEHP Opinion of SCENIHR Update of 2015 published in 2016, it was observed that many alternatives were proposed in the literature, but there was for most of these alternatives for DEHP a serious lack of information on the risk characterization. Therefore, SCHEER emphasizes that it should be encouraged that data are produced for any alternative proposed as replacement of DEHP.
			Page 30, Line 22: Annex I, Chapter II, point 10.4.3 of the Medical Devices Regulation specifies that these guidelines should be reviewed at least every 5 years or when deemed appropriate on the basis of the latest scientific evidence. The guidelines suggest an update after three years, although no argumentation is provided as to what scientific evidence justifies this timeframe. To ensure consistency and alignment with the Medical Devices Regulation, it is recommended to update the guidelines every 5 years. As an additional note, guidance would be welcome on how frequently manufacturers should review the BRAs for their medical devices. We suggest reviewing the BRAs when re-certification occurs or when new guidelines are released.	P30 line 22. SCHEER disagrees. The text does not ask for a revision of the Guidelines. It asks for an evaluation of the use of these Guidelines to consider whether revision might be needed. P30 line 22. "Pending on new scientific evidence, it is recommended to evaluate the use and usefulness of these Guidelines after an experience period of three years." This text is asking for an evaluation of the use of the Guidelines themselves. The BRA for the use of CMR/ED phthalates would also depend on the scientific developments regarding alternatives. As the General Requirements (Annex I, Chapter I, MDR) aim to ensure the continued acceptability of the ~~benefit-~~risk

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				weighed against the benefits to the patient ~~ratio~~, the benefit-risk determination requires regular updates as included in the post-market surveillance system and the periodic safety update report (PSUR) (Art. 83, ~~Art. 84, Art. 85~~to Art. 86, MDR). Added in the conclusions As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, an update of the BRA of the medical device may be needed. The BRA of the CMR/ED phthalate should be updated or when new scientific information becomes available on alternatives for the use of the phthalate, when new Guidelines are released or. as the "overall" benefit-risk determination of the medical device is updated,. (See also comment # 96 and 185)

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79	Romanus,Bart,Terumo BCT Europe N.V.,bart.romanus@terumobct.com,Belgium	3. Assessment of the presence of phthalates in a medical device	Page 51, line 23-28: The assessment of possible alternatives includes an inventory of possible alternatives (step 4) and the identification of the candidates for assessment (step 5). As such, the guidelines should not include a list of specific alternative substances.	SCHEER disagrees. This information is provided as proposals currently under development. It does not endorse the use of these alternatives.

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80	SIRDEY,Thierry,ANSM, thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 16 - lines 31-35 : Alternatives as biodegradable polymers are quoted but without any information on their safety. According to the purpose of this guidelines, information could be given on the safety of these alternatives.The hazard of alternatives has to be highlighted in the whole document. Add information request on the safety of alternatives substances in order to give more extensive and detailed information. Page 16 - line 36 : Footnote n°7 is not enough clear. We understand that "step 4" is the first step of "Non use scenario". A new title, added at this level, could assist in the understanding, Add an intermediate title : "Non use scenario" on line 36 Page 17 - lines 7-8 : The concept of safer alternatives could be more emphassized in step 5. The OECD Substitution and alternatives assessment toolbox website explains their concept as "A process for identifying, comparing and selecting safer alternatives to replace hazardous chemicals with the objective of promoting sustainable production and consumption."Add safer alternatives in the text (step 5) Page 18-lines 26-44 : In order to make the reading easier, for risk assessment Add subtitle : Exposure (l26) - Hazard (l32) risk characterisation is already highlighted (l14-p19) Page 19- line 9 : In the paragraph dedicated to the hazard of alternative substances, we can read "other potential toxic effects associated with phthalates". Mentioning phthalates here could be confusing and limitating for the kind of alternative substances.Delete : "associated with phthalates" Page 19 lines 25-26 : There is a reference made to SCCS/1602/18 note of guidance for cosmetic, We are wondering which added added value is provided by this chaper relates to cosmetics in this chapter.Delete : comparison with a reference MoS (see SCCS Notes of Guidance – SCCS/1602/18).	P16 line 31-35. SCHEER agrees. This paragraph is deleted. See comment#37. P16 line 36. SCHEER disagrees. The title of section 4 is sufficiently clear. Section 4. Assessment of possible alternative substances, materials, designs or medical treatments. P17 line 7-8. The Guidelines are specific for the justification of the use of CMR/ED phthalates. The potential replacement of substances or materials by safer alternatives is included in the general requirements of the MDR already. P18 line 26-44. SCHEER Agrees. P18 line 26 added. Exposure estimation P18 line 32 added. Hazard identification P19 line 9. SCHEER disagrees. The text refers to the EFSA document. P19 line 25-26 SCHEER disagrees. The SCCS Guidance gives information on the use of the MoS principle in the risk assessment.

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81	SIRDEY,Thierry,ANSM, thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 22. Lines 18-19: A reference is made to the Memorandum on weight of evidence and uncertainties of SCHEER (SCHEER 2018). Without any example it could be difficult to apply the classification.Add : an annex with examples could be usefull Page 22 - line 35: Comments 1 : As requested in "step 1" on page 14, it should be mandatory to use available chemical information for identifying target phthalates (e.g. CAS Nº; EINECS Nº; IUPAC name). Indeed, acronyms could be confusing between phthalates. Add chemical information for identifyingsubstances in table 1 Comments 2: Identification of dose levels associated with minimal or negligible risk are DNEL, DMEL, TDI. According to ISO 10993-17 (« Establishment of allowable limits for leachable substances standards for risk characterisation »), the vocabulary used for this point is : Tolerable exposure" TE expressed in mg/d. TE = Tolerable intake (TI) x mB (body mass) x utilisation factor (UTF) where TI = NOAEL, LOEL , etc / Modifying Factor (MF) it could be usefull to add expression used in medical device sector. As ISO 10993-17 is an ISO standard for medical device, it should be mentionned as a reference. Add vocabulary issued from ISO standards and used for medical devices and refernce to ISO standards. Moreover, reference to ISO 10993, as a gold standard for medical device should be appropriately mentioned in the whole document Page 23 - Lines 6-7 : The rules for final decision making could be highlighted in order to help the reader. For example, "When the outcome of the comparison shows that the	P22 line 18-19. SCHEER agrees. However, the reference is intended for information. It would go beyond the Guidelines to provide an extensive example of all methodologies referred to in the Guidelines. P22 line 35 SCHEER agrees. Text added to Table 1. Identification of substances/material etc. Name and CAS number Chemical information Comments 2. SCHEER agrees TE added to Table 1, list of abbreviations, and Step 3 Page 15 line 47. EN ISO 10993-17:2002 calculates a Tolerable Exposure (TE), which is based on a product of the tolerable intake, the body mass and the utilization factor. Footnote added. EN ISO 10993-17:2002 is currently under revision. It is discussed to replace in the updated version TE by TI. P23 line 6-7. SCHEER disagrees. It would not be possible to design a decision tree that would cover every possibility. This is up to the manufacturer

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			alternative fulfils the comparable or better intended functionality as well as performance and shows a reduced risk, the use of a CMR/ED phthalate is not possible" gives only one case amongst the others. Add: For the final decision making, a decision tree could help the reader as many situations could apply. Page 23 : lines 6-19 The paragraph deals more than B/R than justification of use and therefore should be trasnfered in section 8.Add this paragraph in section 8	to decide on the final conclusion. If an alternative would be an improvement over the CMR/ED phthalate the Guidelines would not be used anymore by the manufacturer. It would be sufficient to perform the RA for the use of the alternative chosen and include this in the dossier. In the weight of evidence the final decision is made for the use or non use of the CMR/ED phthalate as indicated in Figure 1. The approach is described in the flow chart. P23 line 6-19. SCHEER disagrees. Section 8 describes how to perform a BRA whereas in section 6 the justification is addressed for use of the CMR/ED phthalate.

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82	SIRDEY,Thierry,ANSM - French National Agency for the Safety of Medicines and Health Products,thierry.sirdey@ansm.sante.fr,France	3. Assessment of the presence of phthalates in a medical device	Page 24 - lines 30-42 : Two paragraphs are dedicated to DEHP. As the guidelines could be used for other substances, general information must be given out or the scope of the guideline should be restricted to phthalates.	SCHEER disagrees. The scope specifically mentions phthalates. Page 6 lines 14-19. The text indicated that a similar approach can also be applied to other substances.
83	SIRDEY,Thierry , French National Agency for the Safety of Medicines and Health Products (ANSM),thierry.sirdey@ansm.sante.fr,France	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 29 - lines 8-19 : Many references are made in the domain of uncertainty (EFSA,SHEER, ECHA) and it is difficult to understand which methodology for uncertainty is recommended for medical devices. Moreover a reference to ISO 14971 is made but it is not easy to understand which methodology is recommended In the guidelines for medical devices. Table 2 (Efsa+scheer) adds also confusion, especially as it is quoted as a reference in the table 1 (confidence estimation, see table 2).Add a final conclusion that indicates how to use these differents approaches for uncertainty. Examples in annex could be useful.	SCHEER agrees. However, as indicated in comment #81 It would go beyond the Guidelines to provide an extensive example of all methodologies referred to in the Guidelines. The conclusion is presented on Page 29 lines 14-19 indicating that extensive scaling like EFSA and SCHEER may not be appropriate for medical devices. Therefore Table 2 was included to be used.

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84	MedPharmPlast Europe,mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 14, Line 7-9: The specifics of medical devices should always be considered in the development on the guidelines. The legal framework used in the food sector should not be used as a reference for Medical Devices as specific migration limits (SML) may differ for medical devices. This comment also applies to Annex 5.	SCHEER disagrees. P14 line 7-9 presents a group TDI for some phthalates. This TDI is based on toxicological evaluation that may also be relevant for hazard dose levels that may be used in the RA of medical devices. Annex 5 provides information on the various regulations dealing with CMR/ED phthalates. See also comments #33, #61, #74.
			Page 15, Line 13-14: Annex 6 points out the use of phthalates in different subgroups, not to the combined exposure. Manufacturers of medical devices will only be able to consider the exposure related to their own medical device(s), from a manufacturing standpoint, and not the combined exposure to substances in multiple medical devices used as part of a medical treatment. Assessing the overall phthalate exposure would further require access to data on the use of phthalates in other medical devices that could be used as part of the same medical treatment. It should be taken into account that a specific medical treatment might also be varied from one country to another.	P15 line 13-14. SCHEER agrees. Text modified based on comment #21 and #50 and #61. Reference to Annex 6 modified. The combined exposure to different CMR/ED phthalates also needs to be considered when present in a medical device. See also comment 21 which specifically asks for exposure assessment based on multiple medical devices used. More details on the use of phthalates in medical devices are presented in Annex 6.
			Page 14, Line 24-26: The reference to ISO 10993-1 would rather fit in step 3 on the assessment of the risks of the CMR/ED phthalate.	P14 line 24-26. SCHEER agrees. Reference is moved to Step 3.

