Notified Body perspective on CE-marked Medical Devices versus Article 117 MDR combination products

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

- Regulatory background for a Notified Body Opinion (NBOp)
- NBOp versus Declaration of conformity
- Example for a Large Volume Parenteral Packaging Device

The European Approach on Combination Products

MDR (10): Products which combine a medicinal product or substance and a medical device are regulated either under

Regulation (EU) 2017/745 (= MDR)

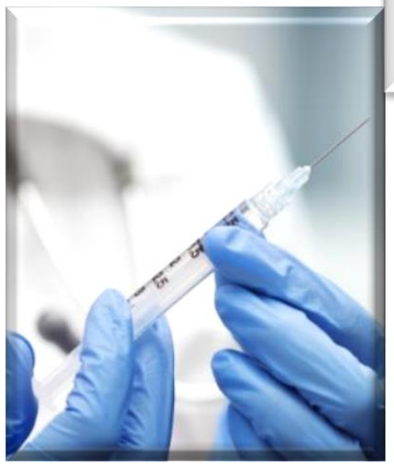
or

Directive 2001/83/EC (= MPD)

There is no discrete Directive/Regulation for “Combination Products”

Either MDR or MPD is the leading regulation/directive

Combination Products leading Legislative Act 2001/83/EC



Device intended to **administer** a medicinal product

Device **incorporating** a medicinal substance

Integral

Medicinal substance: principal mode of action

2001/83/EC Medicinal Products Directive

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Art.117 EU 2017/745

May 26 2021

Medical Device Regulation – Article 117

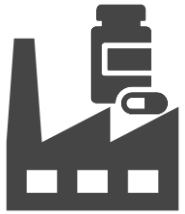
"**If the dossier does not include the results of the conformity assessment** **[….]** and where for the conformity assessment of the device, if used separately, the **involvement of a notified body is required [..]** the authority shall require the applicant to provide **an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I** to that Regulation **issued by a notified body [..]**

