Small volume packaging -
NB Persepctive on CE-marked Medical Devices versus Article 117 MDR combination products
March 2022

Mehr Wert.
Mehr Vertrauen.

Add value.
Inspire trust.

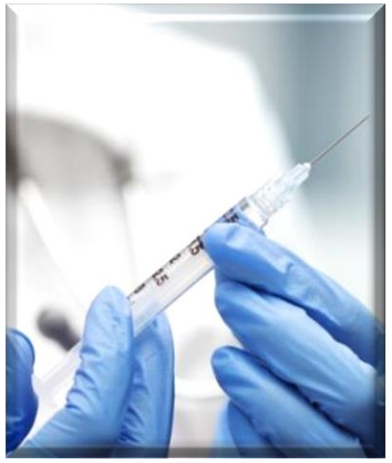
Disclaimer

This presentation is based on information available as of today and prepared to my best knowledge at the date the presentation was given.
The presentation reflects my understanding and is not binding.

Part I Notified Body Perspective on Article 117 combination products by Dr. Christiana Hofmann

- Notified Body Opinion (NBOp) scope and content
- NBOp assessment first experiences
- Conclusions & Outlook

Combination Products leading Legislative Act 2001/83/EC



Device intended to **administer** a medicinal product

Integral

Device **incorporating** a medicinal substance

Medicinal substance: principal mode of action

2001/83/EC Medicinal Products Directive

+

Art.117 EU 2017/745

May 26 2021

Article 1 Subject matter and scope

8. Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorised in accordance with this Regulation.

However, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council ([1]), as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part are concerned.

9. Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product.

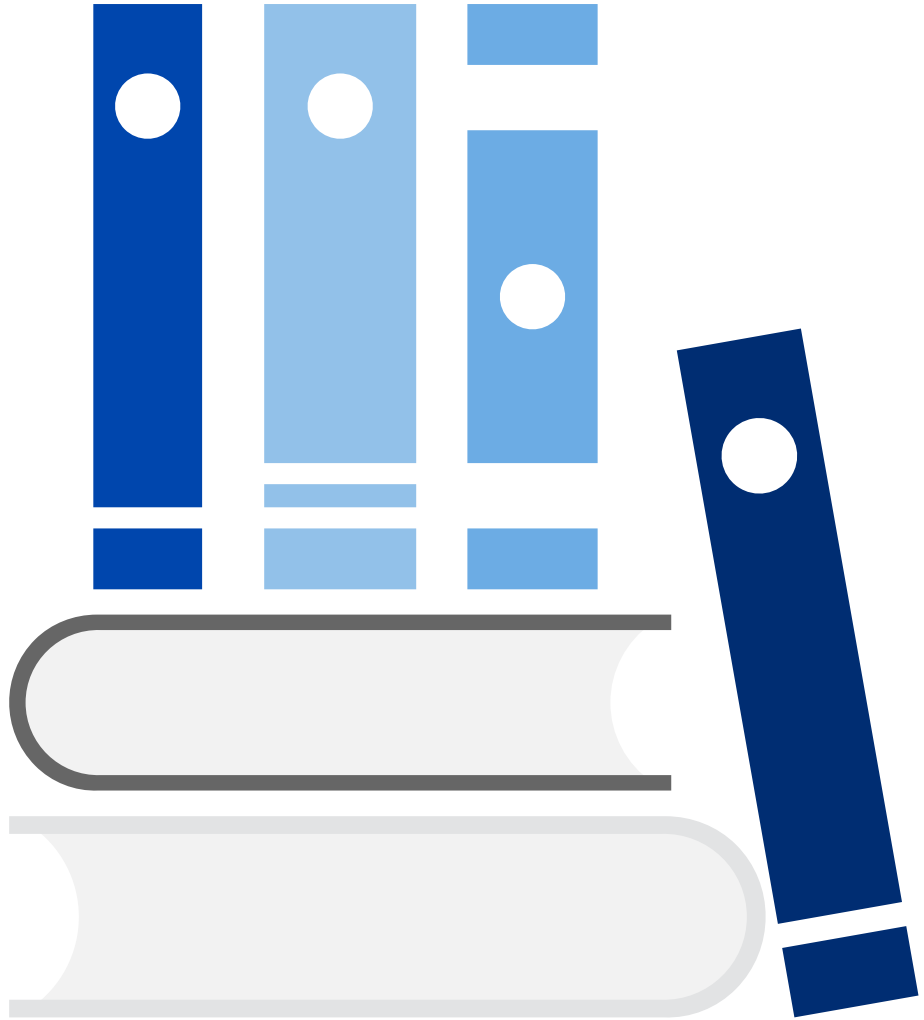
However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.

