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## Evaluation of the Biological Safety over the Whole Life-Cycle of a Medical Device – Aspects to be Considered

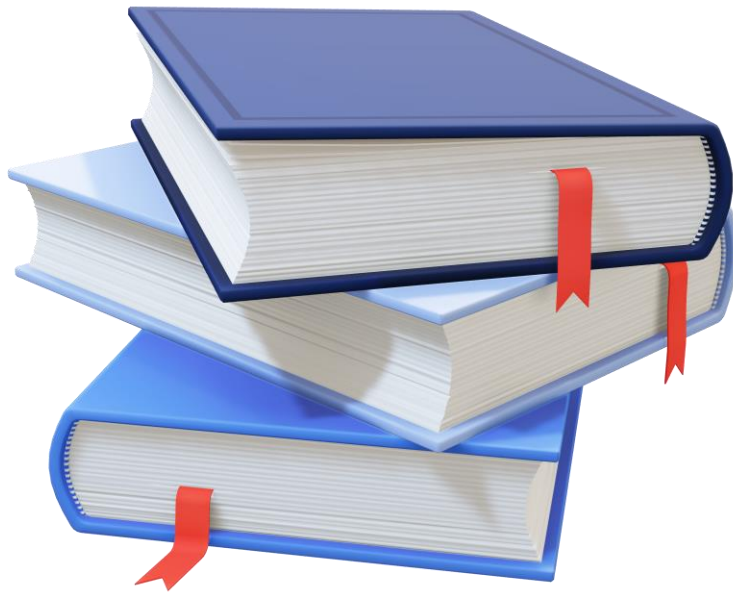
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# Disclaimer

This presentation is based on information available as of today and prepared to my best knowledge as subject matter expert.

This presentation presents my personal understanding of the medical device requirements in Europe and is not necessarily reflecting the view of TÜV SÜD PS.

# Aspects to be Considered with Regard to the Biological Safety over the Whole Life-Cycle



**1** Different Time Points of the Life-Cycle of a Medical Device

**2**  $T_0$  – Manufacturing Processes, Sterilization, Packaging

**3**  $T_1$  – End of Shelf Life

**4**  $T_2$  – End of Intended Use

**5** Reprocessing

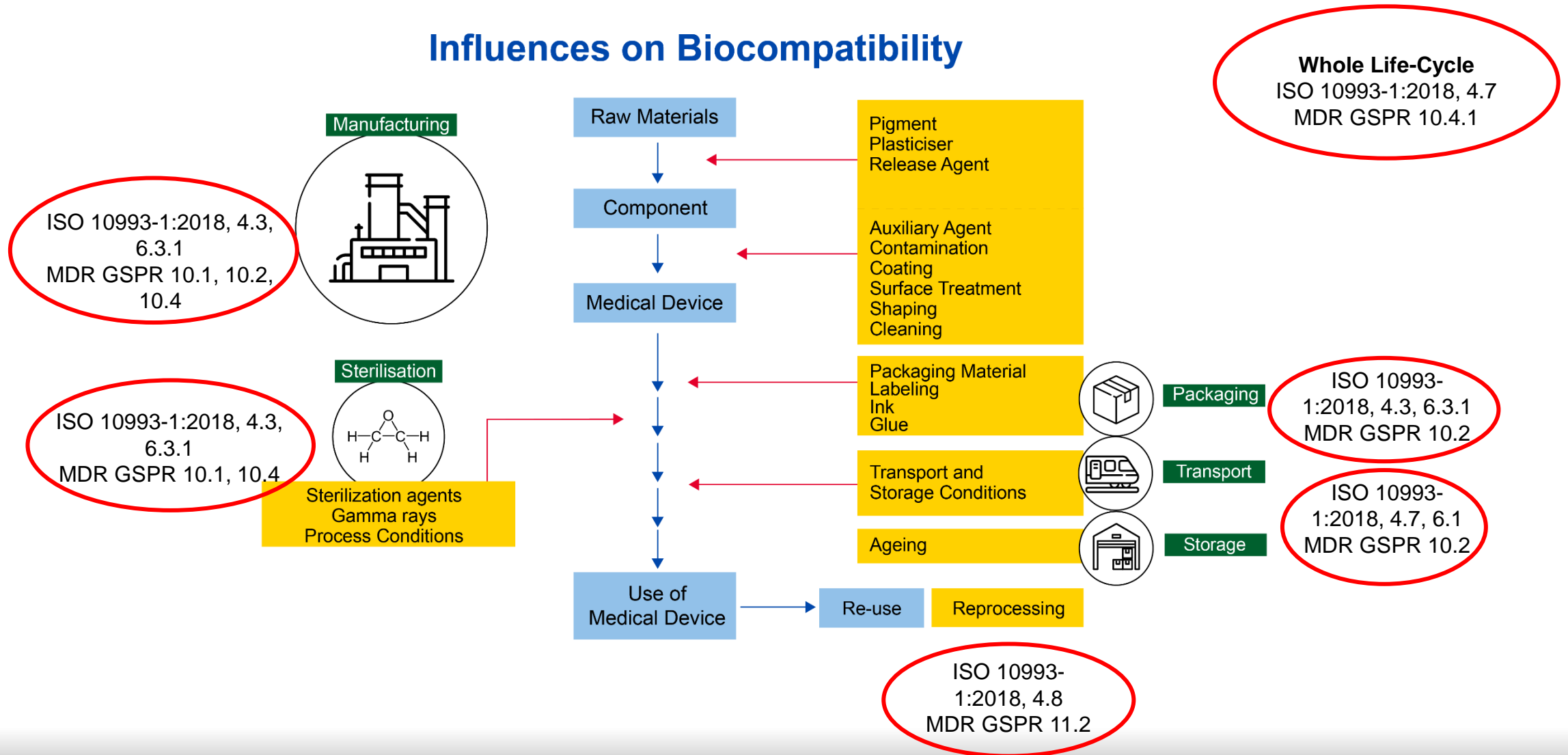
# Biocompatibility Evaluation Applying ISO 10993-1:2018