EU Certificate and Declaration of Conformity CE

Declaration of Conformity CE

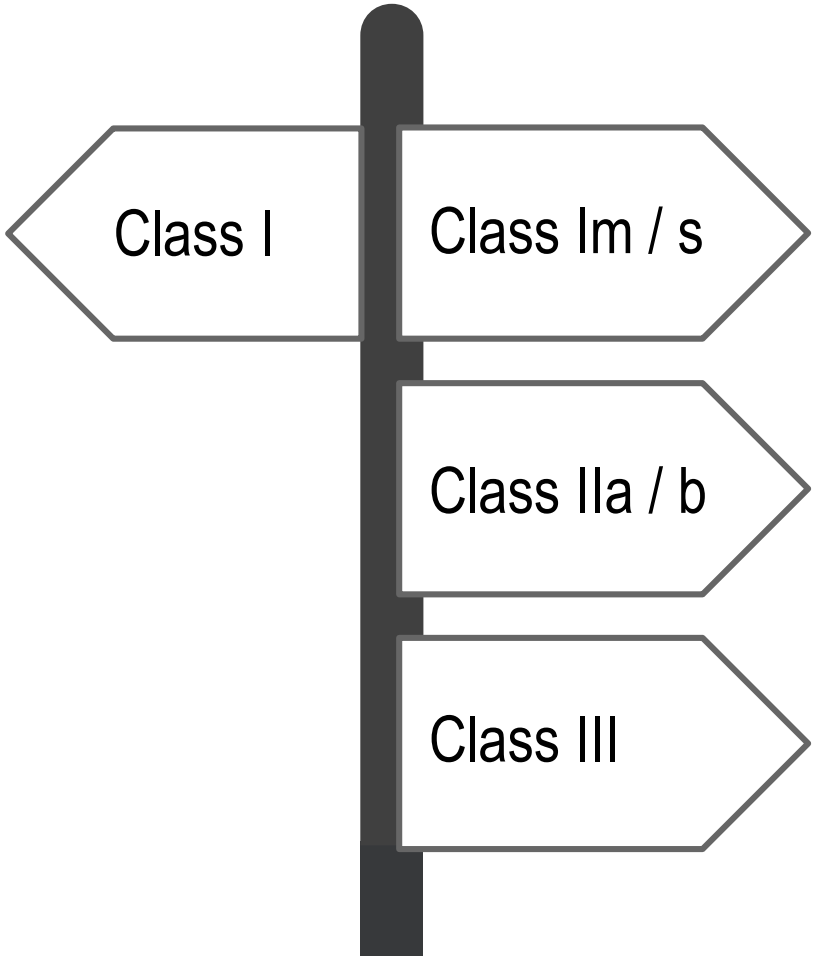
Notified Body Opinion

Risk Classification as Point of Decision on Notified Body Involvement



PHARMA COMPANY

Self-Assessment / Self-Declaration



NOTIFIED BODY

Conformity Assessment
or
Notified Body Opinion

Declaration of Conformity vs Notified Body Opinion

MDCG 2019-15 Guidance

Declaration of Conformity

- MAH becomes Medical Device Manufacturer fulfilling all applicable obligations and requirements of MDR
- Affixing a CE mark to the medical device part
- Put in place a quality management system and draw up the technical documentation According to Annex II and Annex III + Surveillance activities
- Conduct a clinical evaluation in accordance with Article 61, as established in Article 10(3) and Annex XV.
- Assign to the device a UDI which will allow identification and traceability.

Notified Body Opinion

- No obligations as Medical Device Manufacturer
- No CE mark of medical device required
- Quality Management according to the requirements of Medicinal Product Directive
- Clinical Data based on performance
- Labeling requirements following Medicinal Product Directive requirements

NB Opinion: Assessment Focus of Notified Bodies

Conformity of the device part with applicable GSPRs

Assessment of the suitability of a device for its intended purpose, taking into account the relevant quality aspects of the device itself and it's use with the particular medicinal product.
Further aspects of the review process are
complexity of the device,
relevant patient characteristics and
the clinical setting in which the Drug Device Combination is to be used.*

Technical Documentation Assessment limited to the applicable GSPR (Annex I)

* EMA/CHMP/QWP/BWP/259165/2019, Guideline on the quality requirements for drug-device combinations, Draft per May 29 2019

Content of GSPR Documentation submitted

GSPR Checklist

Description of the device part

Instructions for use / package insert of the integral product

Applicability: Yes/No?
No ➔Justification

Methods used to demonstrate conformity

Harmonised standards / Common Specifications
Other guidance or state of the art solutions applied

Identification / Traceability of evidence

Example Large Volume Packaging Medicinal Product – Bag for Peritoneal dialysis - An Art 117 Drug-Device Combination?

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*Immediate packaging of a Medicinal product

*Medical Device

**Combination product acc. article 117

Quellen
*https://ecatalog.baxter.com/ecatalog/loadproduct.html?cid=20016&lid=10001&hid=20001&pid=822129)
**Intrafix® SafeSet (bbraun.de)

Example Large Volume Packaging Medicinal Product – Bag for Peritoneal dialysis - An Art 117 Drug-Device Combination?

"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." Art. 1 (9)

"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." [51] [54]

Quelle: Bauchfelldialyse.pptx (dialysecentrum.de)

Subjected to final decision by EMA

What would the NBOp assessment focus on for a Bag for Peritoneal dialysis?