([1]) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

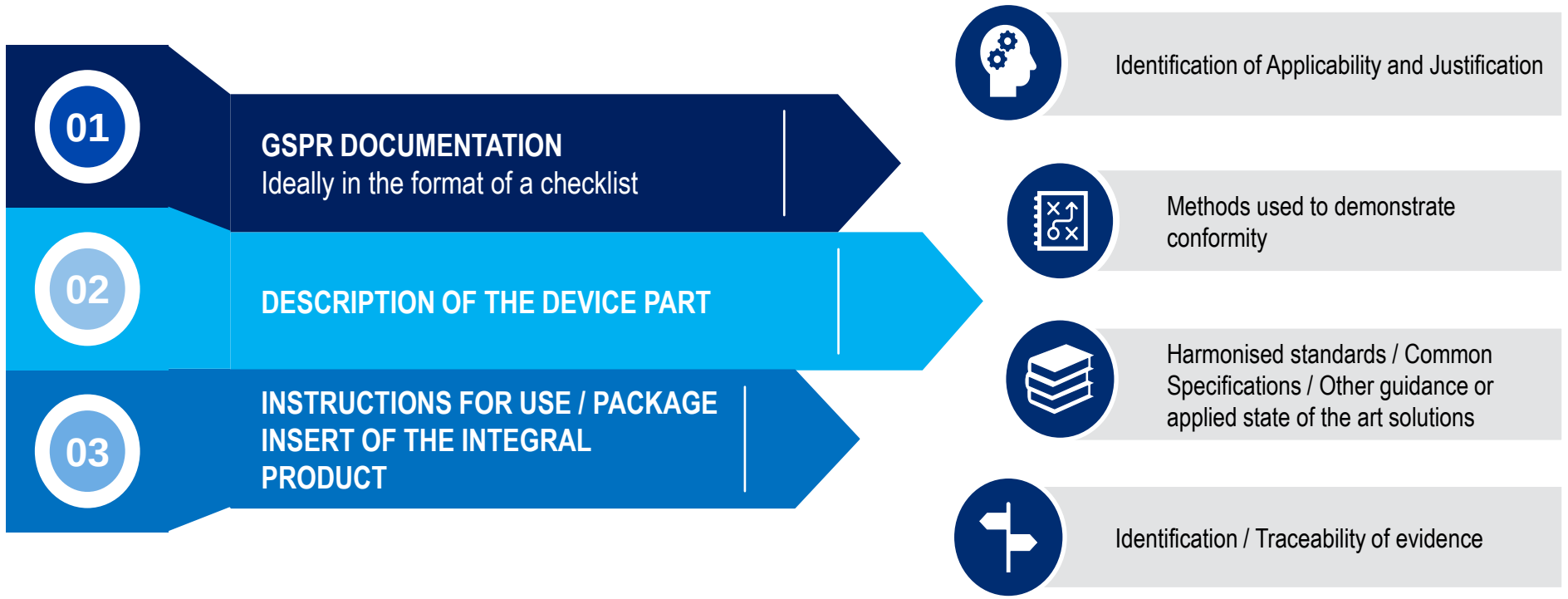
Key Aspects of Article 117

- Amending 2001/83/EC – Selfdeclaration option withdrawn

- Conformity of the device part to relevant general safety and performance requirements
- Notified body opinion on conformity to relevant GSPR
- Manufacturer’s declaration of Conformity
- EU certificate
- Involvement of the notified body (point of decision classification?)



