

USE OF PHTHALATES IN MEDICAL DEVICES

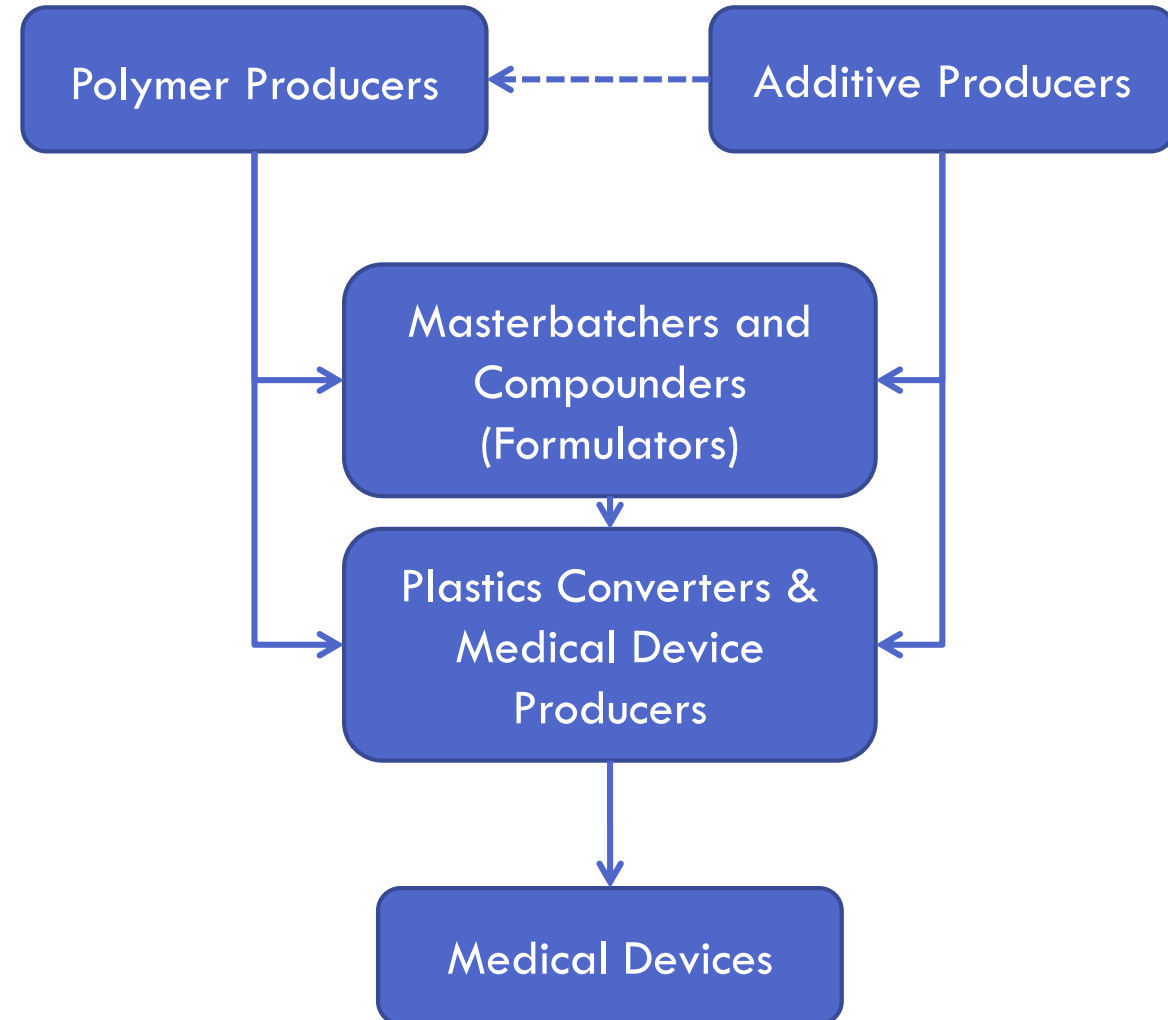


MedPharmPlast
A sector group of EuPC

SCHEER Public Hearing – 4 April 2019

MedPharmPlast Europe – Who we are?

- Created in 2014, MedPharmPlast Europe (MPPE) is a sector group of the European Plastics Converters representing companies involved in the complete value chain of plastic medical devices in Europe.





MedPharmPlast Europe - Mission

- **MPPE Mission:**
 - It assists companies in these industry sectors by keeping them informed about the latest developments in European regulations and their impact on the medical device and pharmaceutical packaging plastics value chain.
 - As an expert group with other trade bodies, MedPharmPlast Europe furthermore represents the interests of the industry to the European legislators and tries to arrive at regulations that are both workable and protect the patient.





