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MEDICAL RESEARCH ORGANIZATION

Clinical Evaluation under MDR and MEDDEV 2.7/1 revision 4 : how to combine with some Biocompatibility to secure the outcome?

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EU MDR (5 May 2017)

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Definitions

- Clinical Evaluation – before (MEDDEV rev3)

The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.

- Clinical Evaluation – MEDDEV rev4

a **methodologically sound ongoing procedure to, collect, appraise and analyse** clinical data pertaining to a medical device and to evaluate whether there is **sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance** when using the device according to the manufacturer's Instructions for Use.

- Clinical Evaluation – EU MDR

a **systematic and planned process to continuously generate, collect, analyse and assess the** clinical data pertaining to a device **in order to verify the safety and performance** , including clinical benefits of the device when used as intended by the manufacturer.

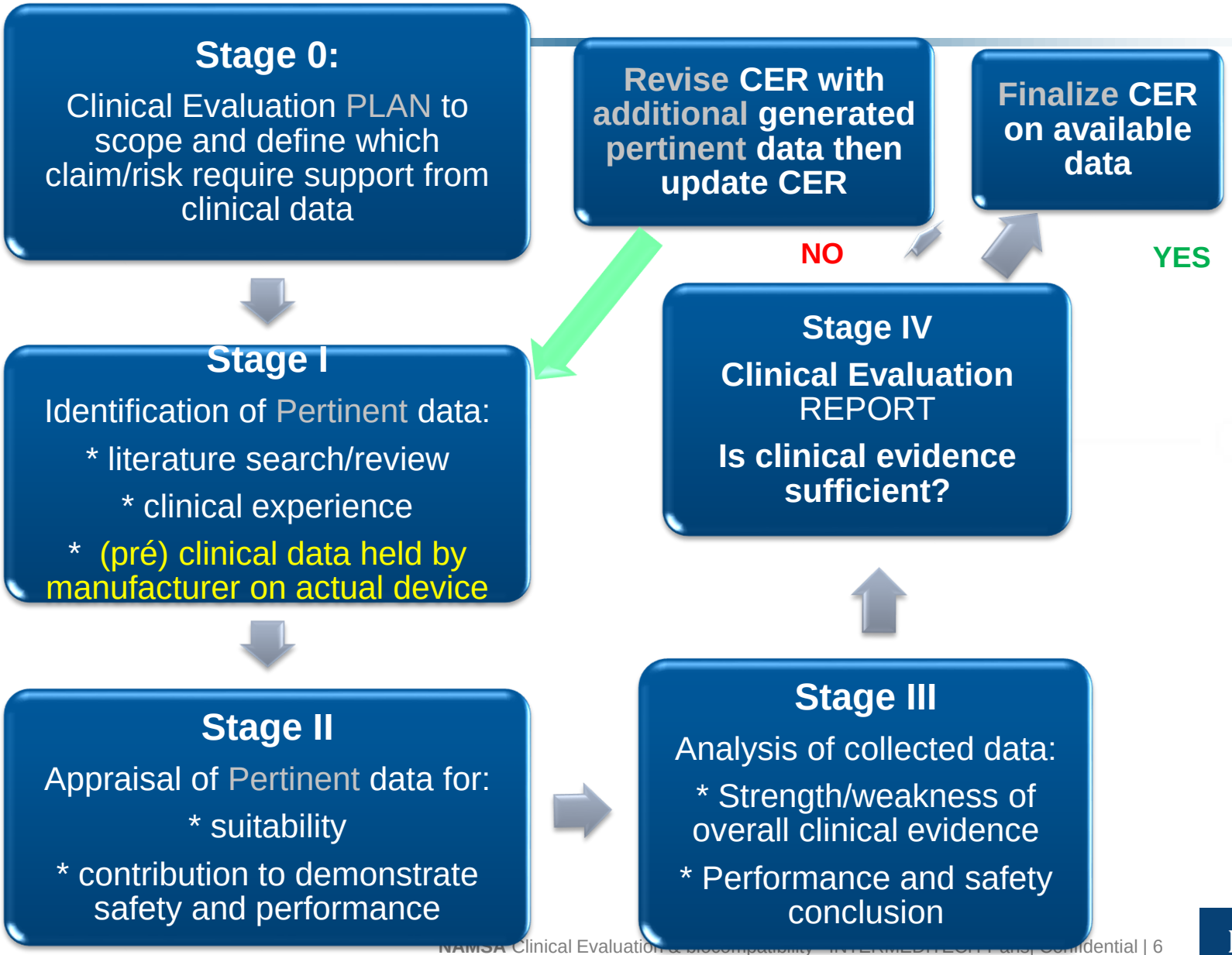
Clinical Evaluation Strategy – EU MDR

- **Plan**:
  - For class IIb implantable and III : Expert panel to advise on the Manufacturer's intended clinical development strategy.
  - Is the device under evaluation equivalent to an already marketed device from same manufacturer and also compliant with GSPR ?
  - OR is my device equivalent to another manufacturer's with whom I have a contract in place for accessing all Tech File and the device comes with sufficient clinical data
  - OR is my device equivalent to a lawfully marketed device exhibting sufficient clinical data or compliance with applicable Common Specification?
- **Do** :
  - Assess on literature available IF the publication is about an EQUIVALENT device demonstrated as such

Clinical Evaluation Strategy – EU MDR

- **Check** :
  - Assess on compliance of retrieved data against GSPR from EU MDR
  - Assess on potential currently available alternative methods
- **Act**
  - Generate complementary Clinical Data as needed (pre-submission and/or post market clinical follow up)
  - Verify and comply with applicable requirements based on the population intended to be treated
    - Incapacitated patients/subjects (art. 64)
    - Minors (art. 65)
    - Pregnant or breastfeeding women (art. 66)
  - Update your CERs as required (annnually for high risks or new technilogies, 2 to 5 years for others)
  - Gather data continuoulsy to proove your Clinical Benefit / Clinical Risk ratio

CER : a 5+ phases process



Appraisal / assessment of pertinent data- stage II-

- Critical evaluation
  - Qualifications of the Evaluator(s)
  - Independance of the Evaluator(s)
  - Procedure : pre-defined tools for evaluation (with quantitative scores, rankings, levels of evidence …)
- Allocation of Pertinent Data
  - To the State Of the Art
  - To Clinical Evidence
- Appropriate Use of Equivalence (see next slides)
- Ultimately assess on
  - **Relevance** of the data (Device, Indication, Population, Statistics)
  - **Scientific Validity** (Level of Evidence of each data)
  - **Weighting** (combination of the above)

Equivalence Assessment

Similar definition between MDR (4a Annex XIII) and MEDDEV 2/7.1

- **Technical**: similar design
- **Biological**: same materials or substances in contact with the same human tissues or body fluids
- **Clinical**: same clinical condition or purpose

"These characteristics shall be similar to such an extent that there would be no clinically significant difference in the clinical performance and safety of the device."

- *Scientifically sounded assessment*
- *Based on appropriate relevant and sufficient data accessible onto the comparator device*

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Equivalence Assessment

- Technical characteristics:

- *be of similar design;*
- *used under similar conditions of use;*
- *have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms);*
- *use similar deployment methods (if relevant);*
- *have similar principles of operation*
- *have similar critical performance requirements.*

Equivalence Assessment

- Clinical characteristics:

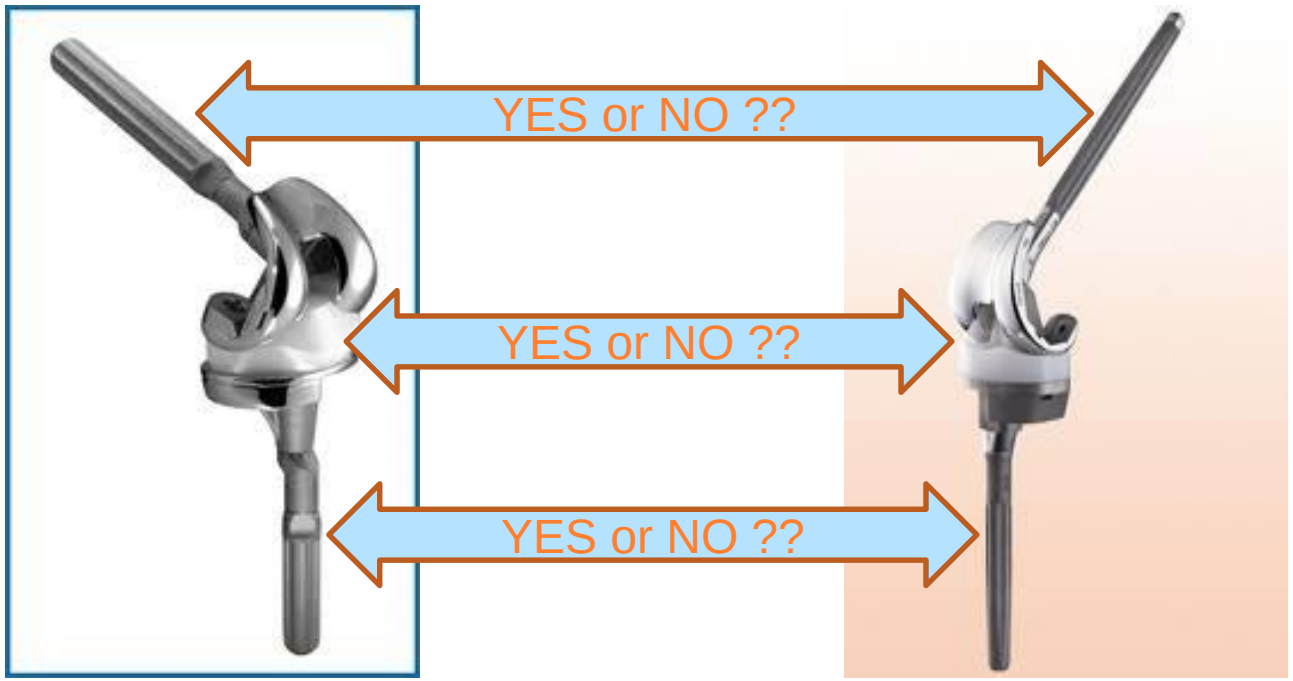
- *Used for the same clinical condition or purpose (including similar severity and stage of disease),*
- *at the same site in the body,*
- *in a similar population (including age, anatomy, physiology);*
- *have same kind of user,*
- *have similar relevant critical performance according to the expected clinical effect for a specific intended purpose.*

Equivalence Assessment

- Biological characteristics:

- *Use same materials or substances*
