Establishing and Maintaining Biological Safety of Medical Devices per ISO 10993-1:2018: *Fundamentals and Impact on Materials*

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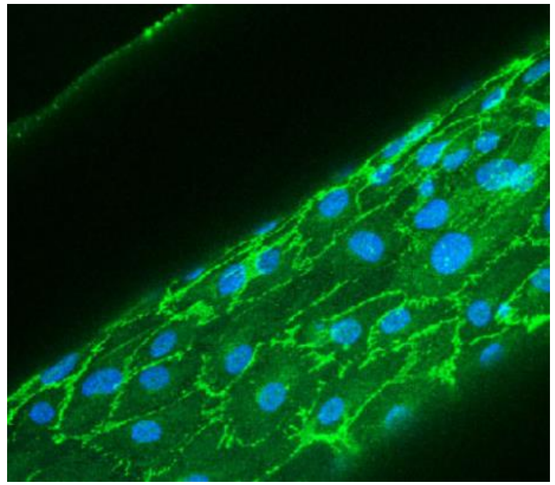
Countries displayed were selected based on familiarity of the presenter and not any ranking system. See publicly available information from each country's regulatory agency for details.

Contents

- Background: Regulations and Standards for Biological Safety of Medical Devices
- Baseline Best Practices & Managing Change
- New Trends in Medical Grade Materials and Impact on Biological Safety
- Definition of Medical Grade Materials & Standardization

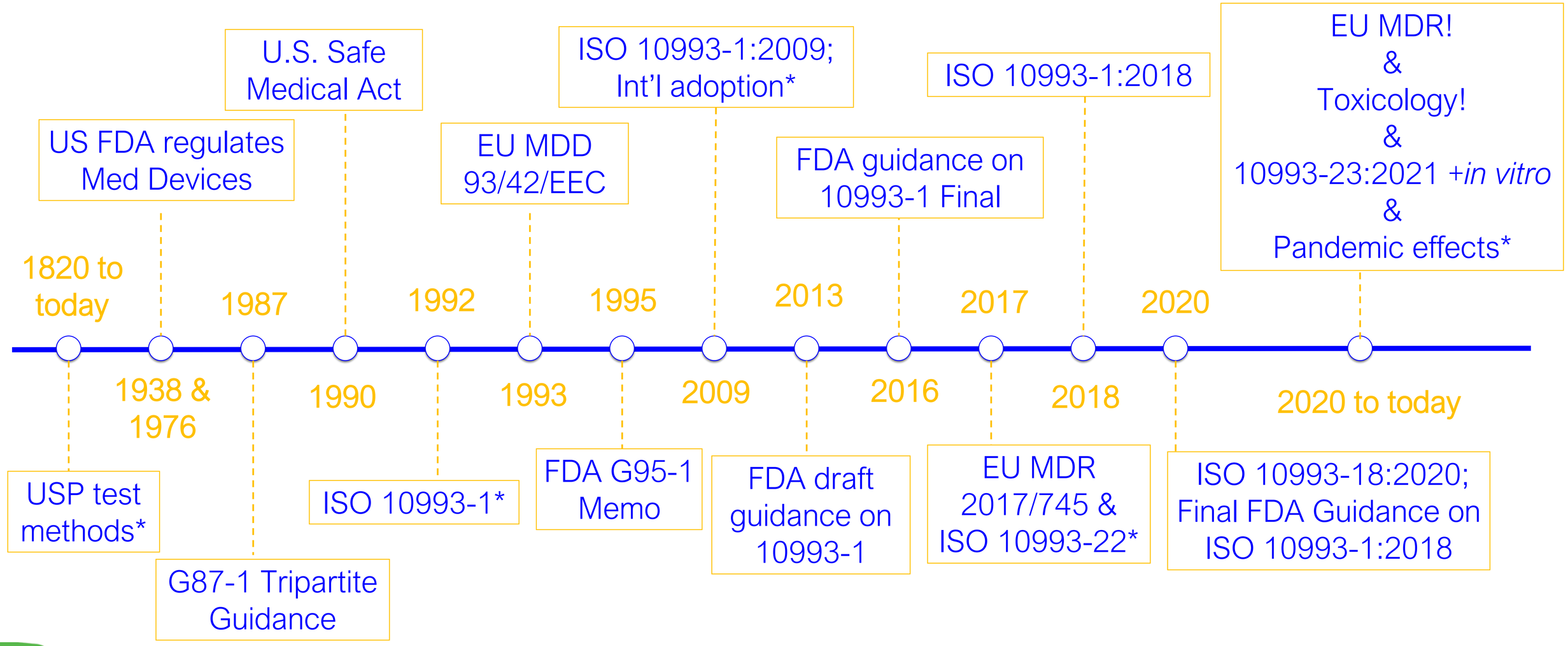
Feb 2023

Motivation: Biological Safety (Biocompatibility) of medical devices is demonstrated by testing and assessments. Medical devices contain a lot of materials!