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MPPE – 20 members from all over Europe

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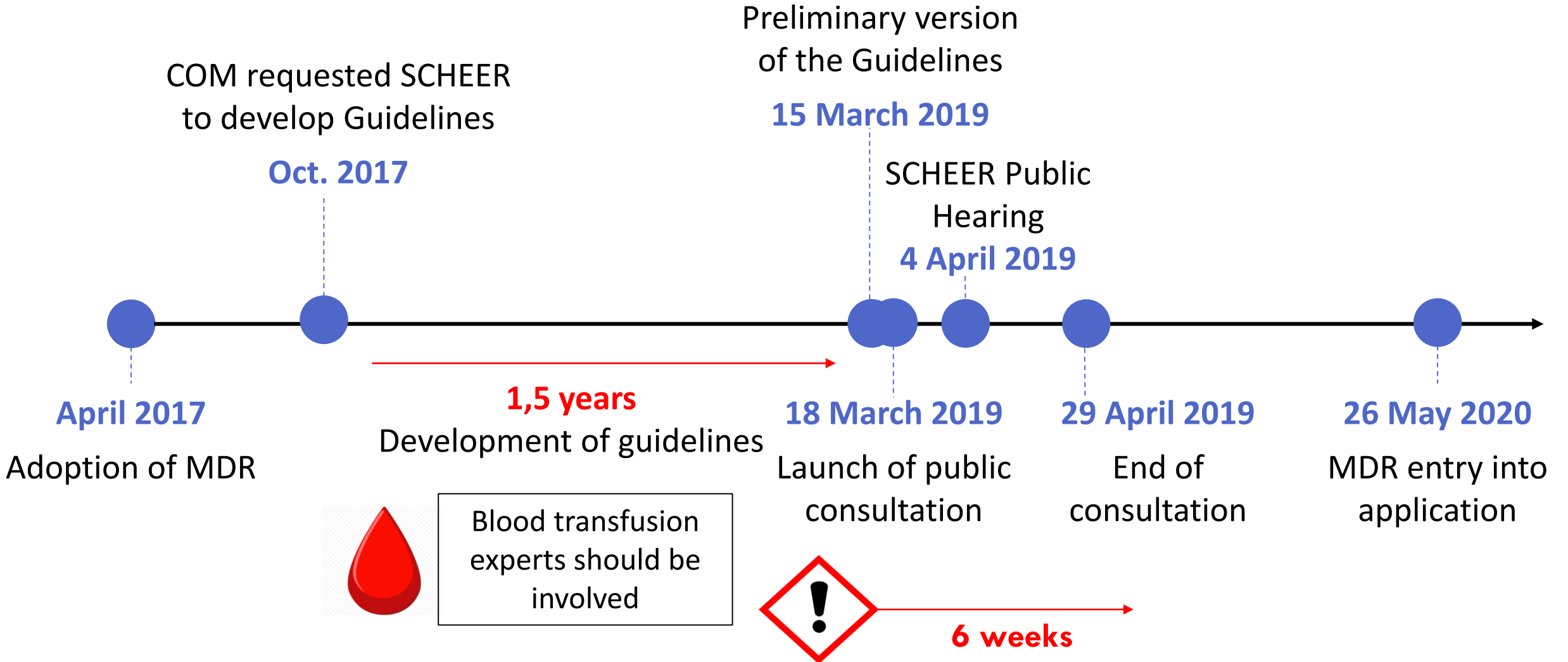


USE OF PHTHALATES IN MEDICAL DEVICES





Procedures & processes





Uniqueness of Blood Bag Systems

The collection of blood and blood components into bags would not be possible without the use of other parts, such as tubing, filters, valves, safety devices and attachments.

European Pharmacopeia – Section 3.2.3

“The containers may contain anticoagulant solutions, depending on their intended use, and are supplied sterile”.

“The container may be in the form of a single unit or the collecting container may be connected by one or more tubes to one or more secondary containers to allow separation of the blood components to be effected within a closed system”.

ISO 3826-1:2013

Part 1: Conventional containers

plastics container: *“bag, of plastics material, complete with collecting tube and needle, port(s), anticoagulant, and/or preservative solutions, and transfer tube(s) and associated container(s), where applicable”*

MEDDEV 2.4/ Rev. 9 June 2010 – Classification of medical devices: *“Blood bags (including those containing or coated with an anticoagulant).”*



Classification of Blood Bag Systems (I)



Not referenced in preliminary version of Guidelines

- The consequences of an up-classification of Blood Bag Systems should be taken into account in the development of the Guidelines on the benefit risk assessment of the use of Phthalates in medical devices for several reasons:
 1. **Anticoagulants & storage solutions** – Approximately 90% of Blood Bag Systems would be classified as class III products since the vast majority of blood bags includes an anticoagulant & other storage solutions.
 2. **Validation process & BRA** – Although an up-classification to Class III would have no effect with regard to donor or patient safety, the validation process and benefit-risk assessment of Blood Bag Systems would have to be redone.
 3. **New clinical studies** – The introduction of new Class III products to the market would require considerably more time due to the extensive clinical trials they have to undergo according to the MDR.