- *in contact with the same human tissues or body fluids*
- *for a similar kind and duration of contact and*
- *similar release characteristics of substances, including degradation products and leachables*

Equivalence 1 by 1



If one (1) NO is answered, then the comparator is not considered equivalent

Leverage Non Clinical Data ??

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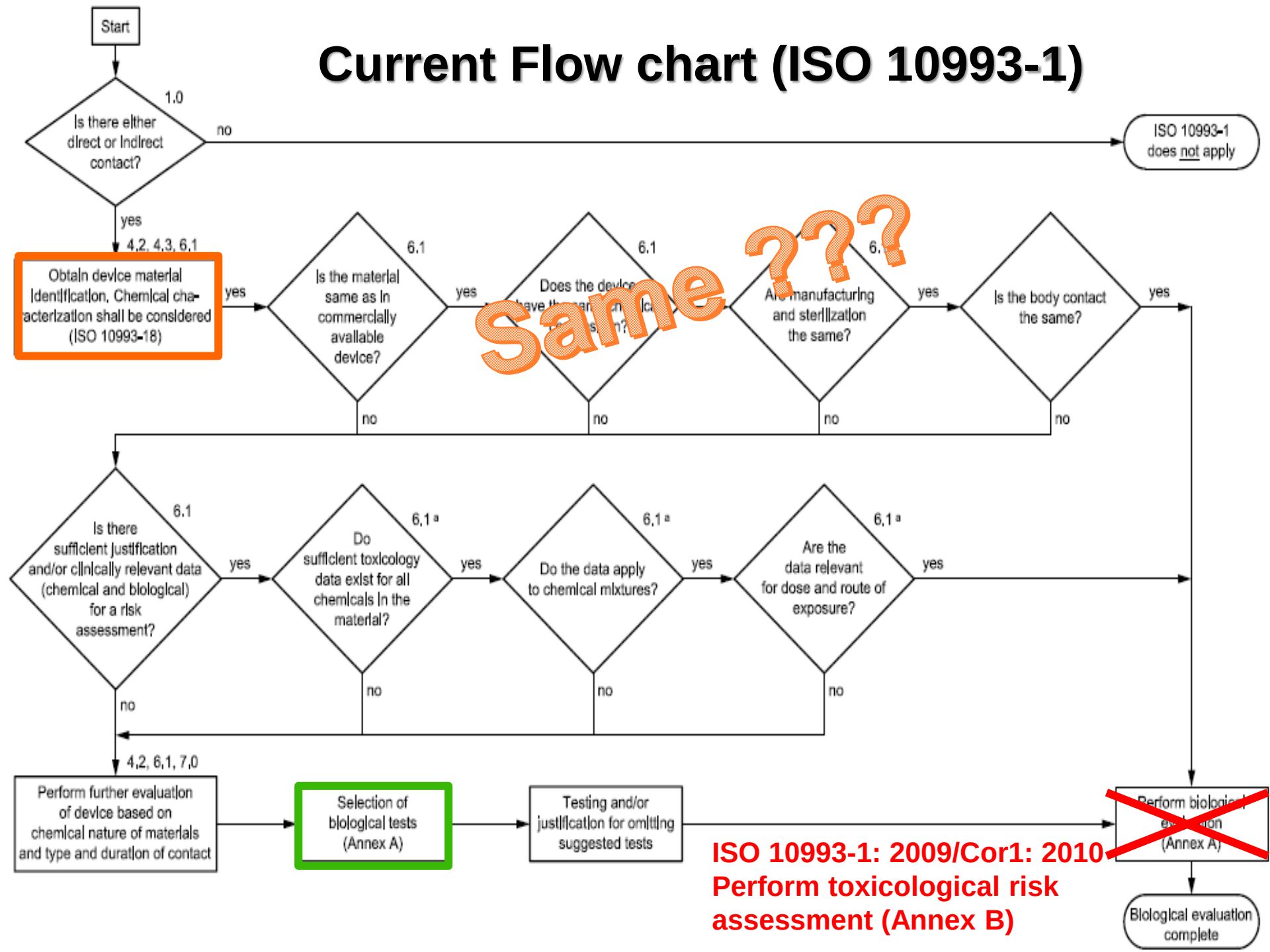
Current Flow chart (ISO 10993-1)