Background: Regulations and Standards

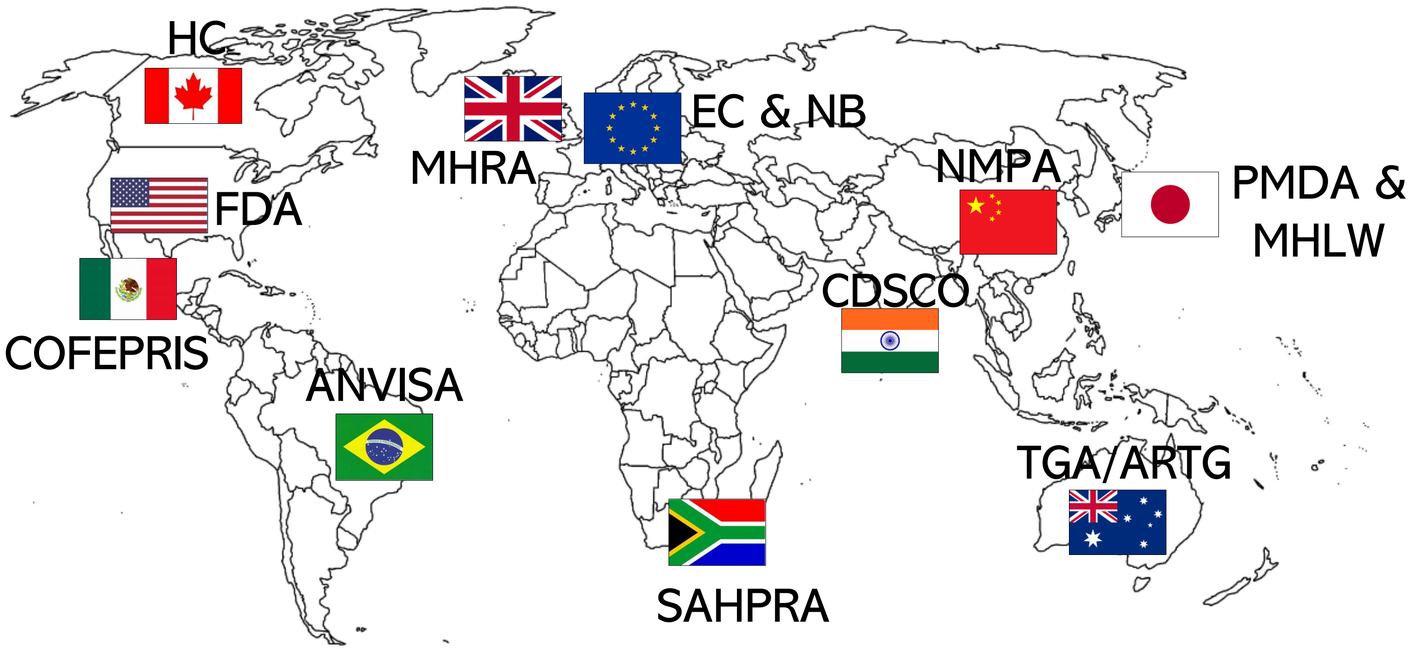
Historical Timeline



Regulations and Standards

- **Primary Standards:** ISO 10993-1:2018 and other ISO 10993-X parts
  - Others may apply: ASTM F2475 for packaging, USP for combination devices, ISO 18562 for respiratory devices, etc.

- **Regulatory Agencies**
  - US: FDA (CDRH for devices, CDER for drugs, CBER for biologics)
  - EU: EC publishes regulations, Notified Bodies enforce them
  - UK: MHRA
  - Japan: PMDA and MHLW
  - China: NMPA
  - Canada: Health Canada
  - Brasilia: Anvisa
  - Australia: TGA/ARTG
  - India: CDSCO
  - Others internationally



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Best Practices per ISO 10993-1:2018

1. Identify device and surgical procedure
2. Categorize device and identify endpoints
3. Collect information
   a) Physical and chemical information
   b) Secondary processes/materials: life cycle, including packaging, cleaning/disinfection/sterilization, storage, etc.
   c) Particulate
   d) Review of literature, similar devices, and bench/clinical data
4. Identify gaps and open risks
5. Select endpoint testing
6. Perform testing
7. Assess final biological safety & any residual risks
8. Update regularly based on new evidence

Pre-ISO 10993-1:2018, records might include items 1, 2, 6, and 7 only.
Shift from ISO 10993-1:2009 to :2018 = more holistic & risk-based with BEP & BER

10993 Endpoints and Test Methods

Caution: some details here are oversimplified; see ISO 10993-1 Table A.1

Endpoint	ISO 10993-x	Typical Method(s)	Device Type
Physical and/or Chemical Information	-1, -18	Material information (BoMs). As needed, E&L Chemical Char.	All
Cytotoxicity	-5	*in vitro:* P, elution, cell lysis, mouse fibroblast cells	All
Sensitization	-10	*in vivo:* P & NP, IC, sensitization, guinea pigs	All
Irritation	-23 (prev -10)	*in vivo:* P & NP, IC, irritation, white rabbit *in vitro:* P & NP elution, cell viability, human epidermis cells	All
Acute Systemic Toxicity	-11	*in vivo:* P & NP, IV or IP, weight & mortality, mouse	All
Material Mediated Pyrogenicity	-11	*in vivo*: P, IV, temp rise, white rabbit	All
Subacute / Subchronic / Chronic Systemic Toxicity	-11, -18	*in vivo:* long-term IV or IP or implantation, mouse/rabbit/rat/etc. *in vitro:* E&L (Chemical Characterization) & TRA/BRA	Implant
Local Implantation Effects	-6	*in vivo:* muscle implantation 1-13(+) wks, white rabbit/etc.	Implant
Genotoxicity	-3	*in vitro* 3 methods: bacterial reverse mutation, mouse lymphoma, mouse peripheral blood micronucleus	Implant
Carcinogenicity	-3, -18	*in vitro:* E&L (Chemical Characterization) & TRA/BRA	Implant
Hemocompatibility	-4	*in vitro:* 4 methods, *in vivo:* 1 method	Blood contact

P=polar extraction, NP=non-polar extraction, IC=intracutaneous injection, IV=intravenous injection, E&L=polar+mid-polar+non-polar extractables and leachables per ISO 10993-18, TRA=toxicological risk assessment, BRA=biological risk assessment.
Sys Tox timeframes = <24h; 1-28d; 1-3mo; 6-12mo

Relevance to Materials Engineers & Suppliers (!)