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85	SIRDEY,Thierry , French National Agency for the Safety of Medicines and Health Products (ANSM),thierry.sirdey@ansm.sante.fr,France	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 47 lines 18-19: It is mentioned that Efsa established specific migration limit (SML) for food, but there isn't any recommendation to help the reader to used such data for medical device risk assessment. Proposed change: Add recommendation on how to use such specific migration limit (SML) for phthalates.	SCHEER disagrees. The information is provided for convenience of the users of the Guidelines regarding regulations on phthalates. However, these are limits below which a risk is unlikely or negligible. These data may be used for comparison of leakage of the used phthalates form medical devices.
86	SIRDEY,Thierry , French National Agency for the Safety of Medicines and Health Products (ANSM),thierry.sirdey@ansm.sante.fr,France	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 51 - line 7: Preadolescent group ranges from 2-12 years and adolescent group from 12-18 years. Preadolescent Sub-population group has to be adjusted as it ranges from 11-13 years and it is outside the adolescent range. Proposed change : Change the age range for group or subgroup. Page 51 - lines 23-27 : "Di-isononyl cyclohexanoate (DINCH, CAS 1166412-78-8), Tri-2-ethylhexyl trimellitate (TEHTM, CAS 3319-31-1) and Dioctyl Terephthalate (DOTP, CAS 6422-86-2) are being proposed". Alternatives from industry are quoted but without any information on their safety. According to the purpose of these guidelines, information could be given on the safety of these alternatives. Proposed change Add information on the safety of alternatives substances for more extensive and detailed information.	P51 line 7. SCHEER disagrees. There are several ranges indicated in different documents. SCHEER choose to use the range indicated in the most recent SCCS Guidance (Guidance SCCS Notes of 37 Guidance – SCCS/1602/18). P51 line 23-27. SCHEER disagrees. This information is given for convenience of the reader. It is clearly stated that these are proposed by industry. It is to the industry to provide data on safety. As indicated in the SCENIHR DEHP update 2015 Opinion (SCENIHR 2016) for many proposed alternatives the safety information is poor. It is not the task of SCHEER to provide safety information on some alternatives proposed by industry. SCHEER does not endorse the use of these alternatives, they are provided as information only.

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87	Lange,Rosa,German Environment Agency on behalf of HBM4EU,Rosa.Lange @uba.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	page 9, line 2-4 Comment: It has to be noted, that the Danish EPA assessed different alternatives and concluded that most alternatives showed a better toxicological profile, espeically regarding the endpoint of reproductive and developmental toxicitiy than DEHP. In addition, some alternatives showed a low migration rates and some of them are already used as substitues in medical devises for traditional DEHP-applications. https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-27-4.pdf	P9 line 2-4. SCHEER agrees. Reference is added on Page 9 line 4. Text added. The Danish EPA assessed different alternatives and concluded that some substances are to various degrees considered to be relevant alternatives to DEHP in terms of human health hazards, especially regarding the endpoint of reproductive and developmental toxicity (Nielsen et al. 2014). However, for a number of possible alternatives the data set was limited. Some alternatives showed a low migration rate and some of them are already used as substitutes in medical devices for traditional DEHP-applications.

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88	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 16, Line 31-35: The guidelines should not include a list of specific alternative substances. Lines 34-35 should therefore be deleted as the list of alternatives could be interpreted as providing directions to manufacturers for assessing potential alternatives. Page 17, Line 25: Considering that in certain cases alternatives may not be available, we propose adapting the wording throughout the text to refer to the "potential alternative, when available"	P16 line 31-35. SCHEER agrees. P16 line 31-35 are deleted. See also comments #37, #62, and #80. P17 line 25. SCHEER agrees. But it does not seem right to mention every time when available. Availability is separately addressed on page 17 line 13 and 23.. In addition to the comparison in terms of functionality, technical performance and risks to patients and users, which are critical elements for the benefit-risk assessment, Annex I Section 10.4.2 of the MDR states that the justification for the presence of CMR/ED substances should also be based on an analysis of the availability of possible alternatives. Availability has several aspects, including for example the availability of necessary quantity (volumes) of the alternative on the market within a required timeframe and the ability to gain access to alternatives that may be proprietary (e.g., via licensing). Page 17 line 25. If potential alternatives can be identified, a short list of the potential alternatives can be established and Page 24 line 9. Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM), however, this may

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			Page 18, Line 20: In line with the previous comment, we suggest the following wording: "If an appropriate alternative was identified under Steps 1-6, a risk assessment..." Page 19: The guidelines are intended to provide a framework for the BRA of the presence of phthalates in medical devices. The consideration of any other hazards would be considered as part of the EN ISO 14971 risk management activities and would therefore not fall within the scope of the guidelines unless further guidance is provided on these hazards other than those of the CMR/ED activity.	not be for other alternatives identified. Page 19. SCHEER agrees. Step 7 mentions the RA of possible alternatives. For the general RA referral is made to EN ISO 14971 and the EN ISO 10993 series on page 19 line 12. These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series.

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89	Lange,Rosa,German Environment Agency on behalf of HBM4EU,Rosa.Lange @uba.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 49, line 12/13 Comment: Naming of values derived under HBM4EU was changed into Human Biomonitoring Guidance Values (HBM-GVs)	SCHEER agrees. Text modified. In the course of the work done within the HBM4EU project, Human Biomonitoring Guidance Values (HBM-GVs)) could be derived for DEHP (see HBM4EU Deliverable D5.2, see https://www.hbm4eu.eu/).

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90	MedPharmPlast Europe,mohammad.hayatifar@medpharmplasteurope.org,	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 23, Line 2: It should be clarified that the table should only be completed for materials/parts/devices that contain CMR/ED phthalates above 0.1% w/w. In addition, those parts of the medical device that: - are not in direct contact with the human body, - do not (re)administer medicines, body liquids or other substances, including gases, to/from the body, - do not transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body should not be considered as they do not contribute to the patient exposure to the substance (e.g. needle protection device, tubing clamp). Page 23, Line 15-17: Lines 15 to 17 ("In contrast, a slight clinically insignificant loss in functionality might be acceptable if there is a large benefit to be gained in terms of reduced or even absence of toxicity") should be deleted. Current biocompatibility testing of medical devices is performed to show medical devices are safe and not toxic. The BRA is more than a comparison of clinical benefits and reduced risk of exposure to the CMR and ED phthalate.	P23 line 2. SCHEER agrees Text amended. This Table shall be completed for every component of the medical device that contains CMR/ED phthalate(s) above the 0.1% w/w level. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated. Also comment #71. The medical devices covered by the Guidelines are mentioned specifically at page 6 line 20. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1. They do not provide information for the BRA of the use of a medical device itself. See also comment #27, #58, #59. P23 line 15-17. SCHEER disagrees. This comparison of risks and benefit is specific for these Guidelines. The text is an example how a weighing might be performed. In addition, biocompatibility testing is for hazard identification, and can never establish that a device is safe. Also for medical devices a benefit risk

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				assessment has to be done.
			Page 24, Line 8-15: As stated in the text, those lines are not the main subject of these guidelines and should be deleted.	P24 line 8-15 SCHEER disagrees. See also comment #7, #8, #71, #88. Text added. Page 24 line 9. Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH and TOTM), however, this may not be for other alternatives identified.

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91	Lange,Rosa,German Environment Agency on behalf of HBM4EU,Rosa.Lange @uba.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	page 49, line 13-14 Comment: HBM-GVs for DEHP (and DINCH) were already derived (Deliverable D5.2) and are published on the website: https://www.hbm4eu.eu/deliverables/ In addition, HBM-GVs for the following SVHC phthaltes are finalised in September 2019 /Deliverable D5.6) and will also be published on the website: DiBP, BBzP and DnBP.	P49 line 13-14. SCHEER agrees and refers to the project website. Text added. ...could be derived for DEHP and DINCH In addition, HBM-GVs for the following SVHC phthalates are finalised in September 2019 (Deliverable D5.6) and will also be published on the website: DiBP, BBzP and DnBP.

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92	Lange,Rosa,German Environment Agency on behalf of HBM4EU,Rosa.Lange @uba.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	General comment from HBM4EU: As representative of HBM4EU we fully support the presented guidelines on the benefit-risk analysis of phthalates with CMR properties in medical devices. These guidelines strengthen the need for assessing the benefit of these phthalates in medical devices by weighing the evidence of using alternatives against the benefit of using CMR phthalates. Because of the high concern among the HBM4EU partners as well as the EU and national policy makers, phthalates were selected as one of the first prioritised substance groups in HBM4EU and decided to investigate the aggregate exposure of people in Europe from all sources and describe the background exposure levels. As of 2019, human samples will be collected in different European countries in which the exposure to phthalates and the other priority substances will be measured. Human biomonitoring data from the European DEMOCOPHES study that included 17 countries showed already widespread exposure to phthalates in European citizens in 2011 when samples were taken (Den Hond et al. 2015). Recent human biomonitoring data from single European countries, e.g. collected within the 'German Environment Survey' (GerES V 2014-2017, paper in preparation) indicate that despite existing regulations, populations are still exposed to these phthalates and that some of the classified phthalates can even be found in every sample investigated. In addition, several studies showed an age-difference in exposure with children having in general higher exposure levels. As DEHP is used in the majority of medical devices, children, neonates and pre-term babies undergoing repeated medical treatment, especially in intensive care units are at risk for higher exposure levels of DEHP (and other CMR phthalates). Unborn children, too can be exposed to high levels of CMR phthalates if pregnant women undergo intensive medical treatment. As the critical effects of those phthalates are on the development, especially on male reproductive development, higher exposure through medical treatment can result in higher risks for developing adverse health effects. For that reason special attention should be paid on the use of alternatives in medical devices and even go further and ban the use of CMR phthalates in medical devices as already done in consumer products. In If benefit-risk analysis comes to the conclusion that CMR phthalates must be used, but also if new alternatives are used, biomonitoring, especially of the high risk subpopulation should be warranted.	SCHEER thanks HBM4EU for their support. The issue of biomonitoring of both the general population and after patient exposure is indicated on Page 15 line 15. In addition, data from biomonitoring programs may become available that could also provide information on exposure levels of phthalates in the general population and more specifically during medical treatment.