- Risk-based approach
- Among others – new requirement

Evaluation of the biocompatibility of a medical device over its complete life-cycle

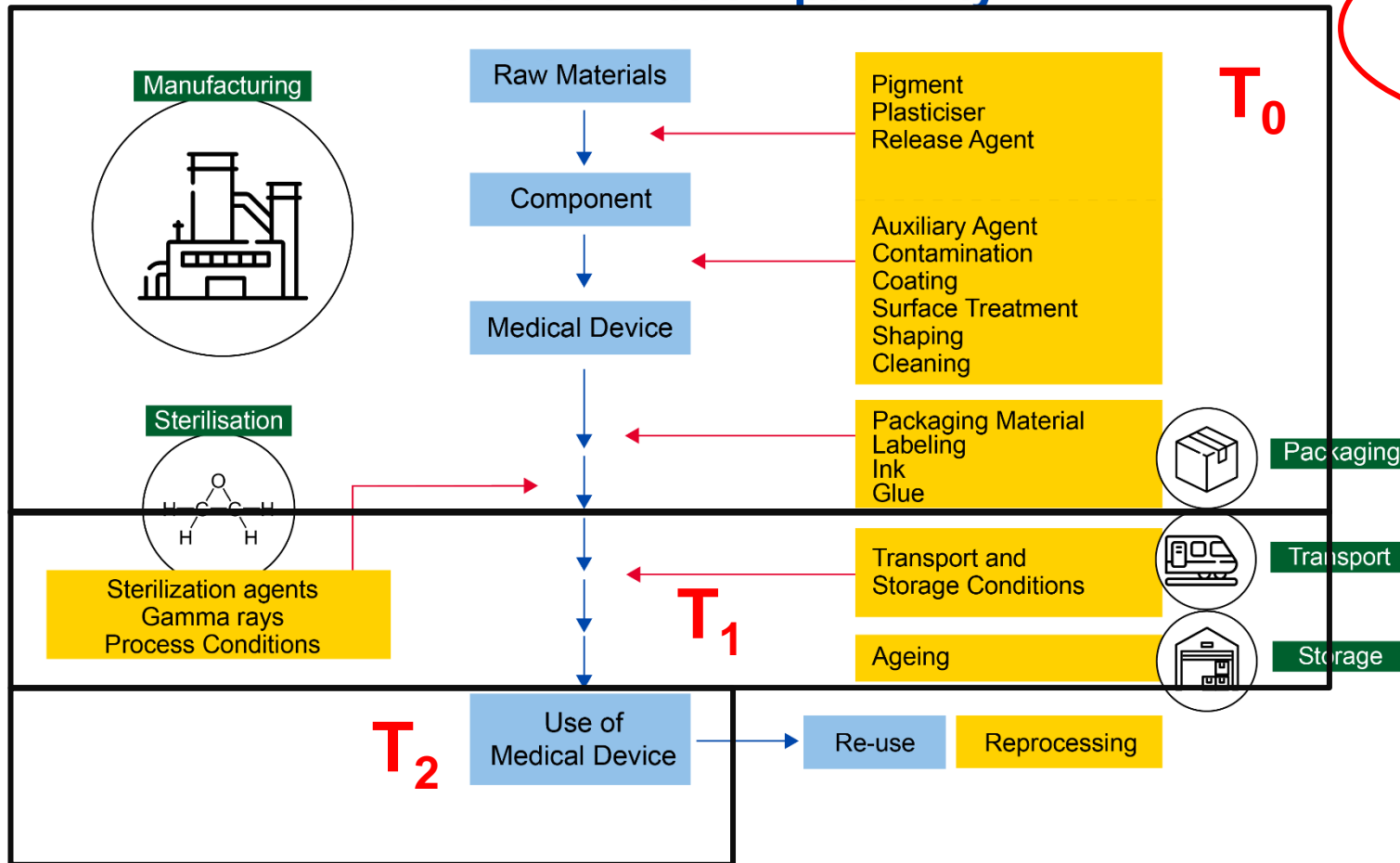
# Different Time Points in the Life-Cycle of a Medical Device