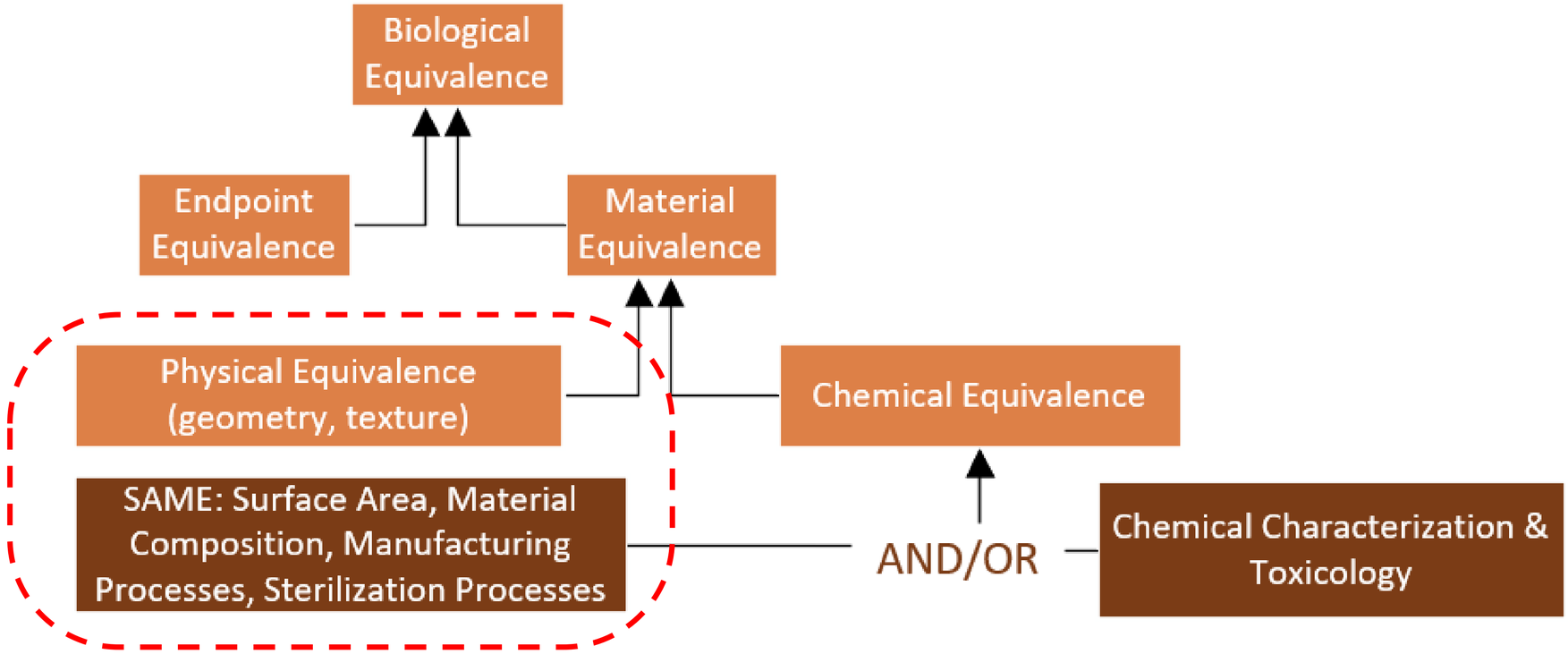
- ISO 10993 test methods are key
  - Historically derived from USP test methods BUT no longer equivalent
- FDA has different requirements than other Regulatory Agencies
  - Registering a medical device is NOT a simple process. Biocomp is one part of several steps
- FDA Devices split into Class I / Class II / Class III
  - Medical resins are often split in a similar way, although more informally:
    non-patient contacting / <24h short duration / >24h long duration
  - Note International Device Classes often I->IV
- Regulatory agencies care about endpoint testing of finished devices, not resins or components
  - But there are exceptions, especially for changes

Baseline Best Practices & Managing Change

Managing Change

- ISO 10993-1, ISO 10993-18, EU MDR (see MDCG 2020-5 and NB guidance), and 2020 FDA Guidance emphasize risk of changes to any patient-contacting components/materials

IF CHANGE is Same or Lower Risk in these categories, then testing may be avoided.
High bar!



Relevance to Materials Engineers (!)

- The biocomp world has:
  - **Already shifted** to more inclusive assessments and tighter scrutiny of biocomp documentation
  - **Currently shifting** to international harmonization, more *in vitro* testing, and more toxicology

  → Changes to materials and processes are special concerns

  → Focus on chemical information & secondary processes/particulates

- Resins with Cytotox/USP Class VI/etc. testing records can help MDM's reduce the risk of adopting these resins
  - BUT this data does not typically help with regulatory approvals

- To support new PD and changes, MDM's need resin suppliers to provide more chemical composition information
  - "Medical grade" resins are helpful for this…

New Trends in Medical Grade Materials and Impact on Biological Safety

Med Device OEM's Ever-Evolving Regulatory World

EU Standards, Directives, and Regulations

Driving intense scrutiny of the *chemistry* of the raw materials (polymers, metals, lubricants, packaging, inks, electronics) used in our devices

Pkg-Pkg Waste
DIR 94/62/EC
DIR 2005/20/EC
EN 13427: Pkg/Pkg Waste
EN13428: Minimize Design
EN 13429: Reuse
EN 13430: Recycling
EN 13431: Energy
EN 13432: Composting
ISO 11465: Plastic Marking
ISO 1043: Plastic Symbols
DIN 6120-1: Label Graphics
DIN 6120-2: Label Marking

Batteries
DIR 2006/96/EC
Battery Labeling

WEEE
DIR 2012/65/EU
DIR 2002/96/EC
EN 50419: Label

EU RoHS
DIR 2011/65/EU
EN 50581: Tech File
EN 62321: Measure
EN 62474: Matl Dec
TS 52476: Guide RoHS

China RoHS
Labeling of electronic devices required
Table of Toxic Substances in IFU

Med Electrical Equip
EN 60601-1-9: Envr Design

REACH
REG 1907/2006
Substances of Very High Concern, required to be in IFU customer communication strategy
Inventory Notification to Authority required.
Development of Safety Data Sheets (SDS)
Global Harmonized Standard (GHS) warnings in IFUs
Classification Packaging Labeling (CLP)
Hazard Labeling (if required in country)

MDD (Medical Device Directive)
DIR 2007/47/EC
EU MEDDEV 2.5/9: Latex
EN 15986: Phthalate
ISO 15223-1: Label Symbols

MDR (Medical Device Regulation), 2016
CMR/EDC substances >0.1% w/w
Classification of all substances in device including polymers and metals
Warning symbols required
Customer communications

Biocide Product Regulation (BPR)

Number of ***Chemicals*** of Concern:

REACH/SVHC	- 224 for now
RoHS	- 10
CA Prop 65	- 1200 for now
EU MDR (from CLP) currently (increase once they add Endocrine Disruptors under BPR)	- 1600
CONEG & EU Packaging Stds.	- 3
SIN List / TedX / CoRAP / Other Watch Lists potentially	- 2000
Customer Concerns	- PVC, Latex, etc.
PFAS	- 12,600+