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93	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 24, Line 25-42: If the aim is to provide some examples of material benefits, reference could be made to examples such as the stabilizing effects of DEHP on RBCs, resistance to heat or chemical as part of sterilization processed, fine tuning of tubing flexibility for certain applications, need for permeability of gases. These properties are not necessarily specific to CMR/ED but could also be considered for the alternative materials as part of the BRA's.	SCHEER agrees. These examples are already included in the text on page 24 lines 29-33 with as example blood bags.
94	MedPharmPlast Europe,mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	For the BRA of medical devices, the guidelines refer to additional information available in other documents. It is not clear whether manufacturers are expected to look at these documents as well for additional guidance. More clarification would be welcome on how to approach and implement the BRA methodology.	SCHEER disagrees. As the BRA itself can be performed by various methodologies, the reader is referred to other more comprehensive documents for information. The Guidelines provide a framework for evaluating CMR/ED phthalates and/or possible alternatives. A full review of BRA methodologies is outside the scope of these Guidelines. See comment #76.

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95	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 27, Line 11: A significant number of uncertainty sources have been mentioned in the guidelines without specifying which of these sources of uncertainty should be considered as part of the BRA. As all authorities and reviewers would not necessarily have the relevant expertise on all of the suggested methodologies/sources of uncertainty, specific guidance would be needed. For some substances like DEHP the uncertainty analysis would also be challenging as there is no common methodology to evaluate how much of the substance would leach from a medical device.	The Guidelines provide a methodology for the justification of the use of CMR/ED phthalates. For specific additional aspects like BRA itself and uncertainty analysis the Guidelines refer to specific literature/documents dedicated to these subjects. It is outside the scope of these Guidelines to include all these aspects.

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96	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 30, Line 19-20: The recommendations for the data generation are not in the scope of the Committee's mandate. As such, the sentence "Therefore, manufacturers are encouraged to produce quantitative data on the use of alternatives for CMR/ED phthalates in medical devices" should be deleted. Page 30, Line 22: The guidelines propose an update after 3 years, although no argumentation is provided as to what scientific evidence justifies this time frame. On the other hand, Annex I of the MDR specifies that these guidelines should be reviewed at least every 5 years or when deemed appropriate on the basis of the latest scientific evidence. We suggest to update the guidelines every 5 years in order to ensure the consistency. The guidance should also provide information on how frequently manufacturers should review the BRAs for their medical devices. It is suggested reviewing the BRAs when re-certification occurs or when new guidelines are published.	P30 line 19-20. SCHEER disagrees. Also in the DEHP Opinion of SCENIHR Update of 2015 published in 2016, it was observed that many alternatives were proposed in the literature, but there was for most of these alternatives for DEHP a serious lack of information on the risk characterization. Therefore, SCHEER emphasizes that it should be encouraged that data are produced for any alternative proposed as replacement of DEHP. See comment #78. Page 30, Line 22. "Pending on new scientific evidence, it is recommended to evaluate the use and 21 usefulness of these Guidelines after an experience period of three years." This text is asking for an evaluation of the use of the Guidelines themselves. The BRA for the use of CMR/ED phthalates would also depend on the scientific developments regarding alternatives. As the General Requirements (Annex I, Chapter I, MDR) aim to ensure the continued acceptability of the ~~benefit-~~risk weighed against the benefits to the patient ~~ratio~~, the benefit-risk

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				determination requires regular updates as included in the post-market surveillance system and the periodic safety update report (PSUR) (Art. 83 to Art. 86, MDR). Added in the conclusions: As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, an update of the BRA of the medical device may be needed. The BRA of the CMR/ED phthalate should be updated or when new scientific information becomes available on alternatives for the use of the phthalate, when new Guidelines are released or as the "overall" benefit-risk determination of the medical device is updated. See also comment #78 and 185

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97	MedPharmPlast Europe (MPPE),mohammad.hayatifar@medpharmplasteurope.org,Belgium	4. Assessment of possible alternative substances, materials, designs or medical treatments	Page 51, line 23-28: The guidelines should not include a list of specific alternative substances as the assessment of possible alternatives consists of an inventory of possible alternatives (step 4) and the identification of the candidates for assessment (step 5).	SCHEER disagrees. The text indicates “are being proposed” so there is no suggestion that these alternatives are indeed full replacements of DEHP. There is quite some literature on proposed alternatives for DEHP. This cannot be neglected in these Guidelines.

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98	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	In the Scope we read from page 6 line 14: “These Guidelines describe the methodology on how to perform a benefit-risk assessment (BRA) for the justification of the presence of CMR 1A or 1B and/or ED phthalates (CMR/ED phthalates) in medical devices at percentages above 0.1% by weight (w/w)… (page 6 line 20) These Guidelines do not provide information for the BRA of the use of a medical device 20 itself.” It is not clear, how the BRA for the justification of the presence of phthalates can be separated from for the BRA of the use of a medical device itself, especially with respect to MDR Annex I, No. 10.4.3, sentence 3, reading: “The benefit-risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments.” Section MDR Annex I, No. 10.4.3, sentence 2 reads: “The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of phthalates which belong to either of the groups of substances referred to in points (a) and (b) of Section 10.4.1”. We would understand this mandate to result in a BRA on substances in specific medical devices rather than in a guideline on how to assess these substances.	A BRA of the use of any medical device is necessary for any medical device and is described in other documents. These Guidelines are limited to CMR/ED phthalates as listed or designated by regulation. The Guidelines provide a methodology to justify the use of a CMR/ED phthalate in a medical device. SCENIHR already performed an evaluation of possible alternatives for DEHP (SCENIHR 2016). SCHEER sees the BRA performed according to these Guidelines as an addition to the dossier already prepared for the whole device. It is not the task of SCHEER to perform a BRA for manufacturers of medical devices.

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99	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	In section 1 Introduction we read on page 7 from line 30, that how to perform a BRA is provided by the standards EN ISO 14971 and EN ISO 10993 1. Nevertheless, we miss a clear structure on how this Guideline shall serve to fulfill the manufacturer's tasks according to these existing standards. Moreover, we miss a reference to EN ISO 10993-17 "Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances". We would expect a specification on tolerable levels (e.g. TDI) to comply with EN ISO 10993-17, and that a TDI must not be understood as a limit value, which a manufacturer can claim in total for his product, but must be understood as a limit value, taking in to account all other expected possible phthalate sources.	SCHEER disagrees. The answer to comment #98 explains why SCHEER did not do a BRA for the use of phthalates. Regarding the EN ISO 10993 series. Several; standards including EN ISO 1099.-17 are now more clearly included in the Guidelines.

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100	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	In the section 2 “Framework for Benefit-Risk Assessment” we read on page 10 from line 22: “Step 1: Description and characterisation of the composition of the medical device. Identification of the presence and concentration of CMR/ED phthalate.” Here, a reference to EN ISO 10993-18 “Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process” is missing.	SCHEER agrees Reference to EN ISO 10993-18 is now included in Step 1 on page 14 line 14. It is also included in Step 3 under exposure determination. Chemical composition and chemistry evaluation can be found in EN ISO 10993-18. It is currently under revision. FDIS is just published. Text added. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019).
101	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	Section 7.2 from page 25, line 8 ff., explains how to assess a clinical benefit of a medical device, whereas section 7 from page 24, line 17 ff., reads: “These Guidelines do not provide information for the benefit-risk assessment of the use of a medical device itself but are limited to the evaluation of potential alternatives to the use of CMR 1A or 1B and/or ED phthalates in a medical device.” Both sections (7 and 7.2) seem contradictory. It should be made clear that the presence or absence of a substance itself cannot have a clinical benefit, but that a clinical benefit can only be assessed for a complete medical device. Please refer also to section 1 of this commentary (see above).	SCHEER disagrees. The benefit of the complete medical device is not addressed in the Guidelines. Mainly the benefit in terms of functionality (and risk) of the phthalates is compared to possible alternatives. The use of a phthalate contributes to the overall benefit of the medical device. However, in view of the comparison with possible alternatives the BRA to be performed is limited. It would not be feasible to manufacture for every possible alternative a prototype for clinical testing.

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102	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	Section 9 Uncertainty analysis, Table 2 on page 29 from line 21: gives an example on how to describe the terms according to Table D4 of the EN ISO 14971 in a semiquantitative way. The necessity of this table is not apparent. The need for re-defining e.g. “occasional” in “as likely as not” is not evident; moreover, the specification of this term with “33-66%” creates puzzlement rather than clarity.	SCHEER disagrees. The use of the EN ISO 14971 probability scale associates better to practices for medical device evaluation, in contrast to the EFSA and SCHEER probability scales. Occasional was translated into “as likely or not” to indicate that it is not really known what the outcome would be.
103	Munzert,Eberhard,BfArM,eberhard.munzert@bfarm.de,Germany	4. Assessment of possible alternative substances, materials, designs or medical treatments	BfArM misses an example assessment. We recommend to identify specific kinds of medical devices with a well known therapeutic history, for example • Tubings for dialysis therapy • Tubings for blood donation apheresis • Blood bags • … This list could be extended upon rising level of knowledge.	Performing a BRA on any medical device as example is outside the scope (and mandate) of the Guidelines.