Content of NBOp documentation



Biocompatibility within Article 117 assessment

- Exclusively focusing on the compliance of the device part with relevant GSPRs (10.1 following)

- GSPR 10.3

Risk of leaching and/or extracting effect that affects the device performance and/or usability

- GSPR 10.4.1

Assessment whether the drug influences the performance of the device part

- GSPR 10.4.2

CRM substances e.g. cobalt – a justification is required why a concentration above 0,1% w/w can be accepted

- Focus on biocompatibilty of the single components of the device with the justification that the assembly does not influence the biocompatibility of the components and therefore the final device

- Example Pen injector
  - a) needle CE marked (biocompatibility covered via conformity assessment procedure)
  - b) staked needlens (biocompatibility data have to be provided from manufacturer)

Common pitfalls identified

APPLICABILITY OF GSPR

Explanation and / or justification why a GSPR is not applicable are often missing

FILE COMPLETENESS

Full File submission
One documentation package including applicable evidence documents

SHELF LIFE DATA

Real time aging studies not available at start of assessment (this can in most cases be accepted due to provided accelerated aging data)

MISSING OBJECTIVE EVIDENCE

GSPR Checklist does not reference the corresponding documents
Summary Reports reference obtained result
without providing the corresponding methods

Complex Structure of submitted documentation package

Evidence document are often difficult to identify in a huge document

STATEMENTS OF SUPPLIER

Without providing the referenced objective evidence via reports

Feedback so far on first NBOp assessments

Clinical evaluation report

Is a CER required for Article 117 device or not? What kind of evidence document are sufficient?

Point of decision risk of device and functionality

NBOp Template requested

Harmonization between NBOp –Position Paper released Oct 2021

NBOp requested by EMA or not?

How to deal with requests for class I products?

Different processes, requirements NB vs CA / Pharma

Predictability of timelines

Ensured with fixed time slots

TÜV SÜD sticked to the timelines

Technical meetings

Especially initial meeting to present the product and the strategy for preparing the document package

Discuss about late coming data

Good communication with assessor

Availability of expert during assessment was ensured

Q&A Document – Updates and Clarifications

INTRODUCTION OF NEW TERMS

Container Closure System

- nozzle on the top of the container for eye drops
- syringe for reconstitution (without purpose for administration of the medicinal product)

Excipients

- transdermal patches (using passive diffusion)

INTRODUCTION OF CLASSIFICATION RULES

- Class I device parts are requested to comply to article 117 with a declaration of conformity

LEGACY DEVICES FALLING UNDER ARTICLE 117

- Assessment of changes leading to a new notified body opinion
- Assessment regulated via contractual agreement between device manufacturer and notified body
- Impact assessment on changes requested – without clarification against which requirements

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

23 June 2021 Rev.2
EMA/37991/2019
Human Medicines Division

Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

Uncertainties

Platform Approach

Problem is different departments are responsible for different products groups; no harmonization of document labeling

Topic addressed to EU Commission but no feedback so far

Generic devices, Biosimilars, Different doses same device

Task force Art 117

NBs are not involved so far

Establish project management team with all stakeholders

Communication between MDCG and NBCG-Med

Moving forward in a positive direction

Lack of resources Competent authorities

Concerns of manufacturer (upcoming number of consultations)

??? How to solve this???

☞Involve all stakeholders in the process (e.g. holistic risk based approach)