Constraints

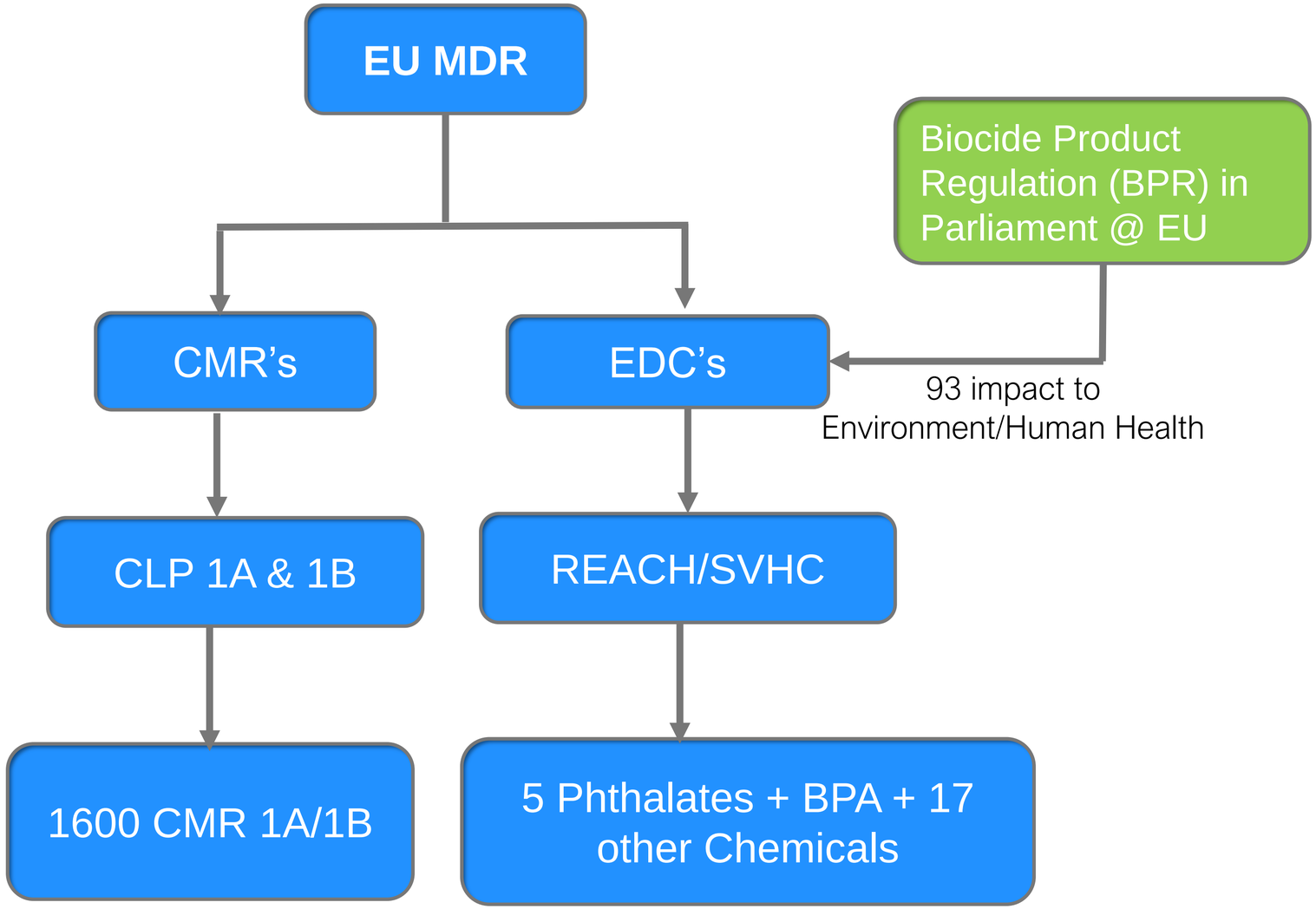
- Conformance with the new EU Medical Device Regulations (MDR) is a significant business challenge today
- Medical device manufacturers must now overcome this challenge in order to have continued access to the European (EU) market
- This is limited to patient contacting materials in medical devices

New Expectations

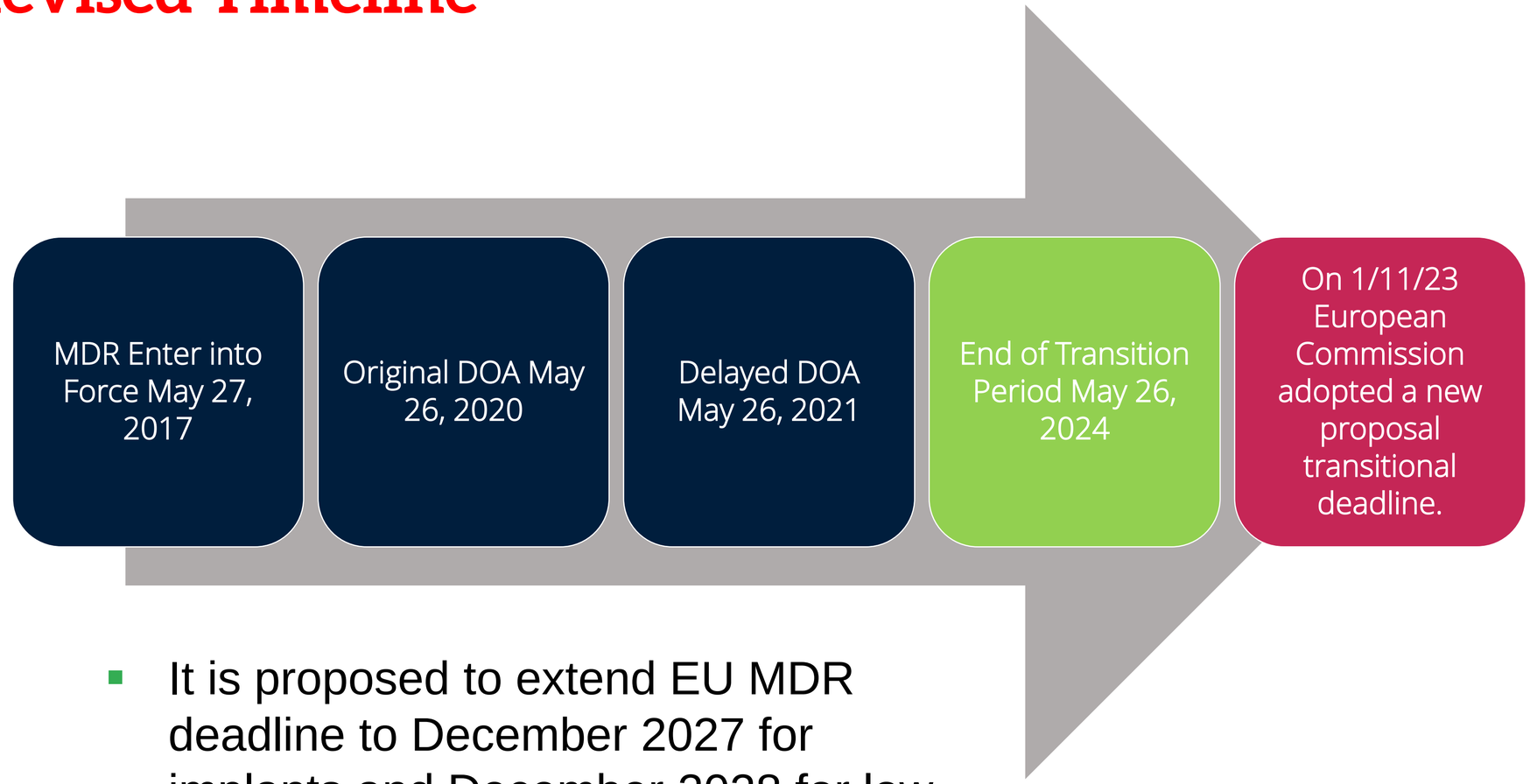
- To meet this new challenge, medical device OEM's must proactively begin strategizing a methodology to comply
- Renewal cases of product registration needs to be EU MDR compliant
- Notified bodies such as TUV and BSI must be recertified to enforce this new requirement for product registration and renewals