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104	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	4. Assessment of possible alternative substances, materials, designs or medical treatments	<<Abstract>> Page 2, Line 19 The ED substances noted in the regulation are ED phthalates substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health covered under MDR Annex I Chapter II point 10.4.1. Please precise.	SCHEER disagrees. It is not needed to emphasize this aspect specifically for ED substances in the Abstract. The regulations on CMR and ED substances are specifically addressed in Annex 4 of the Guidelines. An explanation on the identification of either CMR and designation of the ED substances is beyond the Abstract.
105	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 30-31 The ED substances noted in the regulation are ED phthalates substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health covered under MDR Annex I Chapter II point 10.4.1. Please precise.	SCHEER disagrees. It is not needed to emphasize this aspect specifically for ED substances in teh Abstract. The regulations on CMR and ED substances are specifically addressed in Annex 4 of the Guidelines. An explanation on the identification of either CMR and designation of the ED substances is beyond the Abstract.
106	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 31-32 Please precise what is "parts" and “material” and so what the 0.1% refers to?	This text conform the text of the MDR Annex I, 10.4.1 that describes : “Devices, or parts thereof or those materials used therein that:.....shall only contain the following substances in a concentration that is above 0.1% weight by weight (w/w) where justified pursuant to Section 10.4.2:” As a medical device can be composed of various parts either with or without CMR/ED phthalates, the w/w % should be calculated in those cases in which only some parts contain the CMR/ED

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				phthalate, for the individual parts and not for the whole device.
107	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 33 Please clarify if the word "consider" means that they are guidelines for the evaluation of possible alternative and not only Guidelines on the benefit-risk assessment of the presence of CMR/ED phthalates in certain medical devices	The word consider indicates indeed that the Guidelines are intended for the evaluation of possible alternatives whether they could be alternatives for the use of CMR/ED phthalates in a medical device. Primarily the Guidelines are a methodology to evaluate if the use of a CMR/ED phthalate is justified. Text modified for clarification. “Consider” changed into “describe”
108	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 41 Can we use methods other than those mentioned in the guidelines	The MDR indicates that a justification shall be provided for the use of a CMR/ED phthalate. The Guidelines are a tool how this can be done. Annex I, Section 10.4.2 provides a rule what shall be done, not how this shall be done.

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109	Frizi,Naïma,,Naima.FRIZI@macopharma.com, France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 43-44 There is nothing in the mandate to make such a recommendation, please remove it.	SCHEER disagrees. In view of the limited experience with the various tools for the BRA with medical devices, it is urgently needed that this knowledge becomes available.
110	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	5. Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates	Page 2, Line 46 What if there is no new scientific evidence? Does it mean that the justification is still valid? Precise.	Page 2 line 46 asks to share the experience with these Guidelines in order to evaluate its usefulness. This is not a proposal for revision. The experience obtained can be used in a future update when such update is needed.

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111	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 2, Line 47 The MDR stipulates that: "When deemed appropriate on the basis of the latest scientific evidence, but at least every five years, the guidelines shall be updated." and the mandate stipulates that "to give consideration to what extent of new evidence would be deemed appropriate to justify an update of these guidelines before the maximum period of five years." There is no given justification in the guidelines to change the length of time for the update. Please note five years as it is written in the MDR.	Page 2 line 46/47 asks to share the experience with these Guidelines in order to evaluate its usefulness. This is not a proposal for revision. The experience obtained can be used in a future update when such update is needed.
112	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 2, Line 46-47 Are these guidelines mandatory to use for three years or are they optional?	The Guidelines offer a tool to justify the use of a CMR/ED phthalate in a medical device. Their use is not obligatory as long as the requirements of MDR Annex I, 10.4.2 are met (i.e. a proper justification for the use of a CMR/ED phthalate).

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113	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 6, Line 6-12 In the regulation Annex I Chapter II point 10.4.1 it is written : "Devices, or those parts thereof or those materials used therein that: — are invasive and come into direct contact with the human body, — (re)administer medicines, body liquids or other substances, including gases, to/from the body, or — transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body, ": The guidelines seem to be more general than MDR for the scope of devices or parts of device which could be subject to a need of justification. Could you be more precise and not include parts of devices and devices that are not part of definitions listed above? Moreover, in the scope of parts of devices or devices concerned by the need of a justification, is it needed to justify the presence of CMR/ED phthalate in the device or part of device if the re(adminstration) of the substance is not direct from the device to the body but will be introduced in another device and then diluted with others liquid products which will be introduced in the body. Regarding the concentration of CMR/ED phthalate, this one is referred to the “device", is it different from Annex I "Devices or those parts thereof or those materials used therein "? Could you precise if it is the concentration of the global device and if not, a precision to what is a part of device is needed: for example is a plug (short tube) welded to a bag considered as a part of a device? Or is the bag with its welded plug considered as the part of the device?	SCHEER agrees. Text amended. .....in devices, or parts thereof or those materials used therein, above 0.1%... Page 6 line 20 text is added referring to the MDR for which medical devices the Guidelines are applicable. These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1.of the MDR. This text indicates that also indirect contact by transport devices needs to be considered. Text added to be in line with the MDR. So, it is both the device and can also be a part of a device. .....in devices, or parts thereof or those materials used therein, above 0.1%...

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114	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 6, Line 17 Please clarify if the word "consider" means that there are guidelines for the evaluation of possible alternative and not only guidelines on the benefit-risk assessment of the presence of CMR/ED phthalates in certain medical devices.	Primarily the Guidelines are a methodology to evaluate if the use of a CMR/ED phthalate is justified. Text modified for clarification. “Consider” changed into “describe” See comment 107.
115	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 6, Line 20 Is this BRA a part of the BRA of the use of a medical device? Or is this BRA a proper document?	This BRA is only for the justification of the use of a CMR/ED phthalate, and as such would be a part of the overall BRA of the medical device.
116	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 7, Line 1-5 There are other citations in the regulation that enlarge these definitions so please enlarge the citation or delete the insert. For example blood bags are medical device as mentioned in Annex VIII Chap III 4. 4. 2 "All non-invasive devices intended for channeling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa": but without specific purpose as described in the cited definitions.	SCHEER disagrees. The overall definition of a medical device is presented. The comment refers to a specific classification (blood bags as Class IIa) of a specific device and not to a definition of a device.
117	No agreement to disclose personal data	6. Justification for the use of CMR/ED phthalate	Page 23, line 2: To assess the exposure of DEHP that is used in a blood bag system the leaching of the PVC material into the blood component is the bases. The amount of leaching DEHP is a summative effect of all components, e. g. foil, tubes, Y-pieces, used in the blood bag systems. This does	SCHEER agrees. That is also indicated by the text. % now added for clarification. This Table shall be completed for every component of the medical device that contains CMR/ED phthalate(s) above the

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			determine the patient exposure. It is therefore not reasonable or useful to determine the exposure per DEHP component used in the blood bag system, instead the basis is the blood bag system as a complete set.	0.1% w/w level. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated. See also comment 40 item 66.
118	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 7, Line 22-24 According to MDR Annex 1 Chap I. :"or, where applicable, other persons, "Precise the scope. E.g case of apheresis donation.	SCHEER agrees. Donor exposure is addressed in Step 2 exposure estimation (Page 15 line 10). Page 7 line 22-24 text modified for clarification. .....users and patients, or where applicable other persons (e.g. donors) on which the device is used.
119	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 7, Line 35-36 Is the direct contact the only one considered? Precise how to consider a solution contained in one device and then integrated into another device which contains blood product i.e. buffy coat so the end user will be in contact with another device.	Page 7 line 35-36 is a citation of EN ISO 10993-1 explaining possible exposure scenarios for the risk assessment. For the risk assessment any possible contact needs to be considered. Direct and indirect. See also EN ISO 10993-1.
120	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 7, Line 36-39 Are these endpoints the only ones to consider for condition of migration of phthalate or alternative?	Text has been modified for clarification. EN ISO 10993-1 does not limit the endpoints to consider. This depends on the type of device and the intended use. Text added. According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. In Annex A of EN ISO 10993-1, a series of endpoints is....

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121	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 8, Line 4-5 Could you please confirm the definition of novel material? For instance is a PVC with alternative CMRD/ED plasticizer considered as novel material or is the alternative plasticizer considered as new material?	As indicated in EN ISO 10993-1 Clause 6.1 a novel material is a material that has not been demonstrated an established history of safe use in the intended application. For those materials new testing would be needed.
122	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 8, Line 3-8 Precise relevant: precise in which cases: does it mean that the reproductive and developmental toxicity should be addressed for the devices that are claimed by the manufacturer to be used for a target population. If there is no such claim, should reproductive and developmental toxicity be addressed?	As indicated EN ISO 10993-1 provides a testing strategy to be planned depending on the use of the medical device. It is outside the scope of the Guidelines to prescribe what testing needs to be done for any medical device. Page 7 line 33 text added to clarify this. According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. In Annex A of ISO 10993-1, a series of endpoints is.... See comment 120.
123	FRIZI,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	6. Justification for the use of CMR/ED phthalate	Page 8, Line 16-17 Precise if the concentration is identified for the global set or by part? If by part please give a definition of a part which could take into account the risk of the exposition of the CMR/ED phthalate.	This is indicated in the scope on Page 6 line 12. .....in devices, or parts thereof or those materials used therein, above 0.1%... Text added for clarification. See comment 113.

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124	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7. Benefit assessment	Page 8, Line 19 Please clarify if it is the global concentration of CMR/ED in the device that is considered. Please clarify how the 0.1% w/w is calculated? Example: for a device consisting of a needle, tubing and one bag: should it be 0.1% for the needle, 0.1% for the tubing from the needle to the bag and 0.1% for the bag itself or should it be 0.1% w/w average for the whole set (needle, tubing and bag)?	The calculation should be based upon the medical device or part of the medical device containing the CMR/ED phthalate. Chemical characterization can be done according to EN ISO 10993-18. As is now indicated in added text on page 14 line 14. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019).
125	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7. Benefit assessment	Page 8, Line 41 Please note 2015: Opinion to be cited as: SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), Scientific Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk. 2015.	SCHEER agrees. In SCENIHR reference 2016 changed into 2015
126	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 8, Line 44 According to SCENIHR 2015 ”massive blood transfusion of red blood cells and plasma" and not during “blood transfusion” in general as it is noted in the guidelines. Please precise as it refers to specific practices.	SCHEER agrees. Text modified. ...massive blood transfusions...