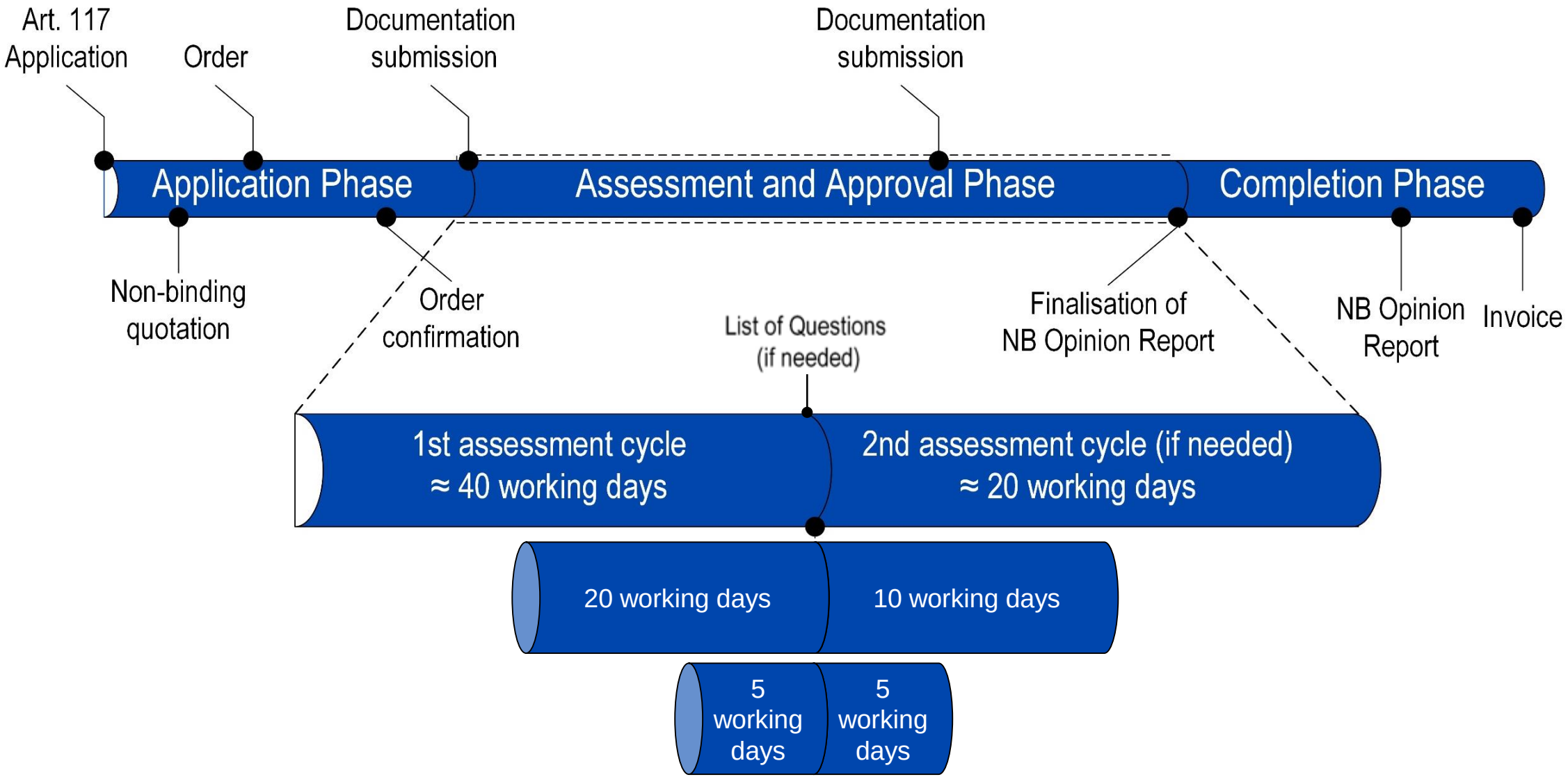
- Conformity of the device part with the applicable GSPRS
- Is the device part designed and manufactured ensuring that the intended purpose can be achieved. Does the drug have negative effects on the functionality of the device?

Sterility in case two times setrilized; device parts in sterile condition

Storage conditions, Transportation, Shelf life

Biocompatibility
Patient and/or user contact with
the device part

Quelle: Bauchfelldialyse.pptx (dialysecentrum.de)


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

- 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

Guidance documents Article 117 “How to”

- Team-NBPosition-Paper-Art117SubChangeLifeCycleMngt-202012

- Multi-stakeholder webinar to support implementation of the Medical Devices Regulation on drug-device combinations | European Medicines Agency (europa.eu)

☞ EMA will address any unanswered questions in a forthcoming update of the

- question and answers on implementation of MDR Article 117

- Team-NB_Position-Paper_on-Documentation-Requirements-Article117-V1.pdf (team-nb.org)

- EMA/CHMP/QWP/BWP/259165/2019, Guideline on the quality requirements for drug-device combinations, Draft per May 29 2019

Thank you!