EU MDR in Flow Chart

- EU MDR states in Annex I, Section 10.4, that devices containing more than 0.1% w/w of a carcinogenic, mutagenic, reproductive toxicants (CMRs) and/ or endocrine disrupting chemicals (EDCs) will require review, justification, and labelling
- Currently approved medical devices will have a transition period to meet the new EU MDR sunset dates.



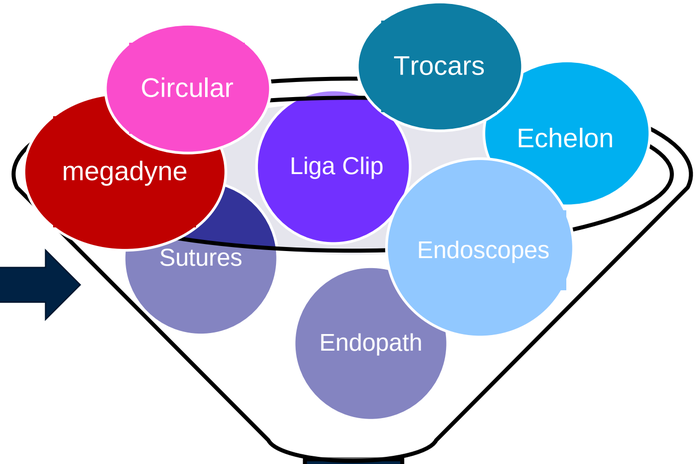
EU MDR Revised Timeline



- It is proposed to extend EU MDR deadline to December 2027 for implants and December 2028 for low-risk medical devices.

Maintaining biological safety for legacy devices – re-registration

- Been on the market for two/three decades
- Approved under MDD
- FDA/Health Canada/ MHRA UK /OUS approved



- Device level of CMRs 1A/ 1B and EDCs evaluated per section 10.4

Results based on material composition analysis

Strategy = reactive

No CMRs/EDCs

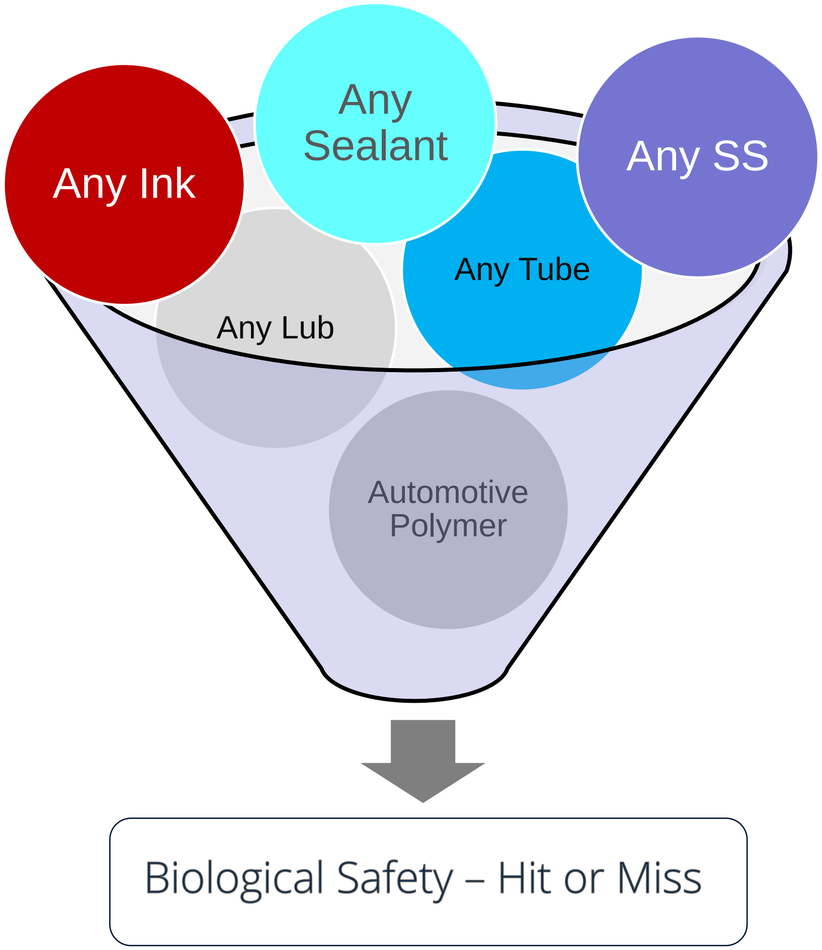
Yes CMRs/EDCs

CMRs and/or EDCs Present > 0.1 w/w ?

Provide Justification for Use/ Label

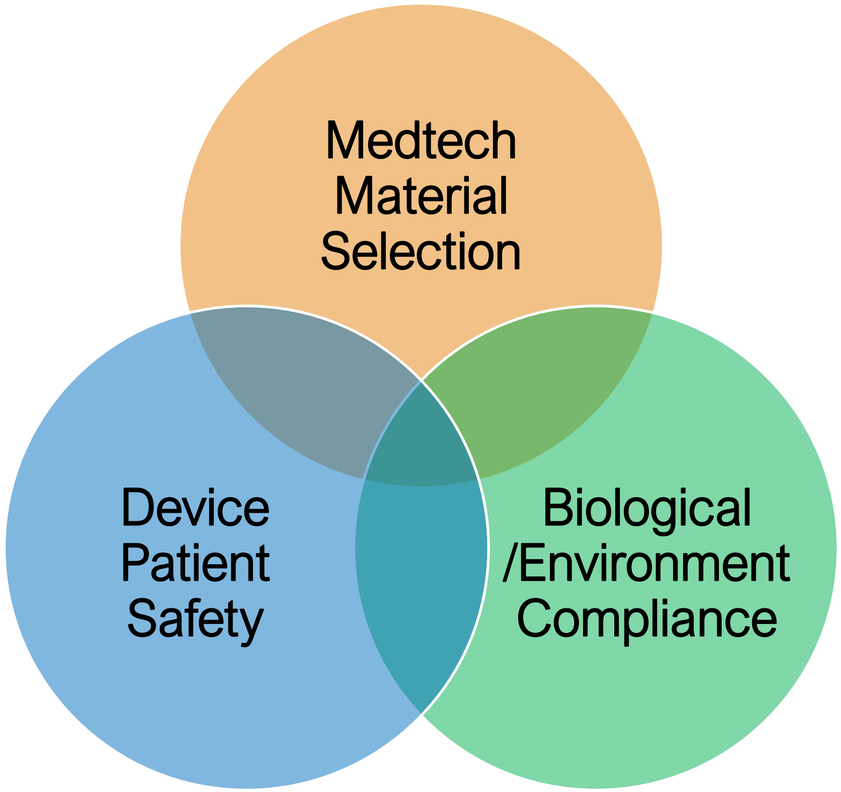
Demerits:
- Force screen for compliance
- Unplanned labeling of devices
- Outright discontinuities of devices
- Impact to patient