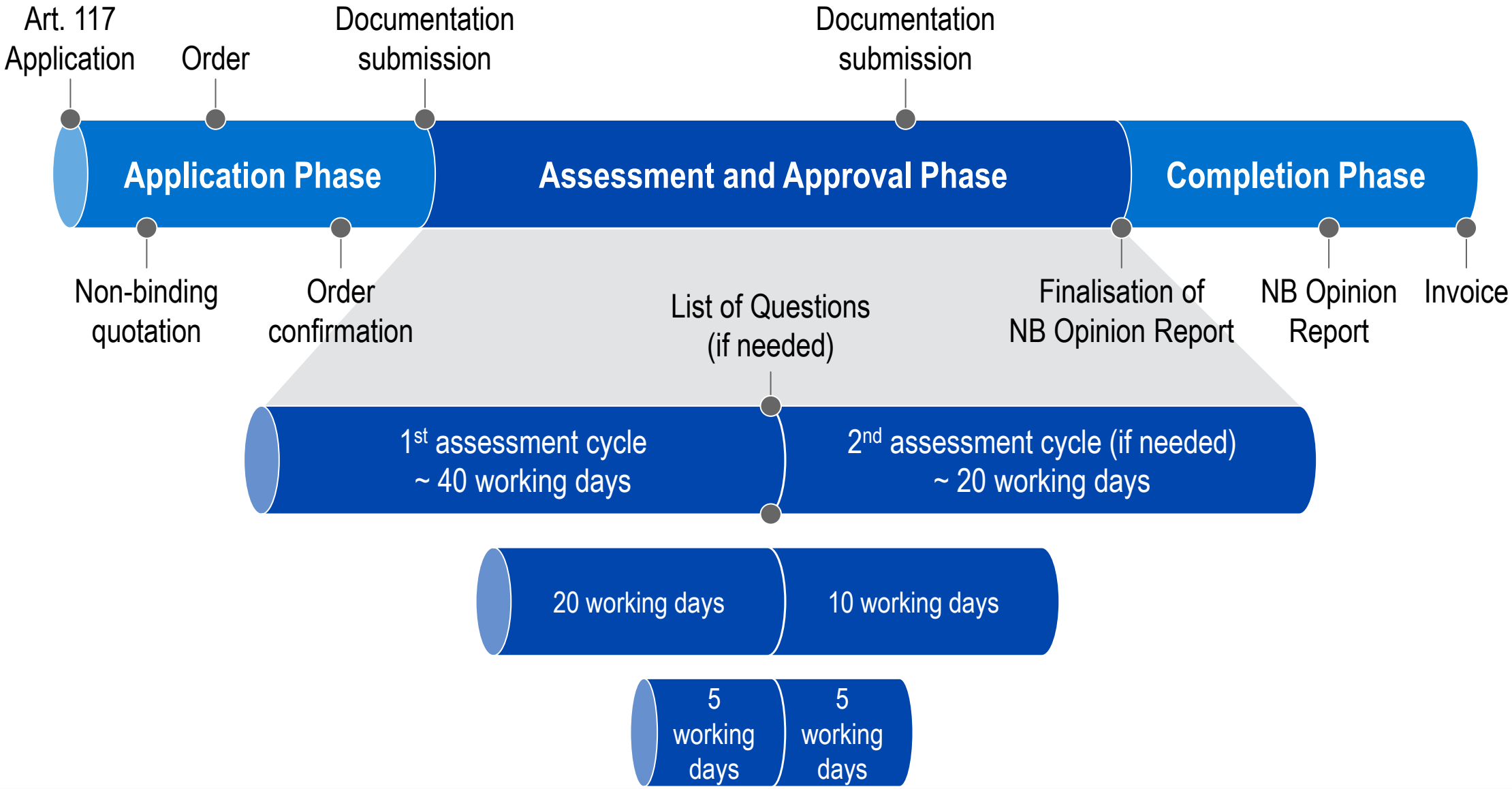
☞ Establish legal framework to facilitate communication and collaboration of all stakeholder

Moving forward to a new mindset in collaboration

2021 Convergence | EUROPEAN MEDICINES AGENCY

Take home messages…

- Complex EU landscape with multiple stakeholders
- Need to anticipate the NB conformity assessment so that this is available for the MAA
- Will need to gain experience and as needed provide additional guidance to address questions on scientific and regulatory aspects
- Need to continue developing a collaborative approach across EMA, NCAs, EC, Notified Bodies and Industry (medicines and devices manufacturers)


Art. 117 Application
Order
Documentation submission
Documentation submission
Application Phase
Assessment and Approval Phase
Completion Phase
Non-binding quotation
Order confirmation
List of Questions (if needed)
Finalisation of NB Opinion Report
NB Opinion Report
Invoice
1st assessment cycle ~ 40 working days
2nd assessment cycle (if needed) ~ 20 working days
20 working days
10 working days
5 working days
5 working days

Take Home Message

Involve medical device experts in early stage of D&D

Establish GSPR list – core element of documentation

Introduce your regulatory strategy to your NB

Address open points to EMA / CA

- **Check your product portfolio for article 117 applicability (in case of doubts contact EMA)**
- **Prepare NBOp documentation for the device part of your combination product**
- **Get in touch with your NB asap**

Thank you!

Questions?