## Influences on Biocompatibility



# Different Time Points in the Life-Cycle of a Medical Device

## Influences on Biocompatibility



# T<sub>0</sub> – Manufacturing Process, Packaging, Sterilization

- Raw materials
- Processing aids, e.g. release agents, pigments, plasticizer
- Cleaning agents or contaminations
- Surface treatment, e.g. coating, polishing
- Transfer of contaminants
- Transfer/migration from glue, ink, desiccants, etc.
- Transfer of packaging migrants
- Adhesion of microscopic or even macroscopic particles from vacuum pouches on electropolished metal surfaces
- Residues from sterilization agent
- Material alterations due to sterilization conditions

# T<sub>0</sub> – Manufacturing Process, Sterilization

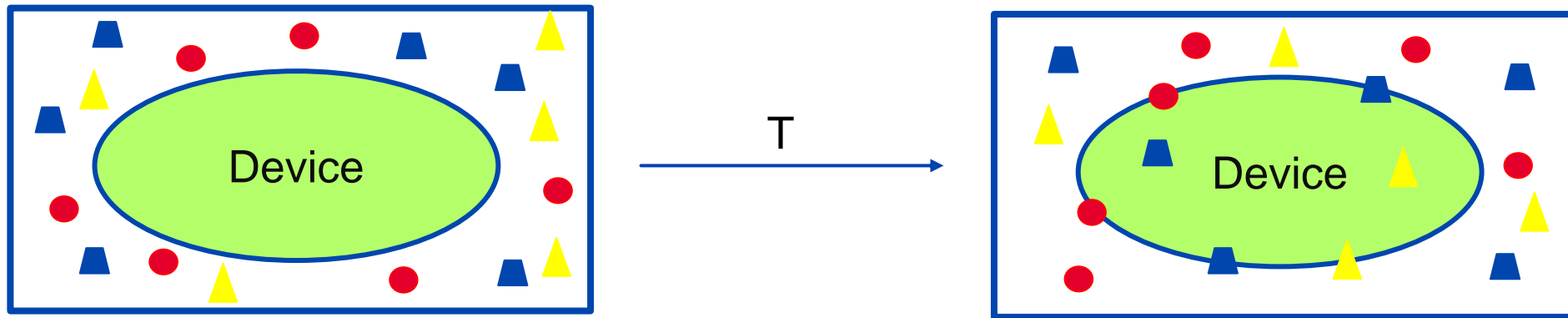
- Categorization according to ISO 10993-1:2018, 5.
  - by nature of contact
  - by contact duration
  
- Risk Assessment considering endpoints according to Table A.1
  - chemical characterization
  - biological and clinical data