Questions?

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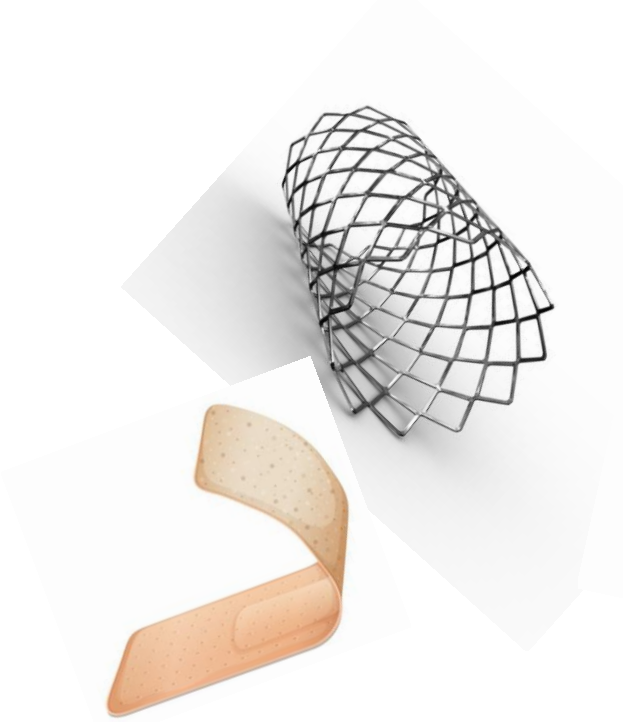
Part II Notified Body Perspective on CE-marked Medical Devices by Dr. Katharina Weidmann

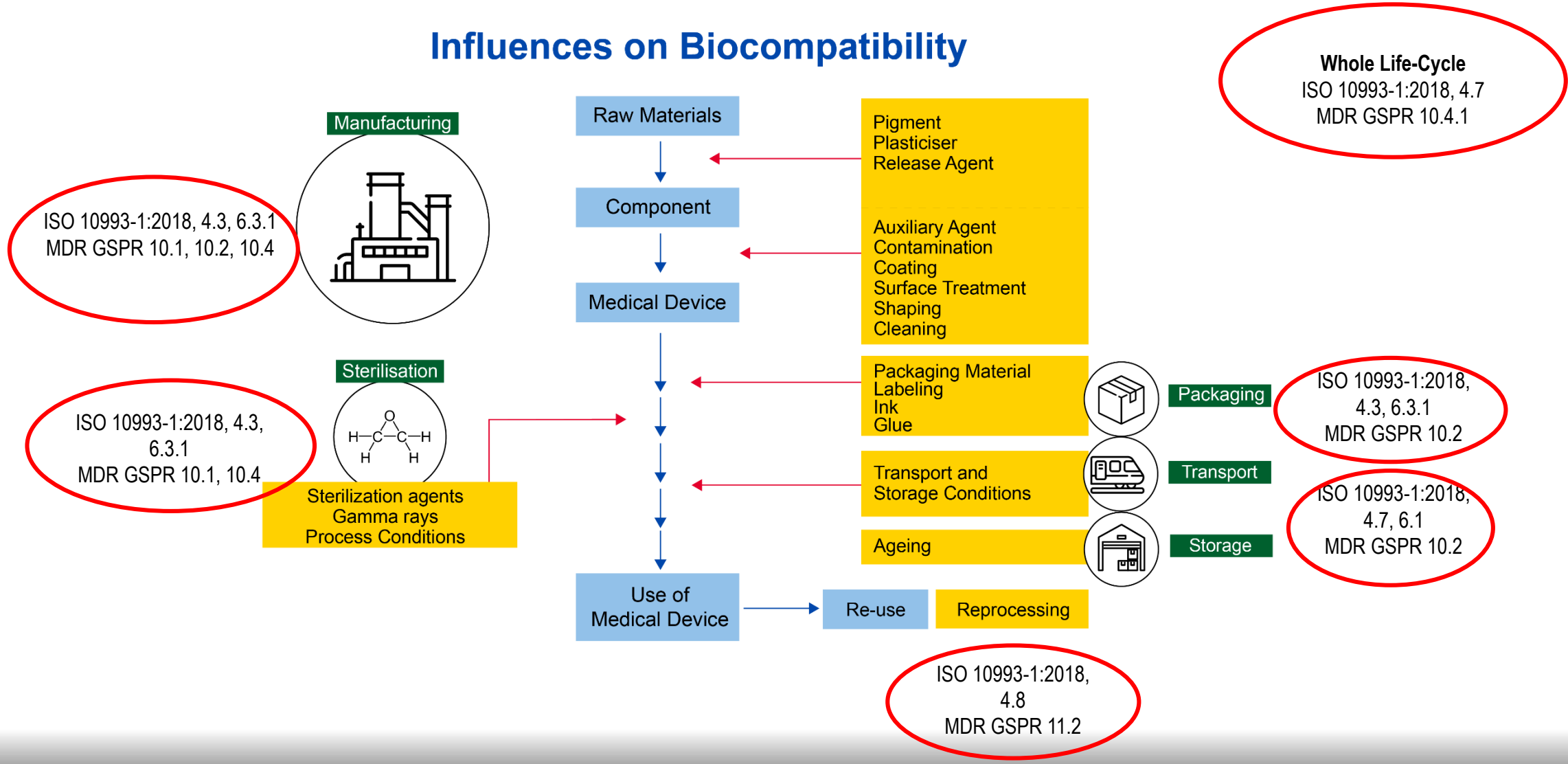
Impact of Packaging Materials on the Biological Safety of a Medical Device