Legacy Approach of Material Selection – Prior Art



- Material selection made from external data sources designed specifically for automotive & aerospace e.g. Campus, Material Universe, prospector etc.
- Simulation analysis (mold flow/Moldex3D) was conducted with characterized data intended automotive /aerospace industry
- Medical prototyping built with available automotive materials in prototype shops e.g. GMP.PC.002, GMP.PP.001
- Material selection focused on physical and functional properties only – biocompatibility was an after thought

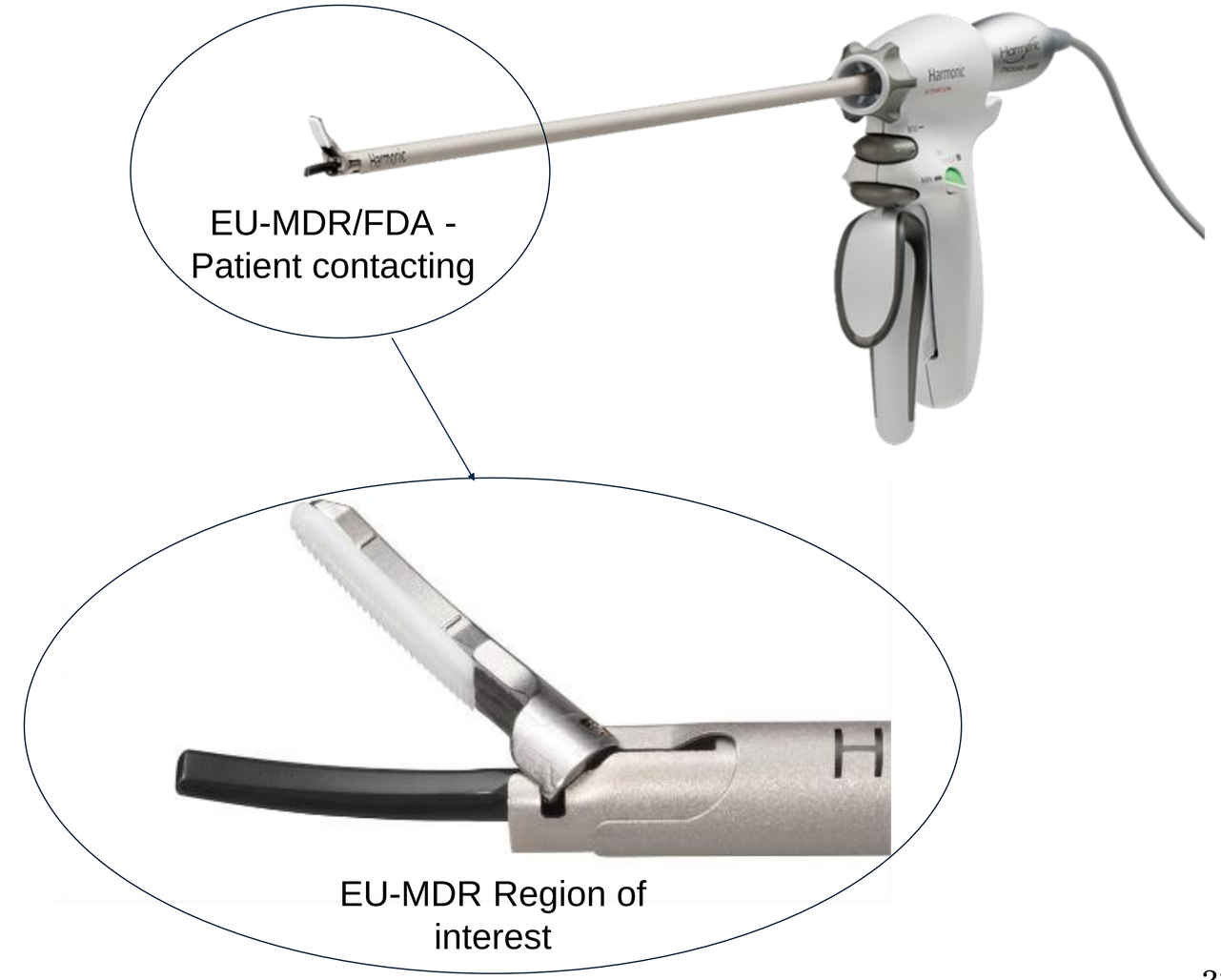
Future State - Interconnectivity Model



- For decades, the business case did not warrant the need to invest in medtech materials until now with the introduction of digital and robotic surgery instruments & changing regulations
- No formal definition for medical materials existed – lacks guideline
- To meet FDA,MHRA and EUMDR requirements, you either hit or miss

Future state - Device Case Study

- For new product development cases
- The adaption of *medtech material selection* strategy to enhance compliance to ISO 10993 -2018, EU MDR compliance /US FDA/OUS Regulations



Generic Bill of Material for a Medical Device

Part Name	Part Number	Material Generic Name	Material Trade Name	Req. Contact (Toxicologist)
Spring Retainer Pin	D44666P01	Stainless Steel	UNS S42000 DIN EN 10088 1.4021	Yes
Pivot Pin Small	D44665P01	Stainless Steel	UNS S42000 DIN EN 10088 1.4021	Yes
Spring Instrument	D44668P01	Stainless Steel	UNS S42000 DIN EN 10088 1.4021	Yes
Shaft Right	D44653P01	Stainless Steel	UNS S42000 DIN EN 10088 1.4021	Yes
Shaft Left	D44659P01	Stainless Steel	UNS S42000 DIN EN 10088 1.4021	Yes
Cutting Blade	D44432P01	Titanium	Medical grade Titanium Grade 1	Yes
Handle Right Plastic	D44653P01	PEBAX 7233 SA 01 MED	Internal specification	No
Handle Left Plastic	D44659P01	PEBAX 7233 SA 01 MED	Internal specification	No
Premium Mineral Oil	N/A	White Mineral Oil	Cutting Oil – processing aid	Yes

Holistic Material Selection Approach for MedTech Applications

- Selecting from ISO 10993-compliant biological evaluated materials – vetted by supplier
- Materials that are either ETO, radiation, autoclave sterilizable, etc.
- Using materials designed and approved by material manufacturer for targeted use (use of questionnaire)

Use of Vendor-Proven Medtech Materials / Selection Philosophy

Medical Grade Processing Aids

GMP

Review vendor disclosure information for patient contacting part of the device.