# T<sub>1</sub> – End of Shelf-Life/Impact of Transport and Storage

- Transfer of packaging contaminants, glue, ink
- Transfer of packaging migrants
- Material alterations due to storage/transport conditions (reaction of substances or degradation/corrosion)
- Particle generation with abrasive device materials (motion during transport)
- Migration of substances from other components (e.g. non contact to patient, e.g. metallic instrument with plastic shaft, adhesives)
- Adhesion of microscopic or even macroscopic particles from vacuum pouches on electropolished metal surfaces

# T<sub>1</sub> – End of Shelf-Life/Impact of Transport and Storage



Whole storage time needs to be considered

# T<sub>1</sub> – End of Shelf-Life/Impact of Transport and Storage

Potential impact of Packaging Materials that come in contact with the Medical Device (primary packaging materials) on the physical, chemical, or biological properties must be evaluated, considering:

- Materials of the device
- Packaging Materials
- Usually, a solid device is less likely to interact with the packaging materials than a device composed of a semi-solid or liquid material

# $T_1$ – End of Shelf-Life/Impact of Transport and Storage

Determination of Worst Case Time Point:

- $T_0$ 
  - volatile residuals/contaminants from manufacturing or packaging materials covered by performed testing
- $T_1$ 
  - non-volatile migrants from packaging materials  
material data from packaging materials
  - non-volatile migrants from non-patient contacting components/parts  
chemical characterization data from device
  - wear particles generated during transportation  
transport validation data
  - material alterations due to storage conditions  
material stability data
  - adhesion of microscopic or even macroscopic particles from vacuum pouches on electropolished metal surfaces  
data from packaging validation / transport simulation / aging

**Result may be that no testing is necessary – for screening purpose often cytotoxicity testing of aged product is performed**

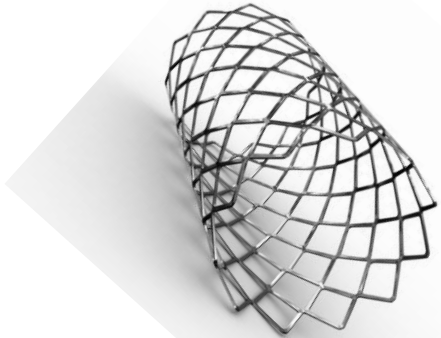
# T<sub>1</sub> – Material Data from Packaging Materials

- can be helpful in order to address the risk of migration of substances from the packaging materials to the device under assessment
- **USP-testing** performed with packaging materials are usually **not acceptable** to address this risk, usually the following gaps appear:
  - testing is typically conducted on raw materials rather than final products
  - extraction conditions typically do not represent whole shelf life
  - potential interactions with the device is not addressed

see also **ISO 10993-1:2018, 6.2**

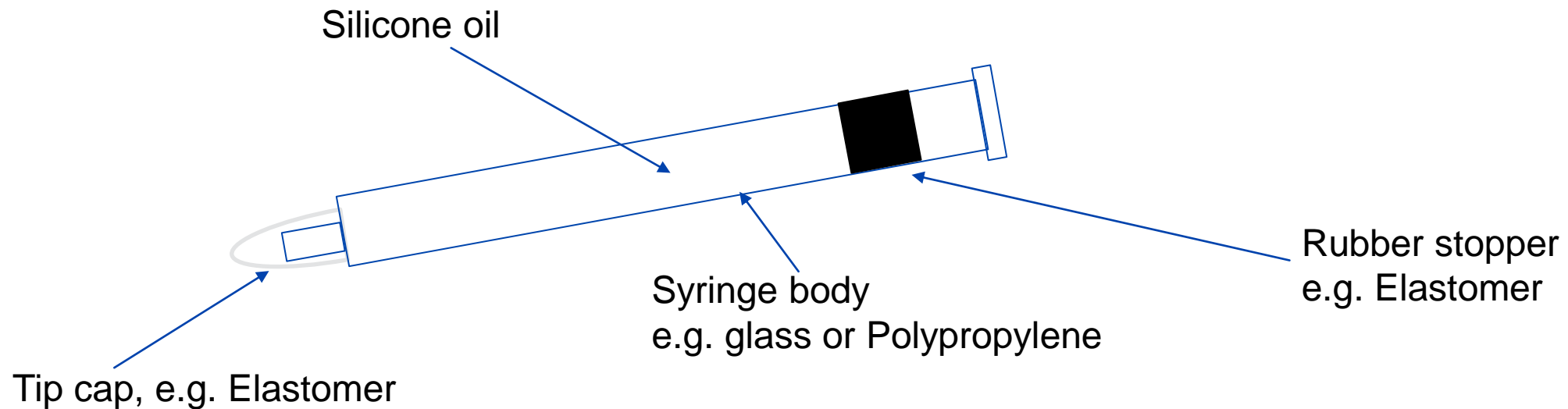
# T<sub>1</sub> – End of Shelf-Life/Impact of Transport and Storage

Influence and depth of evaluation depends on device type (liquid vs. solid) and packaging material (polymer, glass, ...)