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

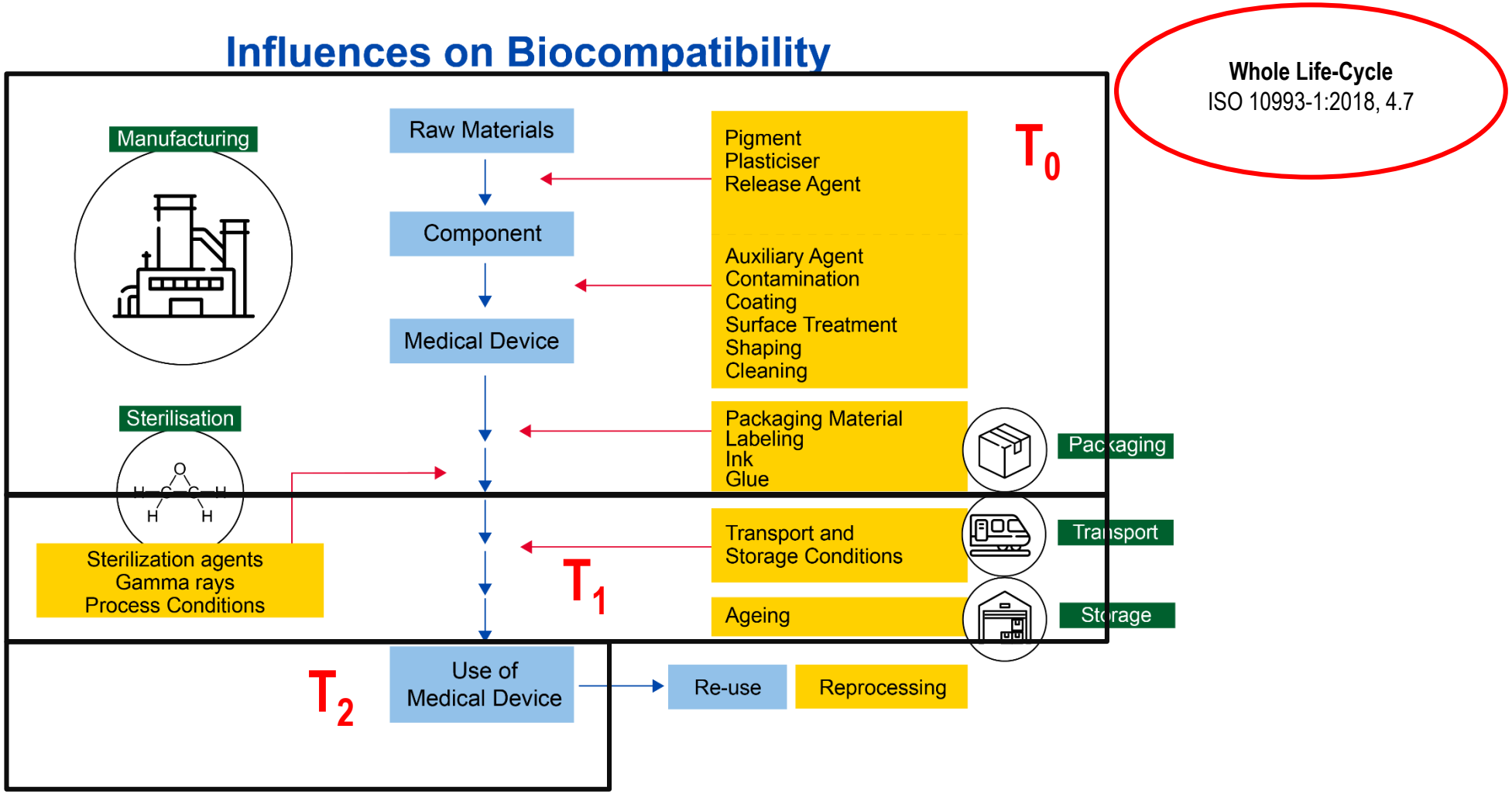


Usually, a solid deivce is less likely to interact with the packaging materials than a device composed of a semi-solid or liquid material

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

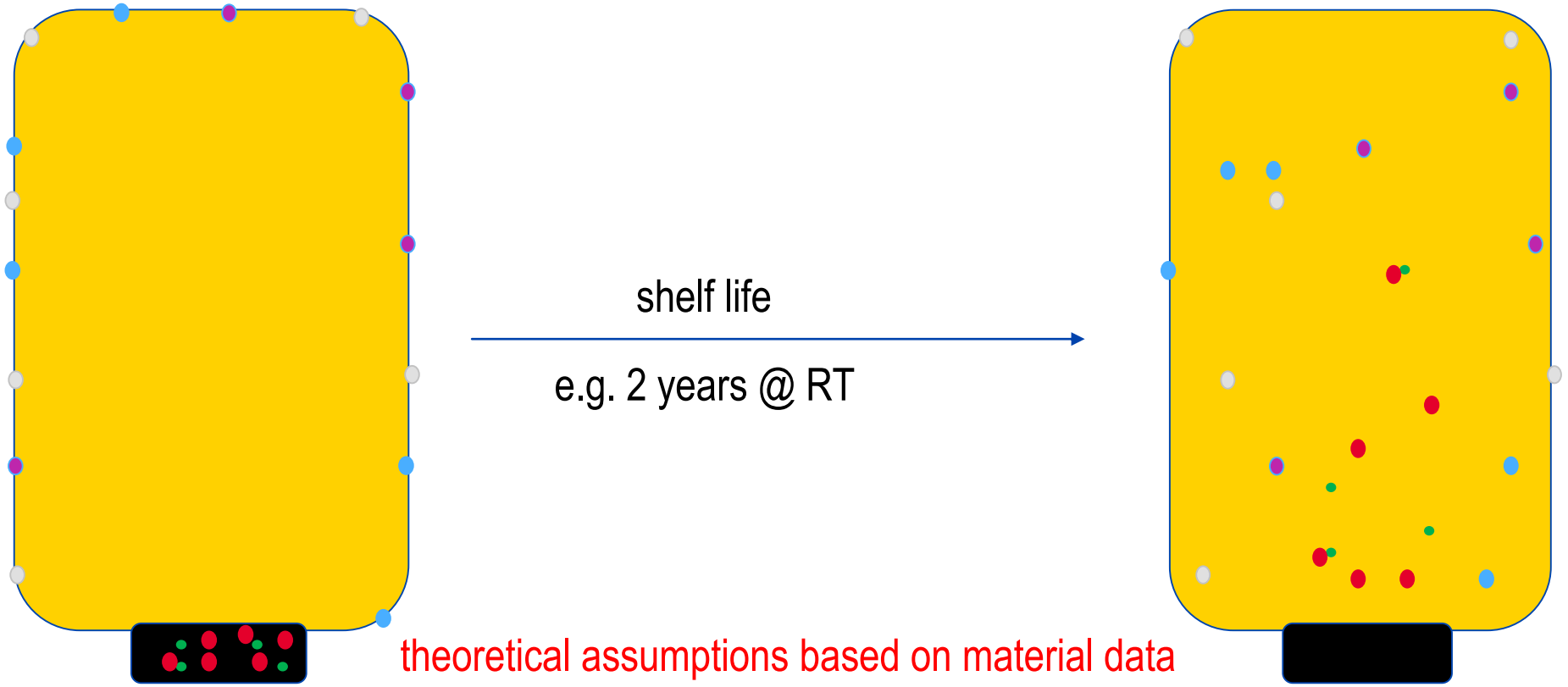
- can be helpful in order to adress the risk of migration of substances from the packaging materials to the device under assessment
- **USP-testing** performed with packaging materials are usually **not acceptable** to adress this risk, usually the following gaps appear:
  - testing is typically conducted 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