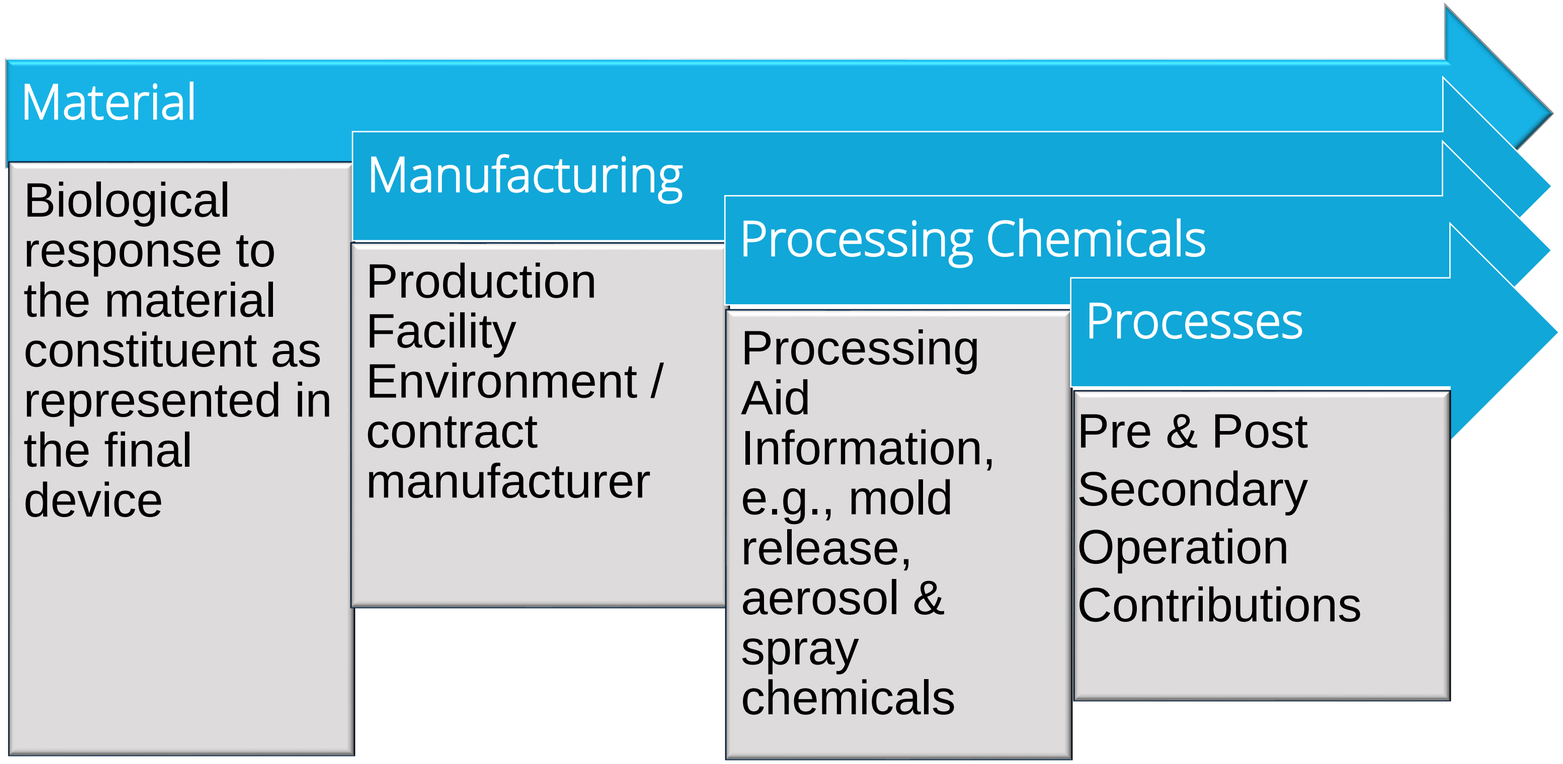
Device OEM to focus on device biological safety