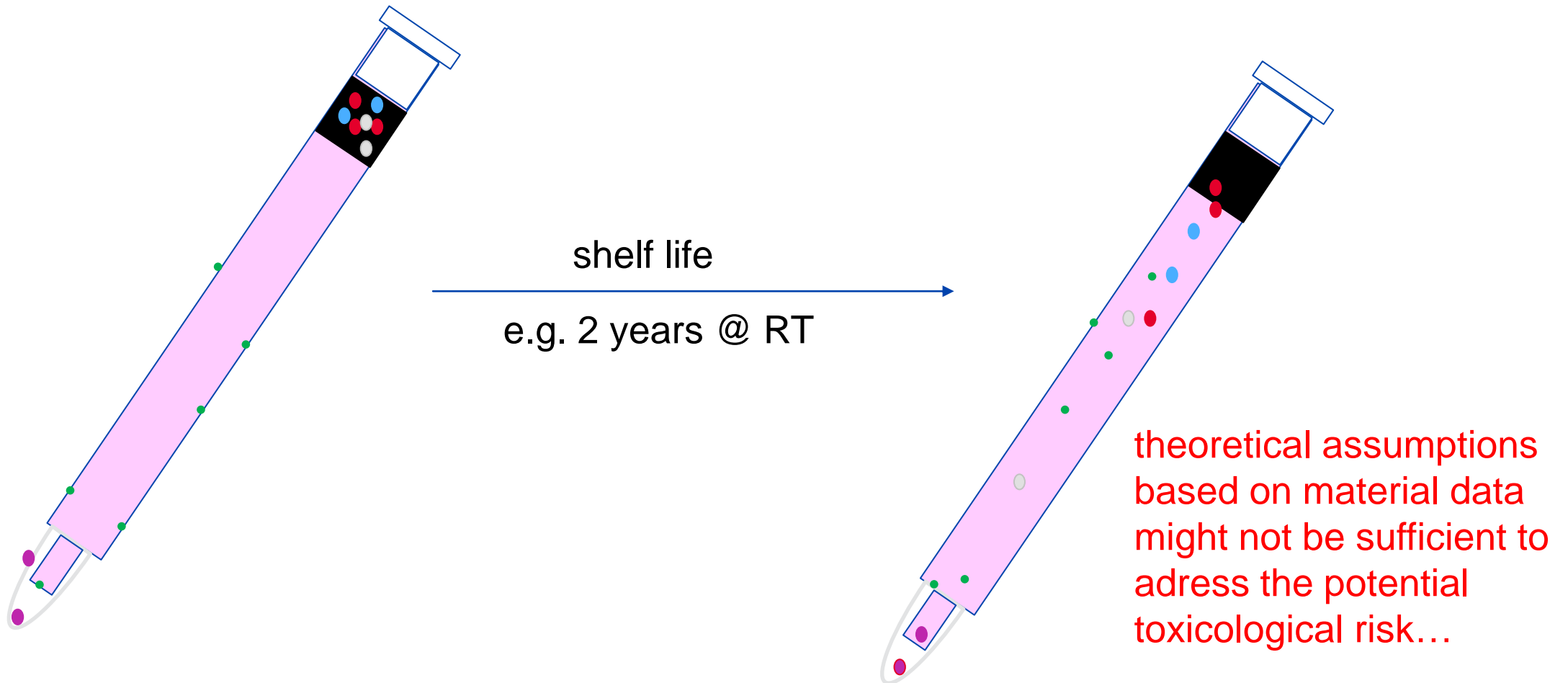


# T<sub>1</sub> – Example Liquid Device

- Worst case with regard to potential leachables from primary packaging materials
- Leaching takes place during the complete shelf-life
- e.g. prefilled syringes are complex packaging systems with several components to be considered:



# T<sub>1</sub> – Example Liquid Device





# T<sub>1</sub> – Example Liquid Device

...but chemical analysis of the device after accelerated/real-time aging for this kind of devices often technically not feasible

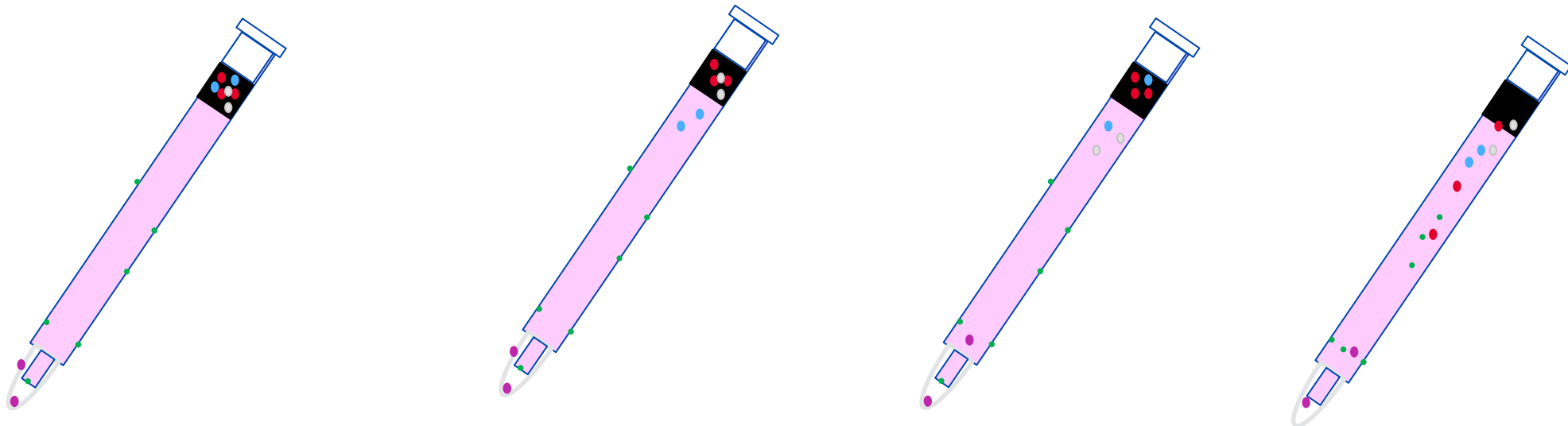


Example: Chemical analytical testing and toxicological risk assessment of the packaging materials

# T<sub>1</sub> – Example Liquid Device

Extraction Conditions – Critical for Representativeness of Results:

- shall be documented and justified (time, temperature, ratio, solvents)
- shall be relevant for conditions during shelf life
- choice of test sample critical (unfilled syringe / syringe filled with extraction medium already during manufacturing)



Before extraction

Condition 1

Condition 2

Condition 3

# T<sub>1</sub> – Example Liquid Device

Exhaustive Extraction Conditions required:

- several extraction steps might be necessary
- until extracted material is less than 10% of initially extracted amount of material

By this the **maximum amount of extractables** is reached the can be released from the material under assessment – Toxicological Risk Assessment of those is considered to assume the **worst case**.

# T<sub>1</sub> – Example Liquid Device

## Selection of Analytical Methods – Critical for Representativeness of Results

- should be able to detect the substances that are **expected** as well as possibly **unknown substances in toxicologically relevant concentrations!**
- should be validated
- should have appropriate sensitivity – LOD/LOQ, AET  
should be considered in the Toxicological Risk Assessment

# T<sub>2</sub> – End of Inteded Use

Risks to be adressed would be:

- Wear particles arising during usage
  - data from functional testing might be employed
  - data from implantation study
  - clinical data
- Reaction of substances or degradation/corrosion
  - material stability data
  - data from implantation study
  - data from corrosion Tests
- Change of physical properties
  - material stability data
  - data from implantation study
  - physical characterization of aged products

# Reprocessing

- Residues from cleaning/disinfection agents
- Material alterations due to processing conditions
- Evaluation of product as subjected to reprocessing instruction (e.g. cleaning agents, conditions, no. of reprocessing cycles)



# Questions?



Thank you  
for your  
attention!!