Classification of Blood Bag Systems (II)

Expected impact in a nutshell

1. **Need for clinical studies** as required under MDR
2. **New materials** to be developed & used
3. **Novel storage solutions** as 90% of Blood Bag Systems would be classified as class III
4. **New benefit risk** although the device's risk profile and design have not significantly changed over the past years



Could result in a 5 year process



Guidelines – Specific considerations

- **Recognition of positive effect of DEHP** – *“Some phthalates (e.g. DEHP) may have an additional function such as the stabilising effect on red blood cells (RBCs). RBCs have increased survival rates when stored in DEHP containing blood bags. DEHP is incorporated into the cell walls of RBCs and stabilises the membrane integrity of the RBCs. This results in a prolonged shelf life and thus patient availability of blood stored in DEHP containing blood bags .” (SCENIHR 2016)*
- **Development of alternatives** – *“The Guidelines state that the plasticiser industry has been investing and developing alternatives to DEHP in medical devices. Today, other plasticisers such as [DINCH], [TEHTM] and [DOTP] are being proposed in medical applications such as medical tubing and blood bags.”*



Considering the limited clinical evidence on the long term benefits of alternative substances, how would this be taken into account when Blood Bag Systems are justified to Notified Bodies?



Guidelines – Assessment of alternatives (I)

ECHA / COM consultation on DEHP Annex XIV entries – 5 June to 6 August 2018

NHS Blood and Transplant – *“Blood pack procurement exercises can take three or more years due to the complexity and scale of the process. Prior to this, up to five years’ worth of development work, validation and trials would be required to ensure that DEHP-free blood packs provide blood components of equivalent quality to those currently in use.”*

Sanquin – *“Blood pack procurement exercises are complex and subject to tendering rules, therefore can take several years. Prior to this, at least five years’ worth of development work, validation and clinical trials would be required to ensure that DEHP-free blood bag systems have the same low defect rate as the current systems and provide blood components of equivalent quality and safety to those currently in use.”*



ECHA / COM consultation on DEHP Annex XIV entries

European Blood Alliance

“A clinical risk will arise should there not be available an alternative bag that is at least as reliable, as safe and as beneficial for red cell quality. Patient safety and the sufficiency of the blood supply could be compromised.”

“Blood bag system procurement exercises can take three or more years due to the complexity and scale of the process as well as tendering rules. Prior to this, up to five years’ worth of development work, validation and clinical trials would be required to ensure that DEHP-free blood bag systems provide blood components of equivalent quality to those currently in use including the proven low defect rate of the systems.”



Guidelines – Assessment of alternatives (IV)

Table to be completed for a comparison of CMR/ED phthalate with potential alternatives

Assessment criteria	Description (examples)	Reference phthalate	Alternative I	Alternative II etc
Functionality/performance	Used as plasticiser	e.g. DEHP		
Clinical benefit/performance	Treatment possibility	e.g. Flexibility of tubing / red blood cells storage		
Concentration (% w/w)				
Leaching from medical device (mg per hour/day)				
Exposure estimation (realistic worst case use scenario)				
Hazard identification				
Identification of a point of departure for risk assessment (LOAEL, NOAEL, BMD, T25, BMD10)				
Identification of dose levels associated with minimal or negligible risk (e.g. DNEL, DMEL, TDI)				
Risk characterisation (MoE, MoS, RCR)				
Confidence estimation (see Table 2)				
Feasibility				

- **Alternatives** – Guidance should be provided on the number of alternatives to be selected.
- **Exposure** – Realistic simulated use scenarios would be more suitable than realistic worse-case scenarios
- **Hazard identification** – Hazards associated with the CMR/ED phthalate should be in the biocompatibility evaluation, not a CMR/ED justification.
- **Risk assessment** – Need for a better definition of “acceptable risk” and of “risk in terms of hazards”.



Conclusions

- **Uniqueness of Blood Bag Systems** must be considered due to:
 - Up-classification concerns – New benefit risk assessment but same risk profile
 - Positive effect of DEHP on flexibility of Blood Bag Systems and storage
- **Assessment of alternatives to DEHP** – Concerns about:
 - Data gaps regarding hazard identification and exposure estimation
 - Adverse effects of some alternative substances
- **Preliminary version of the Guidelines**
 - Blood transfusion experts should be involved in the development of those Guidelines
 - Current version does not provide guidance to Notified Bodies on staff requirements to properly conduct a benefit risk assessment