Contact me:

Dr. Christiana Hofmann

christiana.hofmann@tuvsud.com
or
NBOp@tuvsud.com

Part II Notified Body Perspective on CE-marked Medical Devices by Dr. Katharina Weidmann

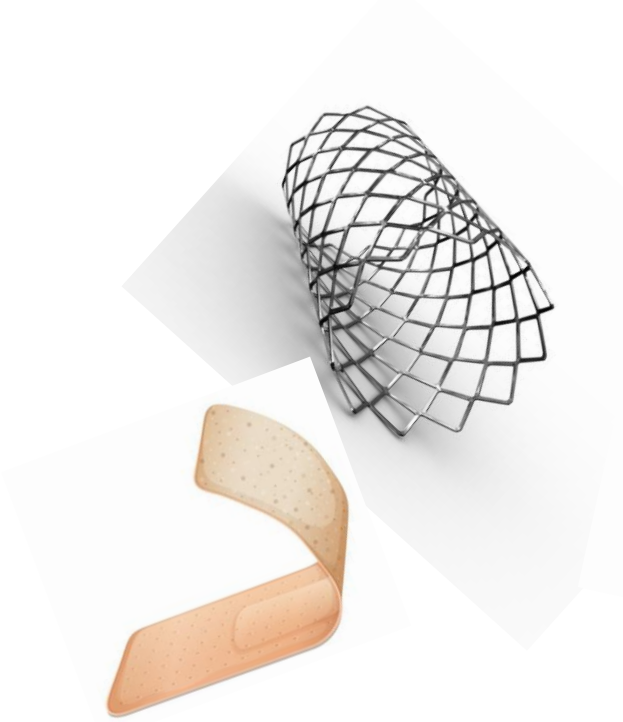
Disclaimer

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.

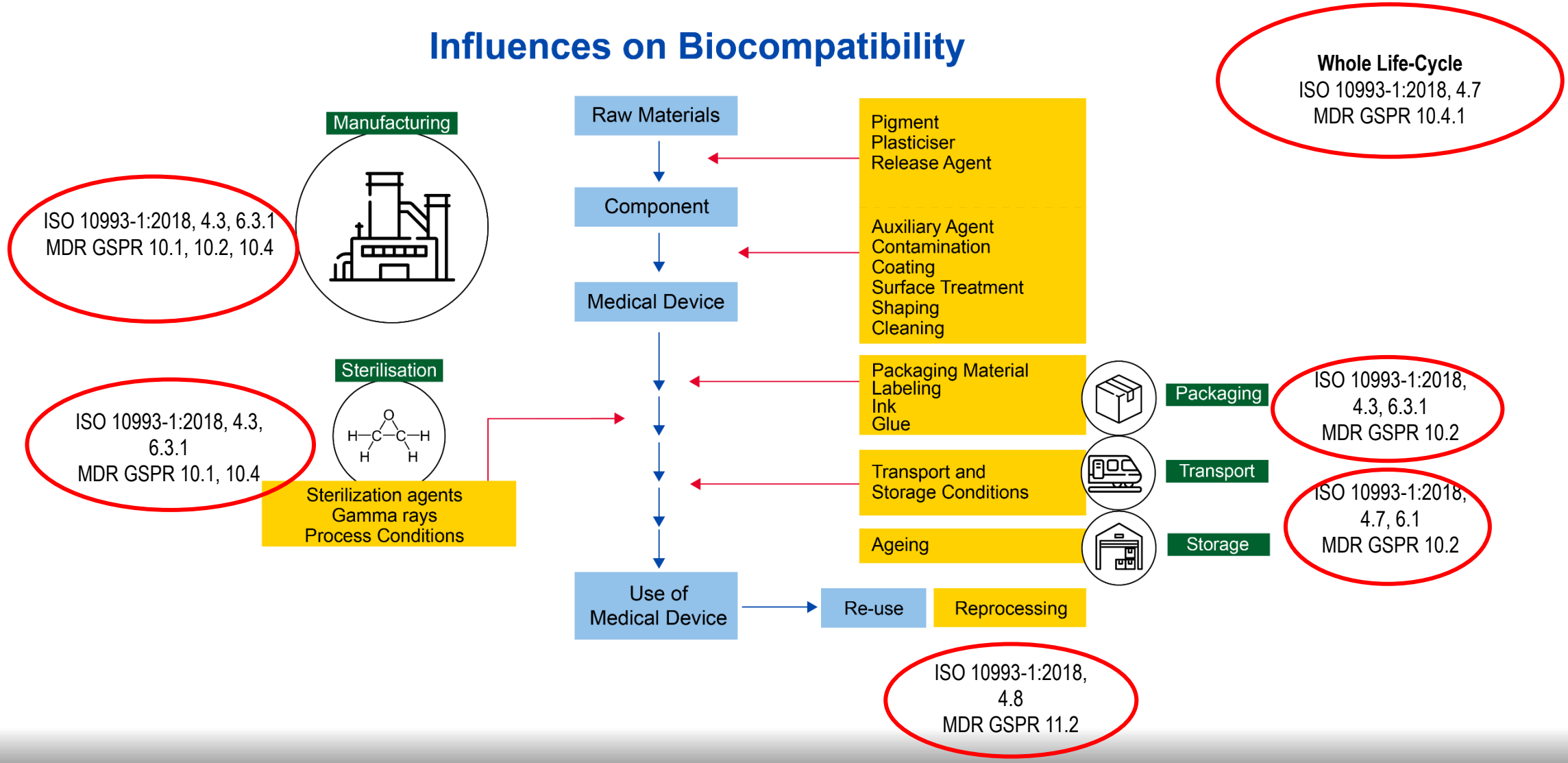
Impact of Packaging Materials on the Biological Safety of a Medical Device