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127	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 9, Line 2 Please note 2015. Opinion to be cited as: SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), Scientific Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk. 2015.	SCHEER agrees. In SCENIHR reference 2016 changed into 2015 See comment 125.
128	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 9 Lines 10-13 Please clarify how the 0.1% w/w is calculated? Example: for a device consisting of a needle, tubing and one bag: should it be 0.1% for the needle, 0.1% for the tubing from the needle to the bag and 0.1% for the bag itself or should it be 0,1% w/w average for the whole set (needle, tubing and bag)?	The calculation should be based upon the medical device or part of the medical device containing the CMR/ED phthalate. Chemical characterization can be done according to EN ISO 10993-18. As is now indicated in added text on page 14 line 14. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019). See comment 124.
129	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 10, Line 1 With regard to "medical treatments", manufacturers do not always have access to the data or the necessary skills to perform the relevant BRAs. Please modulate by "if possible".	SCHEER disagrees. This is for the purpose of the Guidelines the definition used for alternatives for CMR/ED phthalates. In other parts of the Guidelines, the feasibility of the alternatives is addressed. E.g. page 18 line 2.

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130	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 10, Line 8-10 Is it correct to understand with “no clinically significant“ that in the case of blood bags if the blood products produced with the devices are compliant with the EDQM requirements then functionality and performance of the alternative are comparable?	It is not the remit of SCHEER to define functionality and performance of a device. This for the manufacturer to determine. Text changed for clarification: The functionality and performance of the alternative shall be comparable to the extent that there would be no clinically relevant difference foreseen in the performance of the device or in the outcome of the alternative medical procedure.
131	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 10, Line 15-17 Please clarify whether the phthalate concentration is identified for the overall device or for each part of the device?	Text added for clarification. .....in devices, or parts thereof or those materials used therein as intended to be used. See comment 113 and 123.
132	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 10, Line 24 Precise if the concentration is identified for the global set or by part? If by part please give a definition of a part which could take into account of the risk of the exposition of the CMR/ED phthalate.	In various places it is indicated that it is “devices, or parts thereof or those materials used therein”. Chemical characterization can be done according to EN ISO 10993-18. As is now indicated in added text on page 14 line 14. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019). See comment 124 and 128. As indicated EN ISO 10993-1 provides a testing strategy to be planned depending on the use of the medical device. It is outside the scope of the Guidelines to

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				prescribe what testing needs to be done for any medical device. Page 7 line 33 text added to clarify this. According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards. In Annex A of EN ISO 10993-1, a series of endpoints is.... See comment 120 and 122.
133	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 11, Line 7 How many at least? Could you give support, advice on how to do this inventory?	The MDR does not provide a limit. An approach is presented in Section 4 Steps 4 – 7.
134	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.1 Material benefit	Page 11 line 29 Please clarify how the maximum tolerable/acceptable exposure of the alternative for patient should be defined knowing that medical device with the alternative plasticizer can only be used with end-users, donor, patients once it is CE-mark?	In this Step 7 (further explained in Section 4) the risk is assessed by determination of potential toxicological endpoints, that are included in the risk assessment.
135	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.2 Clinical benefits	Page 12, Line 11 Please specify the scope for the justification of the presence of CMR/ED phthalate and for the evaluation of alternatives: here it is mentioned “professional users” whereas there is no such mention in MDR Annex I Chapter II point 10.4.1.	Text has been modified for clarification. Page 12 line 11. ....the risk for professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines.

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				When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. See also comments:17, 19, 30,32,60,65,75,.135.
136	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.2 Clinical benefits	Page 13, step 4, The manufacturers have no the access to data nor the skills to perform relevant BRA. Please delete or modulate with “if possible”.	SCHEER disagrees. Many alternatives for phthalates are already proposed in the literature. The Guidelines also indicate how such information can be obtained Page 16 line 38. The possible feasibility is addressed on Page 17 line 26 amongst others.
137	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.2 Clinical benefits	Page 14 line 13 " Please advise on the best analytical methods to measure the concentrations of plasticizers in PVC.	Information has been added. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019).
138	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	7.2 Clinical benefits	Page 14 line 13 " Has the concentration to be indicated for the device in general?	This depends on the composition of the device. As indicated in the text: .....in devices, or parts thereof or those materials used therein as intended to be used. See comment 113, 123 and 131.
139	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	8. Methodologies for Benefit –Risk Assessment	Page 16, Line 14-16 We do not understand what this note brings to the method, could you please delete or explain?	SCHEER disagrees. This notes indicates the issue of non-threshold effects. This is important for the risk assessment as indicated at Page 15 line 47 in which text is added. Starting points (points of departure, PoD) for exposure levels that are considered

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				safe could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD) for threshold substances. For non-threshold substances, a T25 value or the benchmark dose associated with a 10% response (BMD10) could be used. From these PoDs, acceptable exposure values can be derived such as “Derived No-Effect Level ” (DNEL), “Derived Minimum Effect Level” (DMEL) or intakes over lifetime without presenting an appreciable risk to health (ADI or TDI/TWI or TE). As such data are often obtained in rat studies, the use of the TDI seems more appropriate in view of the critical effect window for androgenic reproductive toxicity in rats has been reported to be a few days (Welsh et al., 2008). In addition, patients may be exposed to medical devices only for a limited period of time. EN ISO 10993-17:2002 calculates a Tolerable Exposure (TE), which is based on a product of the tolerable intake, the body mass and the utilization factor.
140	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	8. Methodologies for Benefit –Risk Assessment	Page 14 Line 29 How to manage with donor cases for whom there are no direct benefice? For example case of apheresis donation.	The risk for such donors in now indicated on Page 12 line 11, ...professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of the Guidelines.

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				When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. See also comments:17, 19, 30,32,60,65,75,.135. And Page 15 line 12. Consider repeated use scenarios (e.g. dialysis, apheresis donations, chronic treatment) and different population groups. See comments 17, 33, 67, 118.
141	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 16, Line 39-40 Could you please indicate on the basis of what criteria we could prepare such a list?	This is up to the manufacturer to decide. Step 4 is a general inventory, followed by Step 5 identification of possible relevant alternatives.
142	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 16. 31 to 35 Please clarify the scientific proofs available for medical devices with non-PVC material as alternatives to PVC with a phthalate as plasticizers.	Based on comments 37 and 80. this text has been deleted as it is not the task of SCHEER to identify alternatives.
143	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 19 Line 38 Does it mean that monitoring programs could be considered as sufficient to reduce the risk even if there is a lack of clinical data regarding alternative?	The monitoring programs can give an indication of the exposure to the alternatives.

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144	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 20 lines 1 to 10 Please be aware that for blood bag kits and transfusion, alternatives to DEHP have been identified although the large majority of the performance studies on the quality of red blood cells stored for up to 49 days is obtained with whole blood collected with a DEHP-medical device. As a result, additional data with DEHP-free devices need to be generated and published.	The issue is addressed in the cited SCENIHR 2015 Opinion on DEHP. The lack of data for certain alternatives was clearly identified in the SCENIHR 2015 Opinion.
145	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 20, Line 23 Should we systematically have to do the comparison between the use scenario and the non-use scenario to justify if it is possible to use alternative? If yes, are all steps mandatory?	The Guidelines provide a methodology for justification of the use of CMR/ED phthalates in a medical device. The use can be justified if no proper alternative could be identified.
146	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 22, Line 35 Could you clarify the table please? For example, how do we have to read line 3 of the table: does clinical benefit correspond to treatment possibility and does performance correspond to the flexibility of tubing?	The table provides examples what to consider. Clinical benefit could be the availability of a tubing with a specific level of flexibility. So, functionality might be seen as introducing flexibility (e.g. use as plasticiser), while performance might be seen as the level of flexibility needed.
147	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 22, Line 35 Line 3 of the table: it is written clinical benefit however also material benefit should have to be described.	SCHEER agrees. Material benefit added. The Table is not exclusive. As indicated on Page 22 line 31, the table should be extended depending on the number of criteria evaluated.

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148	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	9. Uncertainty analysis	Page 22, Line 35 In the table 1, develop the word “other”: as parameters such as availability, economical end point have to be taken into consideration for the choice.	The Table is not exclusive. As indicated on Page 22 line 31, the table should be extended depending on the number of criteria evaluated. “Other” is indicated on Page 23 at the end of the table.
149	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 24 page 32 Other requirements also include behaviors during centrifugation at low or high speed and conformity to several mechanical tests (Iso 3826).	SCHEER agrees. However, it is not the intention to give a summing up of all requirements. A number are indicated as examples.
150	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 24, Line 33-35 Typing mistake, at 4°C and not 40°C.	Typo corrected.

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151	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 24, Line 33-35 As published in Transfus Med Hemother 2016;43:19–26, BTHC is not a good alternative for replacing the CMR/ED DEHP regarding red blood cell storage . It is not appropriate to cite it as if it was. Please modify. See joined file.	Text has been modified. See comment 42 and 151. For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen et al. 2012, Prowse et al. 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags (Prowse et al. 2014). This potentially will allow the storage of platelet concentrates for up to 7 days, if measures to prevent bacterial contamination can be safely implemented.
152	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 30, Line 21-22 Please describe post update scenario.	This is a recommendation of SCHEER in order to have the possibility to evaluate the use and usefulness of the Guidelines. This is not the time period for revision. The MDR Annex I, 10.4.3 indicated when a revision/update should be performed.

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153	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 35 line 1 Could a definition of medicines be provided in annex 3?	According to SCHEER a definition of medicines is not needed as the word “medicines” is commonly known.
154	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 35, Line 7-9 Regarding blood products chain complexity, number of stakeholders, time effort to qualify any new device or new procedures in this field, time required to demonstrate compliance with general requirements of MDR for example stability studies that could take several years, blood shortage risk associated with a non-controlled implementation, which is a public health issue, how are the time limits for the validity of justification envisaged? Please develop as the justification shall be based on these guidelines.	The Guidelines provide a methodology for the justification of the use of CMR/ED phthalates. The implementation of new substances/materials is the responsibility of the manufacturer as is the case for any medical device brought to the EU market.