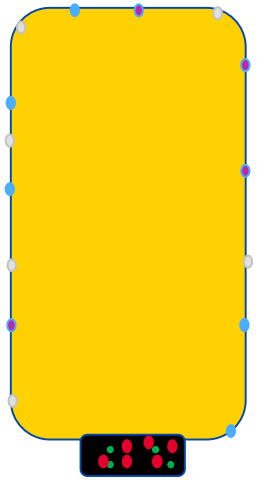
…but chemical analysis of the device after accelerated/real-time aging for this kind of devices often technically not feasible

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

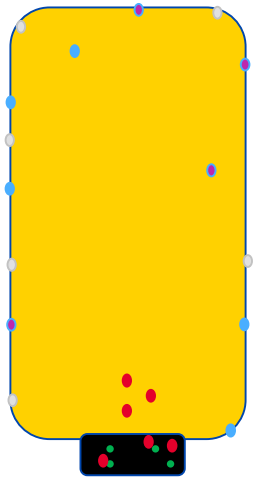
T_1 – Example Liquid Device

Extraction Conditions – Critical for Representativeness of Results:

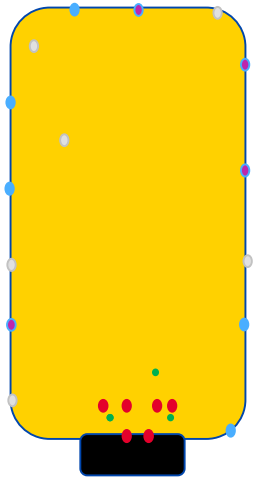
- shall be documented and justified (time, temperature, ratio, solvents)
- shall be relevant for conditions during shelf life
- choice of test sample critical (unfilled syringe / syringed filled with extraction medium already during manufacturing)



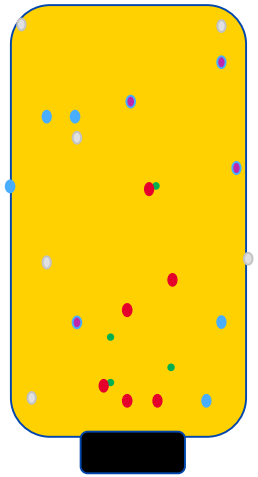
Before extraction



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 the 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!!