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

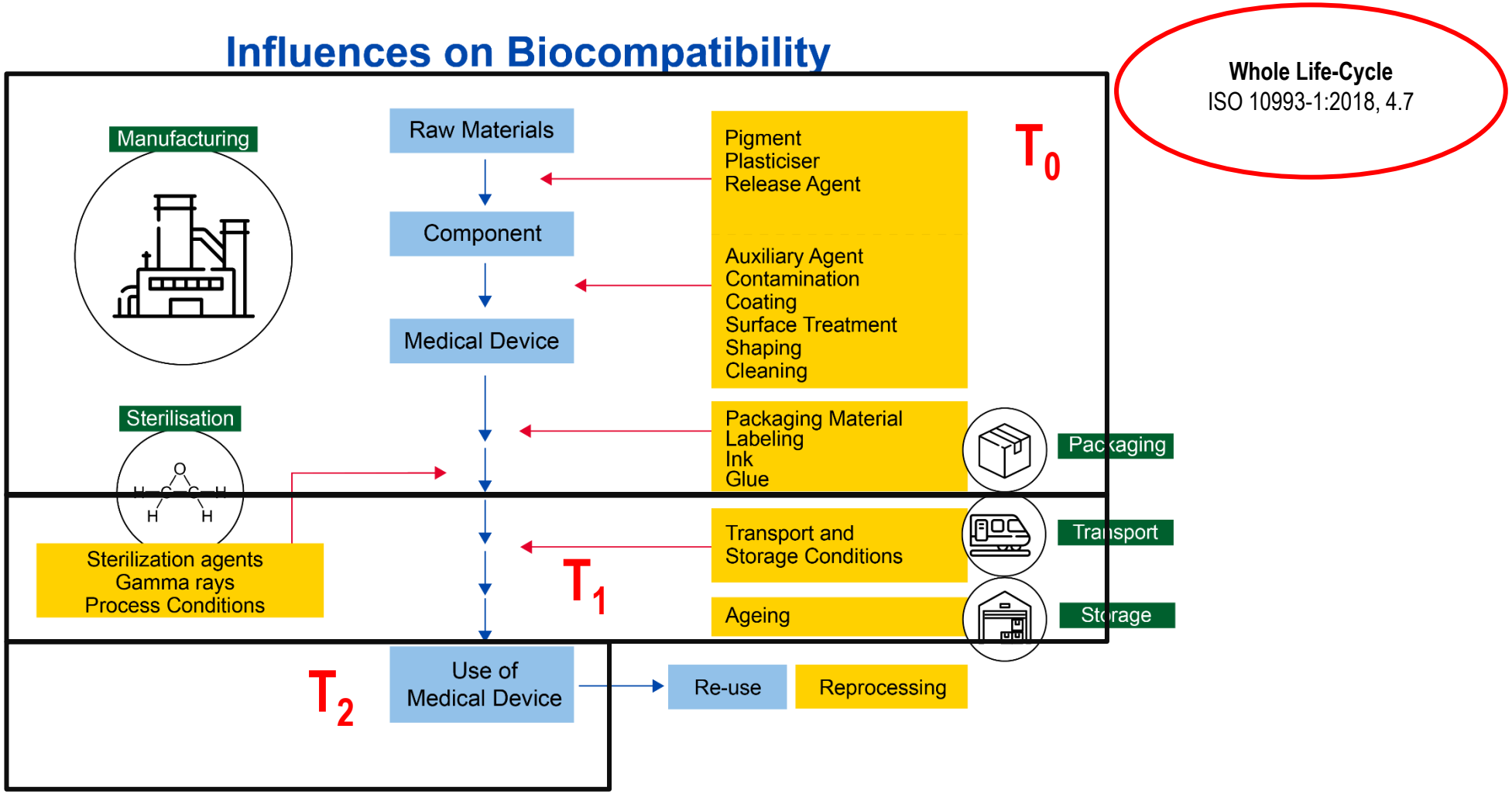


Usually, a solid deivce is less likely to interact with the packaging materials than a device composed of a semi-solid or liquid material

Potential Impacts on Biological Safety



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



T_0 – Manufacturing Process, Packaging, Sterilization

- Raw materials
- Processing aids
- Cleaning agents or contaminations
- Surface treatment
- Transfer of contaminants
- Transfer/migration from glue, ink, label, etc.
- Transfer of packaging migrants
- Material alterations due to sterilization conditions