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155	Frizi,Naïma,Macopharma,Naima.FRIZI@macopharma.com,France	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 40, Line 24-27 Is it to be understood that if the alternative is not ready to be produced with adequate level of qualification, and if the device intermediate user is not ready because internal validations are required, then the justification could be still valid? In other words, please develop when it is needed to update the justification?	Page 40 lines 24-27 are definitions as presented in the OECD toolbox on the assessment of alternatives. Updates of a justification would depend on the scientific developments and availability of alternatives. It is the task of the manufacturer to follow such developments. EN ISO 14971 provides information for risk management.
156	Lisa,Moloney,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Please see all comments and proposed redlined text included in attached file. The comments and redline are captured for all sections within the one uploaded document.	The comments indicated in the attached file are for the majority addressed in the comment number 157 to 187. Regarding the request for an example of a completed BRA or reference to one completed already. SCENIHR has evaluated alternatives for DEHP already (see DEHP update 2015). This is also referred to in the Guidelines.
157	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	General comment: Can the requirement to consider the potential for a chemical reaction which would result in changing an identified non-CMR/ED phthalate back to a CMR/ED listed phthalate? e.g. through processing/sterilisation etc. Can it be clarified that the chemistry of the phthalate chemistry in the final device needs to be considered as well as the raw material.	The CMR/ED phthalates are identified according to the regulations, either by being included in Annex of the CLP regulation (Regulation (EC 1272/2008), REACH regulation (REACH EC 1907/2006) or specifically designated by a Commission Decision (e.g. Commission Implementing Decision (EU) 2017/1210). The comment on chemical reaction is a general issue that should be addressed in the risk assessment of a medical device that can be performed according to EN ISO 14971 and EN ISO 10993-1. This is not an issue to address in the Guidelines.

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158	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	An example of a completed risk benefit assessment or reference to one already completed in another guidance document would be very helpful.	SCHEER agrees. SCENIHR did such an evaluation for DEHP in its DEHP Opinion of 2015. So far, no specific risk benefit analysis were available for medical devices The Figure 1 was based on the publication below which provides an evaluation of the general use of DEHP and possible alternatives. Eliason P, Morose G Safer alternatives assessment: the Massachusetts process as a model for state governments. Journal of Cleaner Production 2011, 19, 517-526
159	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Concern, that the presence of phthalates in food and daily consumption etc will be used as a justification for why concentration of phthalates in device is acceptable. Is it possible to include statement to prevent this?	SCHEER disagrees. The reference to migration limits from food contact material is useful for medical device manufacturers. These limits are based on a toxicological risk assessment that can support the risk assessment of medical devices. For the actual risk assessment there is a considerable difference in exposure, and this should be taken into account when doing the risk assessment for the medical device.

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160	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	If biological safety data not available for alternative in literature review, would we expect dosing toxicity testing to be performed? If so, can this be clarified.	Yes, only if the manufacturer decides to use such alternative in a medical device. + see answer to comment 31: In the event that the risk assessment of a potential relevant alternative cannot be performed due to lack of information, documentation should be presented on the actions undertaken to obtain information to characterise the risk, including the outcome (for example, QSAR /read across could be performed). (before chapter 5),
161	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Throughout the guidance document where functionality and performance is included can biological safety be included i.e. comparison of functionality, performance and biological safety for the alternatives.	This is included Section 5 step 9 and step 10, and in the summary table 1. In the risk assessment biological safety remains an important issue. This is exemplified by the answer to comment 34.

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162	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 9: Line 23-25: would it be possible to include the requirement for the review of reducing the concentration of phthalates.	SCHEER disagrees. The justification would usually start with a review on the possibilities for alternatives for the phthalates. Risk management (and thus risk reduction) is part of EN ISO 14971.
163	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Line 30: to include understood i.e should be evaluated/understood	SCHEER disagrees. The Guidelines deal with a justification for the use of CMR/ED phthalates. So, an evaluation of possible alternatives versus the CMR/ED phthalate is needed.
164	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 10: Line 3: please include lower concentrations of phthalates as a possible alternative.	SCHEER partially agrees. A lower concentration should be below 0.1% w/w as indicated in the MDR Annex I 10.4.1. Also for a lower CMR/ED phthalate but above 0.1% w/w a justification needs to be provided. So, this would not be considered an alternative. However, it might result in a reduced risk. So, text was added. ....production process/techniques/lower concentration of substances)....

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165	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Line 24: Pleas include the following: Identification of the presence and concentration of each individual CMR/ED phthalate and cumulative concentrations where same mode of action.	SCHEER disagrees. Every chemical component of the medical device (or parts thereof) need to be identified. On page 14 line 14 additional text referring to EN ISO 10993-18 is provided. The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019).
166	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 11: line 1: Cumulative and individually where same mode of action.	SCHEER disagrees. Page 10-12 provide a general description and introduction to the framework. So, detailed information is not provided. This is done in pages 14-21. The aspect of multiple exposure to more than one phthalate is addressed on page 14 line 6.
167	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 11: Line 3: can it be included that the risks for different use scenarios and patient groups which will need to be rationalised per the intended use for the device.	SCHEER disagrees. Page 10-12 provide a general description and introduction to the framework. So, detailed information is not provided. This is done in pages 14-21. The issue of patients groups is addressed on page 12 line 11 where text is added. ....professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. In view of the importance of this aspect this text is now included in the Scope of

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				the Guidelines. When the word “patient” is used in these Guidelines, this includes users and other persons exposed to the medical device as well. (Chapter 2) See also comments:17, 19, 30,32,60,65,75,135, 140..
168	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 11: Line 3: include that the information can be demonstrated via literature on proven equivalent or testing performed.	SCHEER disagrees. Page 10-12 provide a general description and introduction to the framework. So, detailed information is not provided. This is done in pages 14-21.
169	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 14: line 3: please clarify what is meant by elements	SCHEER agrees. Word “elements” changed into “information”. The information to be provided according these Guidelines should already be part of the dossier of the medical device, as the phthalate is present as a component of that device. So, for the phthalate no new information needs to be generated.

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170	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 14: line 9, please clarify mode of action, is the mode of action *in-vivo.*	SCHEER disagrees. For a toxicologist MOA is a common terminology in relation to the induction of a toxic response. So, this does not need further explanation.
171	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 14: Line 9: Can a statement be included that where more that one phthalate is in the device where similar mode of action, the combined concentration is considered in the toxicological assessment portion of the risk benefit analysis. And a similar statement for when assessing alternative phthalates.	SCHEER disagrees. The aspect of multiple exposure to more than one phthalate is addressed on page 14 line 6. In Annex 5 page 46 some examples are provided for migration limits for presence of multiple phthalates/substances.
172	moloney,lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 14: Line 11: Step 1: What about details regarding the type of chemical /physical binding of the phthalate in the formulation/device? Should the legal manufacture consider these as part of the assessment?	Yes, this aspect need to be considered. But this information will become clear when migration/leakage of the substances is determined in relation to possible exposure and risk. See step 3 page 15 line 3. Text added for clarification in Step 1, (page 14 line 15): And the type of chemical /physical binding of the phthalate in the formulation/device when there is an impact on leakage.

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173	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 14: Line 28: Concern that vunerable groups will be contraindicated for use on labelling so that the CMR phthalate will fall within the required risk benefit ratio.	SCHEER disagrees. This is for the manufacturer to decide which vulnerable groups need to be excluded from the use of the device.
174	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 17: line 7: It would be great to have guidance included to ensure a systematic and non-biased approach is taken for the literature review when researching potential alternatives etc.	SCHEER agrees. But this is not the task of SCHEER. The Guidelines describe a methodology for the justification of the use of a CMR/ED phthalate. Any review should be performed by a knowledgeable person and be unbiased.
175	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Line 7: Is lack of toxicity date on an alternative an acceptable reason for exclusion of an alternative or would it be expected that testing would be performed. Can this be clarified in the document?	It is not the task of SCHEER to decide on this issue. See also MDR Annex I, 10.4.2. Yes, only if the manufacturer decides to use such alternative in a medical device. See answer to comment 31 and 160: In the event that the risk assessment of a potential relevant alternative cannot be performed due to lack of information, documentation should be presented on the actions undertaken to obtain information to characterise the risk,

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				including the outcome (for example, QSAR /read across could be performed). (before chapter 5).
176	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 17: Line 25: Please include guidance as to what a short list is, 3-5, 5-10 etc.	It is not the task of SCHEER to decide on this issue. See also MDR Annex I, 10.4.2.. Text is modified for further explanation. Step 5. If potential alternatives can be identified, a shortlist of the potential alternatives can be established for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, availability (e.g. sufficient availability or accessible to the manufacturer), and technical performance.
177	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	A Guidelines on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices	Page 18: line 6: Can it be included that when considering alternatives, for phthalates identified as possible alternatives, if not identified as a CMR/ED that the metabolism and excretion of the phthalate is outlined to understand if it has a similar ADME as the current phthalate used. i.e. that a cumulative effect is considered	Page 18 line 6 describes the possibility that an alternative could be present for one functionality while it would not be suitable for another functionality. But the limitation as presented in the MDR Annex I, 10.4.1 is limited to phthalates listed or identified by regulation. So, other phthalates not listed can serve as alternatives if suited in terms of functionality, performance, safety etc.

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178	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates	Page 18: Line 29: Can it be detailed if testing is required to establish the rate of leaching or if this can be done via literature or if worst case, all leaching at one time is acceptable.	SCHEER agrees. Both approaches are possible. This is to the manufacturer to decide as part of the risk assessment.
179	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates	Page 19: lines 23-26: consider rewording, cannot follow, bracket missing etc.	SCHEER agrees. There is a bracket missing. Text corrected. ....exposure (e.g. realistic worst case use scenario)....
180	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates	Page 20: Line 34: Concern regarding the interpretation of what is required for functionality and performance. It is interpreted worst case that all design inputs for the device will need to be retested for the different number of alternatives. Further concern that this will result in biased screening process to avoid the testing requirement.	The functionality, or lack thereof, need to be determined. If an alternative performs worse than the phthalate this would be a reason to discard such an alternative. This is addressed in step 6 page 18 line 10, and step 5 page 17 line 23. Information/data on functionality (e.g. level of flexibility in tubes) as well as performance and/or chemical safety assessment (e.g. hazard profile) may be used for rejection of the less likely alternatives (see below) and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance.