Evaluate CMR's/EDCs if > 0.1% w/w & ISO 10993-1:2018

FDA, MHRA, Health Canada

Will abandon black box material use for Medtech applications

Adaptation of E2E Material Mgmt. per – ISO 10993-1:2018

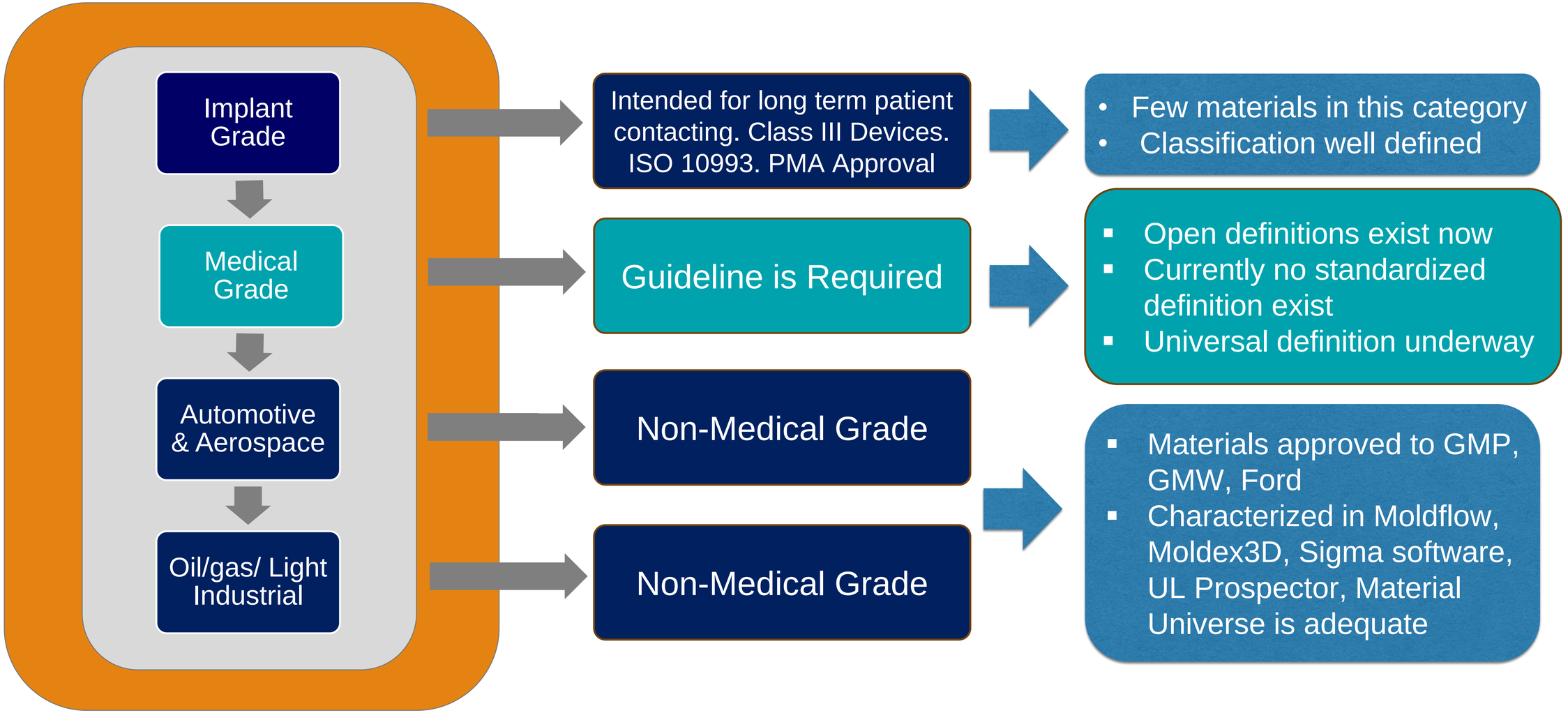


- Chemical characterization information, collected, generated and augmented with additional supporting information is appropriate for supporting the overall biological safety of the medical device.
- Information to be used to determine the level of chemical substances that might be leached from a medical device under clinical use.

EU MDR Regulation/US FDA/OUS

Definition of Medical Grade Materials & Standardization – MGMC Guideline

Changing Regulation Driving Medtech Material Management



North America MGMC

Open Definitions

Care Grade	Implant Grade
ColorRx	MED = Medical Grade
Dental Grade	Mevopur = Medical Masterbatch
Excipient Grade	MT= Medical Technology
FC = Food Grade	NS = No Substitute Grade
H = Health Care Grade	ORG = Operating Room Grade
HC = Health Care	PCG = Pharmacopeia Compliance Grade
HC = Health Care Grade	PG = Premium Grade
Health Care Grade	Premium Grade
Health Care Plus	Pure = Pure Grade
Health Care Unit Grade	Regulated Grade
HMG = Health Management Grade	Rx = Medical or Pharmaceutical Grade
HP = Health Care Policy	SC = Specialty Grade
HP = Health Care Policy Grade	SC = Sustainable Grade

Draft Guidelines for Medtech Grade Materials

General Assurance	Regulated Grade	Non-Regulated Grade
Complaint to FDA and EU Requirements	Yes	No
Avoidance of CMR 1A /1B & EDC's	Yes	No
Certified biocompatibility (USP Class VI/ ISO 10993)	Yes	No
Notification of Change	Yes	No
Support Regulatory Approvals	Yes	No
Change management to GMP-Principles	Yes	No
Expanded Certificate of Inspection	Yes	No
Animal and latex-free Formulation	Yes	No
DMF	Yes	No
Packaging/transportation	Yes	No

Reference white paper and draft guideline 1.0 released December 2022

Medical Grade Vs. Non- Medical Alternative

PEBAX® 7233 SA 01 MED

Polyether block amide Pebax® 7233 SA 01 MED is a thermoplastic elastomer made of flexible polyether and rigid polyamide. This grade offers the highest quality and it is specially designed to meet the stringent requirements of the medical applications such as minimally invasive devices. Pebax® 7233 SA 01 MED also offers an excellent combination of properties such as: kink resistance, low friction coefficient and superior dynamic response. Upon request, letters regarding USP Class VI compliance can be provided.

MAIN CHARACTERISTICS

Property	Typical Value	Unit	Test Method
Density	1.01	g/cm³	ISO 1183
Water Absorption at Equilibrium At 20°C and 50 % R.H.	0.7	%	ISO 62
Water Absorption At 23°C and 24 h in water	0.9	%	
Melting Point	174	°C	ISO 11357
Vicat Point Under 1 daN	164	°C	ISO 306

PEBAX® 7233 SA 01

Polyether block amide Pebax® 7233 SA 01 is a thermoplastic elastomer made of flexible polyether and rigid polyamide. This SA grade is suitable for food contact applications.

MAIN CHARACTERISTICS

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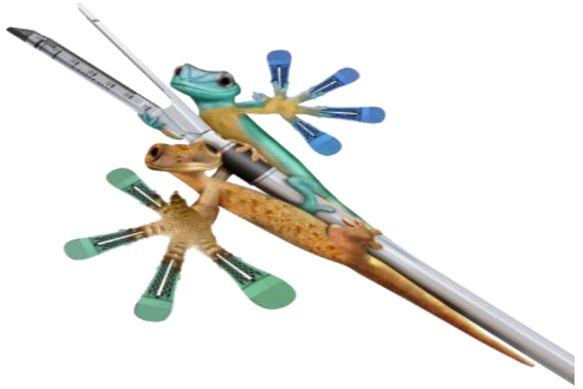
Vicat Point Under 1 daN	164	°C	ISO 306

Courtesy of Arkema

Conclusion

- Evolving regulations are a moving target
- Using medical grade materials provide confidence that devices will pass biocompatibility testing per ISO 10993-18
- Device OEM is still responsible for ensuring device biological safety
- This new approach will prevent labeling surprises
- The use of medical grade materials will minimize potential use of chemicals that could be carcinogenic, mutagenic, or toxic to reproduction (CMRs) substance or endocrine disrupting compounds (EDCs)



Thank You!
Q&A

Acknowledgements

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