Endpoint-specific risk-assessment based on chemical and biological data

T_1 – 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)

T_1 – 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 – Material Data from Packaging Materials

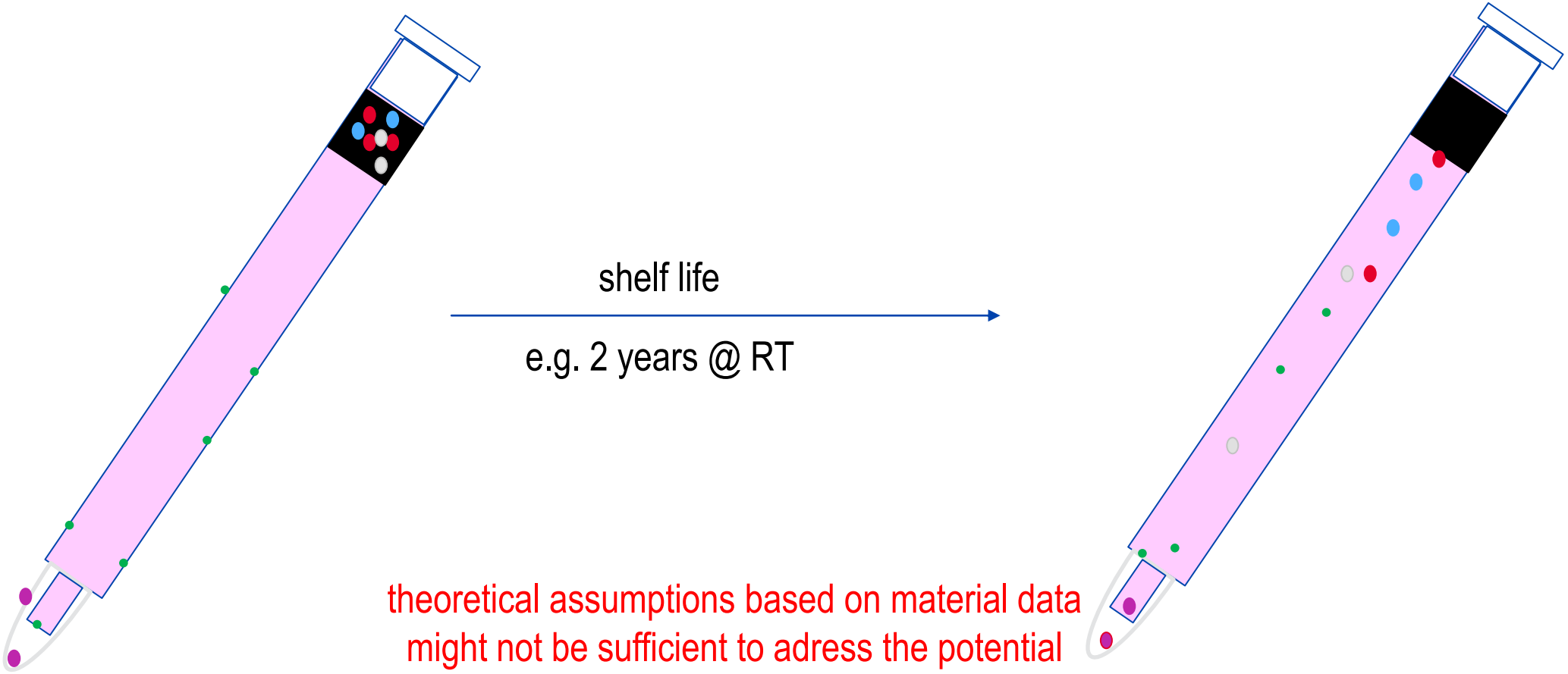
- can be helpful in order to adress the risk of migration of substances from the packaging materials to the device under assessment
- **USP-testing** performed with packaging materials are usually **not acceptable** to adress this risk, usually the following gaps appear:
  - testing is typically conducted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