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181	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates	Page 20: Line 36: please consider including If equivalence can be demonstrated, literature data can be used to demonstrate functionality and performance of the alternative, otherwise functionality and performance will need to be tested for each candidate. Pilot samples are deemed acceptable for this analysis?	SCHEER disagrees. Whether equivalence is applicable is for the manufacturer to demonstrate. It is expected that for certain aspects (e.g. compatibility of chemicals with materials) some pilot material production might be needed. But this would be part of the normal R&D done by a manufacturer. See also added text on Page 17 line 23 on research efforts. In addition to the comparison in terms of functionality, technical performance and risks to patients and users, which are critical elements for the benefit-risk assessment, Annex I Section 10.4.2 of the MDR states that the justification for the presence of CMR/ED substances should also be based on an analysis of the availability of possible alternatives. Availability has several aspects, including for example the availability of necessary quantity (volumes) of the alternative on the market within a required timeframe and the ability to gain access to alternatives that may be proprietary (e.g., via licensing).
182	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates	Page 20: Line 41-42: consider rewording, sentence difficult to follow.	Text added for clarification. Risk management is described in EN ISO 14971. In this comparison also additional issues not directly related to the functionality and performance of the alternative itself, like technical possibilities, sterilisation effects

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				and interactions with infusion liquids, are important for the application of the alternative and the comparison with the CMR/ED phthalates, and thus should be considered.
183	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 3: Definitions/descriptions – References - Glossary	Page 22: Line 1: will the legal manufacturer need to demonstrate state of the art as part of the review to fully consider alternatives. If so can this be included.	According to the MDR the manufacturer is responsible.
184	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 3: Definitions/descriptions – References - Glossary	Page 26: Line 1: this section was difficult to follow, but understanding what is meant by including it. Would it be possible to amend the terminology used to align more with guidance that is somewhat familiar in the medical device regulations to ensure that a thorough literature review is performed and the data reviewed is from reliable sources. Alternatively if further definitions can be included so that the terminology is clarified.	Any review should include the latest scientific developments. This is the responsibility of the manufacturer. Text has been added to reflect the necessity of a systematic literature review: Page 7 line 39. A systematic literature review is part of the biological evaluation of a medical device in order to avoid unnecessary testing (EN ISO 10993-1). This systemic literature review should also be performed for a CMR/ED phthalate or potential relevant alternatives identified to be used in a medical device.

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185	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 3: Definitions/descriptions – References - Glossary	Page 30: Can a statement regarding the expectation with how often the risk benefit will need to be re-reviewed to ensure up to date. Is it once per certification cycle or for each revision of the REACH regulations etc	SCHEER disagrees. This is not the task of SCHEER to decide when a new justification is needed. This is the task of the manufacturer and depending on the current legislation. This text is asking for an evaluation of the use of the Guidelines themselves. The BRA for the use of CMR/ED phthalates would also depend on the scientific developments regarding alternatives. As the General Requirements (Annex I, Chapter I, MDR) aim to ensure the continued acceptability of the ~~benefit-~~risk weighed against the benefits to the patient ~~ratio~~, the benefit-risk determination requires regular updates as included in the post-market surveillance system and the periodic safety update report (PSUR) (Art. 83, ~~Art. 84, Art. 85~~to Art. 86, MDR). Added in the conclusions: As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, an update of the BRA of the medical device may be needed. The BRA of the CMR/ED phthalate should be updated or when new scientific information becomes available on alternatives for the use of the

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				phthalate, when new Guidelines are released or. as the "overall" benefit-risk determination of the medical device is updated,. See also comment #78 and 96.
186	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 5: Legislation on CMR and/or ED phthalates	Line item 21 on: Please outline the purpose of including these examples within the document. If it is meant that these levels are acceptable to base the risk benefit analysis on, then please state so. If not concern that they will be used, so please outline that this is not the purpose or maybe remove altogether.	These are migration limits considered safe for food contact materials. They are included as further information. In terms of migration there is some comparability with biomaterials for medical devices. However, the risk assessment need to be performed for the medical device as teh exposure between food and medical device can differ.
187	Moloney,Lisa,BSI Group,lisa.moloney@bsigroup.com,Ireland	Annex 5: Legislation on CMR and/or ED phthalates	Page 16 line 41, please further define/clarify the non-use scenario.	The non use scenario is included as opposite from the phthalate use in a medical device. For the justification of the use of a CMR/ED phthalate the non-use scenario (i.e. alternatives) need to be evaluated and discarded.

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188	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 5: Legislation on CMR and/or ED phthalates	General: • This document is primarily intended for the medical devices domain, which has a well established approach for risk management, including a particular approach to perform biological evaluation and to determine allowable limits for leachable substances. While the method used in the SCHEER guidelines is basically in line with this approach, there are no/hardly any references to the harmonized standards involved and the terminology used is somewhat different – the classical approach and terminology for chemicals/substances toxicological risk assessment is used. This makes it difficult for medical device stakeholders to integrate these guidelines in their risk management system. Proposed solution: amend the terminology and approach to bring it in line with that used in the harmonized standards for medical devices, in particular with EN ISO 14971, EN ISO 10993-1 and EN ISO 10993-17. Examples will be indicated in comments on following chapters. • In multiple places in the document, the words “functionality”, “performance” and “benefit” are used, sometimes in combination. It is not clear why a particular term is used in a particular context. Examples will be indicated in comments on following chapters. Proposed solution: define all three terms at the beginning, explaining what is meant by them, and review all places in the document where one or more of these terms are used. • The guidelines are not covering the full Terms of Reference as included in the mandate with regard to the types of alternatives to be evaluated: guidance is given only on principles to do the evaluation with regard to alternative plasticisers, and even some guidance on how to actually do this. There is no guidance on alternative materials, designs or medical treatments. Proposed solution: 1) In Scope, p.6, end of lines 17-18, add “, as well as alternative materials,	SCHEER partially agrees. AT various locations in the Guidelines now references are made to the various EN ISO standards dealing with risk assessment and safety evaluation of medical devices (e.g. EN ISO 14971, EN ISO 10993 series). Thank you for your comments. See for SCHEER answers below. Regarding the indication to use other materials, designs, and/or medical treatments this is indicated in several locations in the Guidelines. However, information on these subjects is limited. SCHEER agrees. Text modified. 1.....medical devices, as well as alternative materials, designs or medical

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			designs or medical treatments". 2) include the relevant additional guidance on this at appropriate places in the document. 3) in the guidance introduce the terminology "alternatives to devices with phthalates" instead of / in addition to "alternatives to phthalates". • The terms "shall", "should", "can", "might" are used in multiple statements. It needs to be reviewed whether the correct term is used in the correct place. • Scope, p.6, lines 20-25: this is rather confusing text. It would make much more sense to explain that the BRA as described in this guidance should be integrated within the risk management system for individual medical devices, for example using the system described in EN ISO 14971. After that, reference to further guidance in ISO/TR24971, the MEDDEV and the FDA docs could be made. • Scope, p.6, bottom of page: footnote 2 should be deleted. It is a redundant and irrelevant statement. In the 2012 version of the standard, the Annex Z is an integral part of the standard, where the content deviations in relation to the directives are listed, so the statement is redundant. In addition this guidance is not related to the directives, but rather to the MDR, so the statement is irrelevant. NB: Revised versions of the standard as well as the related TR24971 will be available at short notice, linking to the MDR. Moreover, no footnotes are being made on the limitations of the other documents mentioned, e.g. TR24971 is not a standard, and the FDA docs are obviously not designed to provide compliance with the EU Regulations. Yet they could be useful to mention as sources of guidance.	treatments. And also included in the Abstract page 2 line 34. 2. this is included where appropriate 3. SCHEER disagrees. The Guidelines describe the alternatives for phthalates including use of alternative materials, designs or medical treatments. This is indicated at several locations in the Guidelines. Page 6 line 20-25. Text added to emphasize BRA of whole device. However, the BRA as described can be integrated within the risk management system for individual medical devices. Scope, p.6, bottom of page: footnote 2. SCHEER agrees. Footnote deleted.

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189	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 5: Legislation on CMR and/or ED phthalates	1. Introduction • p.7, line 30 to p.8, line 8: although mostly true, it is not clear why this text is included in the introduction of the guidance: it provides information that is not used further down in the document. As also indicated in the general comments in relation to the scope, it would make much more sense to include a reference to EN ISO 14971 in chapter 2, requiring that the BRA as described in this guidance should be integrated within the risk management system for individual medical devices, as described for example in the standard. In addition, guidance on how to use the 10993 series of standards in the BRA framework in chapter would make much more sense than give a broad description here. That way, explaining how to use the well established concepts in BRA of medical devices for the purpose in the scope of this guidance, this guidance would really become useful to users from the medical devices domain. See also comments on Chapter 2. NB: the most relevant part of the 10993 series , Part 17, is not even mentioned. • p.8, lines 9-12: again, such a general statement mentioning some available other documents does not have much value. It will become of value when you refer to such documents at the relevant places in the BRA framework.	SCHEER disagrees. The information is provided to introduce the EN ISO 10993 series that are an important aspect for medical device risk assessment. EN ISO 10993-17 is added. Text added for information. Page 8 line 8. For the risk assessment EN ISO 10993-17 describes determination of allowable limits for leachable substances, whereas EN ISO 10993-18 describes methods for chemical characterization of materials used in medical devices. SCHEER disagrees. These documents are also referred to at relevant places in the Guidelines.

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190	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 5: Legislation on CMR and/or ED phthalates	2. Framework for BRA • p.9, line 26: “shall” instead of “should” • p.9, line 27-28: delete “by itself” • p.10. lines 1-7: very good! keep this, and make sure the rest of the guidance dealt with all alternatives in the scope of what is described here. • p.10, lines 1-17: See also general comments and comments on Chapter 1 : in this introduction to the step-wise approach, it should be clearly explained how this links into the well established risk management system using EN ISO 14971, EN ISO 10993- 1, 17, 18, and possibly other part of the 10993-series. • p.10, line 24: specify that concentration needs to be in %w/w • p.10, line 29: explain what is the material benefit • p.11: lines 13-15: suddenly the focus is narrowed to alternatives for phthalates only. Rephrase to make this applicable to alternatives for devices with phthalates • p.11: steps 5-7: from this text, it is not clear why this should be done in three steps. Looking at p.13 it makes more sense, so the text on p.11 should be clarified. • p.11, step 8, lines 37-38: how do the functionality an performance relate to the benefit as requested in step 10 on p.12?	 Should changed into shall. By itself deleted. Thank you for the comment. The connection to the EN ISO 14971 and 10993 series is indicated where appropriate. Done. Text modified ...phthalate in weight by weight percentage (% w/w). Material benefit is explained in Section 7.1 page 24. SCHEER disagrees. Page 11 lines 13-15. Text is not limited to phthalates. “candidates for assessment as potential alternatives for phthalates” Step 4 clearly identifies all possibilities.. SCHEER disagrees. Text on page 11 and 13 is similar. Functionality is a first prerequisite of any alternative. The benefit (use, applicability) is dependent on the functionality and performance.

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			• p.13, 2nd box from below “uncertainty analysis”: this is not described in the text before the figure.	SCHEER agrees. It is added to complete the BRA. It is not part of the stepwise approach but completes the BRA.

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191	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 6: Use of phthalates in medical devices	3. Assessment of PHT in device • This entire section should be changed to fit with EN ISO 10993-17	SCHEER partially agrees. Where indicated both EN ISO 10993-17 dealing with the determination of allowable limits, and EN ISO 10993-18 are referred to.
			• p.14. line 1 + footnote 5: this does not make sense: this is guidance on the MDR which is a regulatory action requiring specific justification – the current use scenario is not an acceptable one – that no longer exists under the MDR	SCHEER disagrees. These Guidelines provide a methodology for the justification of the use of a CMR/ED phthalate in a medical device. So, the use scenario remains an option with appropriate justification.
			• p.14, line 28: change to “benefits of the device with PHT	SCHEER agrees. Text added. Benefits of the device with CMR/ED phthalates should also be considered....
			• p.15, lines 17-31: this text only helps when applied by a toxicologist	SCHEER agrees. But the BRA should be performed by a team including a toxicologist. This is now added in the Introduction page 9 line 15.
			• p.16, lines 5-8: this is no guidance – out of the blue a general reference to 14971 ; these 3 line do not tell the user how to do this.	SCHEER agrees. Text modified. The benefit risk assessment for the use of the CMR/ED phthalate can be performed using for example MEDDEV 2.7/1rev4 and EN ISO 14971 (see also Section 8).

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192	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 6: Use of phthalates in medical devices	4. Assessment alternatives • p.16, lines28-30 mention 5 types of alternatives – very good. However, lines 31-35 only elaborate on 1 and 2 • p.17, lines 10-13: what is the basis for this? The following lines 15-19 contain weak language that does not really help to specify a relevant selection. • p.17, lines 21-28 clearly illustrate that it is necessary to explain the inter-relationships between functionality, performance an benefit. In line 25, “short list” is vague language. • p.17, line 37: further explanation is needed that this refers to the optimal flexibility, i.e. flexible, without kinking. • p.18, line 4-6: not a clear example	 Page 16 lines 28-30. SCHEER agrees. Page 16 Lines 31-35 were deleted as example these were seen as a very specific possibility. Page 17 lines 10-13. SCHEER disagrees. The MDR does not indicate a limit for the evaluation of alternatives. However, it would not be feasible for a manufacturer to evaluate tens or hundreds of alternatives. The burden for a manufacturer would be too high. A manufacturer should consider a number of relevant alternatives, and demonstrate that he has done this. Page 17 lines 21-28.SCHEER disagrees. This text is on the possibilities to limit the number of alternatives for further evaluation. Page 17 line 37.SCHEER agrees. Example added within brackets. ...fine tuning the flexibility (e.g. optimal flexibility without kinking) of a PVC-based .... Page 18 line 4-6. Other examples were added. . Also other aspects related to performance of the alternatives need to be considered like material processing conditions (Crespo et al., 2007), material

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				quality after sterilisation (Burgos and Jiménez 2009), and possible interaction with drugs in therapeutic infusion systems (Treleano et al., 2009, Salloum et al., 2015, Tortolano et al., 2018).
			• p.18, lines 7-9: this is on benefit, with reference to section 7 on risk at the end – please explain.	Page 18 lines 7-9. The text explains itself. Besides risks also benefits of any alternative should be considered.
			• p.18, lines15-16: comparison should be about benefit-risk, not just risk	Page 18 lines 15-16. SCHEER agrees. Text modified. ...lead to lower benefit and/or risk to human health for patients...
			• p.18, line 17: step 3 I not about replacing	Page 18 line 17. SCHEER agrees. But text does refer to step 3 in relation to the risk evaluation for the alternative. Text modified for clarification. ....the phthalate to be evaluated with reference to the alternative.
			• p.18, lines 24-25: vulnerable groups are added just as an afterthought, without any guidance on how to do this – this happens at multiple places in the document.	Page 18 lines 24-25. SCHEER agrees. Vulnerable groups are added to several places in the text as reminder that the evaluations should also consider those specific groups of patients.
			• p.18, line 48 – p.19, line 12: this text with references related to substances is not useful without guidance on how to apply it to medical devices	Page 18 lines 48/page 19 line 12. SCHEER disagrees. As the phthalates are of concern for their CMR/ED activity, any alternative should not have similar concerns. This is about hazard

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				identification for the alternatives in general. Text has been added for further clarification. . These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series. See also Table 1.
			• p.19, lines 20-21: refer to EN ISO 10993-17	SCHEER agrees. EN ISO 10993-17 added as reference. For medical devices allowable limits of their chemical constituents can be determined by EN ISO 10993-17
			• p.19, lines 23-34 make this text better applicable to medical devices	Page 19 lines 23-24. SCHEER agrees. Text added. ..., due to the substances present in a medical device, which....
			• p.19, lines 36-39n is mixing up requirements from 14971	Page 19 lines 36-39. SCHEER agrees. Reference to EN ISO 14971 deleted for clarity.
			• p.19, line 43: this would be a useful place to refer to MEDDEV 2.7.1/rev4	SCHEER agrees. Reference added. ...a systematic literature review (see MEDDEV 2.7/1rev4).
			• p.20,lines 11-12: obvious, this was the starting point	SCHEER agrees. This is a reminder that for those alternatives (alternative designs or medical treatments) other endpoints may need to be considered compared to a substance alternative.
			• p.20, lines 14-15: there can also be a lack of data or conflicting data	SCHEER agrees. This is now addressed by adding a new paragraph.

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			• p.20, lines 16-17 plus above paragraph: in fact, guidance is addressing only tox eval of alternative substances, not other types of alternatives.	In the event that the risk assessment of a potential relevant alternative cannot be performed due to lack of information, documentation should be presented on the actions undertaken to obtain information to characterise the risk (for example, QSAR /read across could be performed). SCHEER disagrees. It is clearly indicated that “alternatives” comprise more than just alternative substances. In the Abstract, Scope, and specific definition plus text in Section 2.

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193	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 6: Use of phthalates in medical devices	5. Assessment alternatives vs PHT • p.20, line 38: why does the hazard profile have to be introduced here? • p.20, lines 39-40: risk reduction should always be pursued • p.21, line 16: other risk, instead of other substances • p.21, line 25: again, suddenly benefit is introduced; before only functionality/performance were mentioned.	 Page 20 line 38. When several alternatives are available the alternative with the lowest risk should be chosen in view of risk reduction.. SCHEER agrees. Reference is made to EN ISO 14971. Risk management is described in EN ISO 14971. Page 21 line 16. SCHEER agrees. Substances changed into risks. exposure to other risks previously not present in the treatment modality. Page 21 line 25. SCHEER disagrees. The risk has to be evaluated versus the benefit. That is what step 10 explains as last step of the weighing of an alternative against the use scenario of a CMR/ED phthalate.

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194	,,RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 6: Use of phthalates in medical devices	6. Justifcation • p.22, line14: what are performance criteria? They were not introduced before • p.22, lines 18-22: can this be made applicable to other risks besides tox? • p.22, lines 225-27: again, how to take into consideration these vulnerable groups? some guidance? • p.23, lines 4-5: a table may not be the right format for this • p.23, line 16: confusing that benefit is now used in the sense of reduced risk instead of in its normal sense • p.24, lines 8-15: can this be made into a stronger requirement?	 Page 22 line 14. SCHEER agrees. Performance is deleted. Page 22 lines 18-22. SCHEER agrees. Text added. Any weight of evidence evaluation needs to show the overall confidence in the assessment. Page 22 lines 25-27. SCHEER agrees. Text is self explaining. Text indicates the intended use of a device. So, if used for a specific groups this group should be included in the evaluation. Page 23 lines 4-5. SCHEER disagrees. Besides text presenting the data and results, the table is an additional method to present an overview of the evaluation. The evaluation does not consist of only the table. Page 23 line 16. SCHEER agrees. Text modified. .....thus accepting a risk from a toxicological perspective, in case the clinical benefit is very high. In contrast, a minor loss in medical functionality might be acceptable if there is a large reduction or even absence of risk.

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195	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	Annex 6: Use of phthalates in medical devices	7. benefit assessment • why this topic after chapter 6? • p.24, lines 19-21: confusing: 7.2 is on clinical beneft • p.25, line 20 and below: the list is not clear with regard to its applicability to PHT – where did this come from? any references?	The BRA is described in section 1 – 6. Section 7 and 8 are added explanatory sections for further support in the BRA. Page 24 line 19-21. SCHEER disagrees. The statement is made to emphasize that the BRA described in the Guidelines is not the only BRA to be performed. The Guidelines are limited to the justification for the use of CMR/ED phthalates. For clarification the references to the MEDDEV 2.7/1rev4 and EN ISO 14971 are added. The evaluation of the overall benefit-risk assessment of a medical device is presented in other documents (e.g. MEDDEV 2.7/1 rev4, EN ISO 14971). SCHEER agrees. This is a listing of possible clinical benefits in general, so also applicable to phthalates. Text has been changed for clarification: SCHEER identified the following examples that may be relevant for the use of phthalates (list not exclusive)...
196	RIVM - National Institute for Public Health and the Environment,Robert.Geertsma@rivm.nl,Netherlands	B. REFERENCES	9. uncertainty analysis • this is a very lengthy, theoretical, scientific discussion: how can the user apply this to a particular device?	Reference is provided to the EFSA guidance on uncertainty analysis. It is not on a particular device but for the data collected during the evaluation of either the use of a CMR/ED phthalate or the use of an alternative.

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197	RIVM - National Institute for Public Health and the Environment,Robert.Gertsma@rivm.nl,Netherlands	C. ANNEXES	10. conclusions • conclusion for the SCHEER members, or part of the guidance? is this needed?	The conclusions are part of the Guidelines. Importantly they refer to the generation of quality data (which is for a number of proposed alternative lacking). In addition, the call for experience with the use of the Guidelines is important in relation to the revision of the Guidance as indicated in the MDR after at least 5 years.