see also ISO 10993-1:2018, 6.2

T_1 – Example Liquid Device

- Worst case with regard to potential leachables from primary packaging materials
- Leaching takes place during the complete shelf-life

T_1 – Example Liquid Device



theoretical assumptions based on material data might not be sufficient to adress the potential toxicological risk…

T_1 – Example Liquid Device

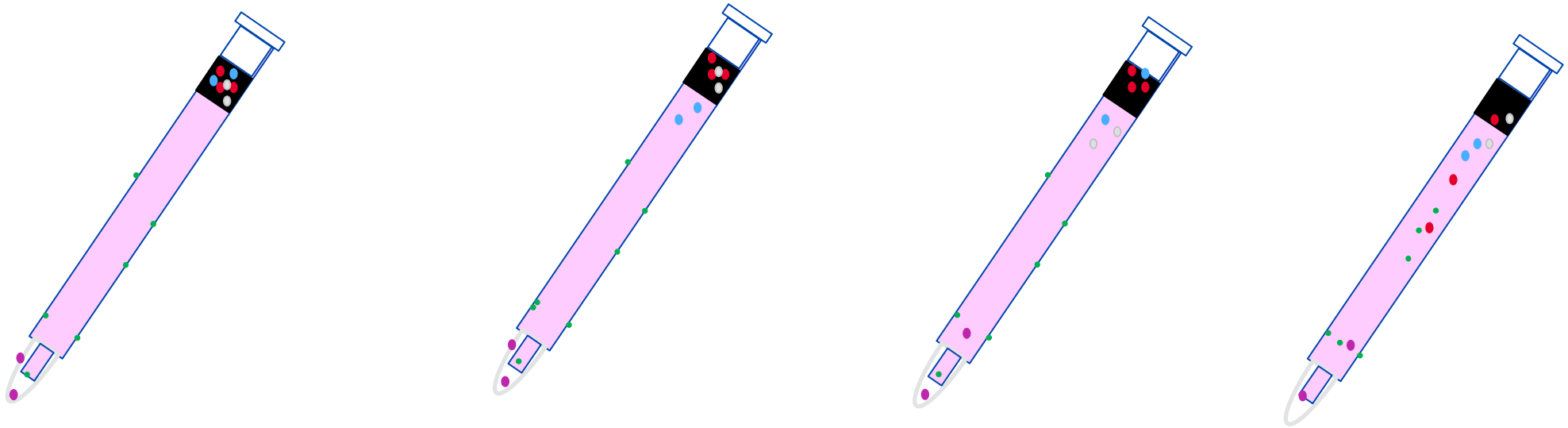
…but chemical analysis of the device after accelerated/real-time aging for this kind of devices often technically not feasible

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

T_1 – 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 / syringed filled with extraction medium already during manufacturing)



Before extraction | Condition 1 | Condition 2 | Condition 3

T_1 – 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 that can be released from the material under assessment – Toxicological Risk Assessment of those is considered to assume the worst case.

T_1 – 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

Questions?

Thank you for your attention!!