Why leveraging ISO 10 993-1

- Because this ISO 10 993 also challenges « same » and gives tactics to demonstrate « biological equivalence »
  - To be leveraged for MEDDEV equivalence assessment of Biological features

- Devices with same material, are these showing same biological profile so are they obviously « biologically equivalent per MEDDEV »?
  - No, see next slide !

Is A biologically equivalent to B per MEDDEV definition ?

Sample	Metal/Element Analyzed	Sample Concentration (ng/mL)	Amount per Device (µg/device)‡
A	-	-	-
B	**Zinc (Zn)**	17.4	1.4

Sample	GC/MS Match	CAS No.	Estimated Concentration (µg/device) ‡
A	Decane	124-18-5	84
	Tetradecane	629-59-4	56
	Hexadecane	544-76-3	119
	Octadecane	593-45-3	116
	Heneicosane	629-94-7	74
B	Decane	124-18-5	99.6
	Tetradecane	629-59-4	42
	Hexadecane	544-76-3	48
	Decanoic acid, 2-ethylhexyl ester	73947-30-5	62.4
	Carbonyl Containing aliphatic hydrocarbon	NA	3840
	Carbonyl Containing Aliphatic hydrocarbon	NA	1320
	Carbonyl Containing aliphatic hydrocarbon	NA	588
	Carbonyl Containing aliphatic hydrocarbon	NA	116.4

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Case study 2 :
Biological/Clinical Equivalence ?

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Is my comparator Biologically Equivalent ?

Device of interest –Externally communicating device in contact with circulating blood for a limited period of time (< 24 hours)	Comparator device-Externally communicating device in contact with circulating blood for a limited period of time (< 24 hours)
Stainless steel AISI 304, PEEK, Pebax	Stainless steel AISI 304
ETO sterilized	ETO sterilized
All materials have established biocompatibility	
Is the addition of PEEK and Pebax modifying **performance** with regards to blood ?	

The Materials are not the same => Equivalent ?

In Vivo Thromboresistance Following Acute Implantation in the Jugular Vein of the Domestic Pig

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Outcome ?

- Study synopsis: The articles were left in the vessels for one hour. At the end of the implantation period, the pigs were euthanized and each article and jugular vein was examined macroscopically for thrombus formation. In addition, selected organs were macroscopically and microscopically evaluated for evidence of possible thromboembolism
- The extent of **thrombus** formation was graded as follows for both devices:

0 = No thrombosis (small clot at insertion point possible)

Conclusion :

- <u>for this claim</u>, these two confirmed as **equivalent** despite the difference in material.
- On paper “not similar”, but biologically equivalent on this parameter, demonstrated via clinically relevant data on the device under evaluation

Case Study 3 :
Cinical Equivalence ?

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Is my comparator Clinically Equivalent ?

Actual Device (D01)		2 Comparators (D02 or D03?)	
intracranial endoluminal braided chrome cobalt stent coupled with a coil			
Exact same clinical use with same population, same performance claims,			
All materials have established biocompatibility			
CoCr Stent	**Coil A**	**Nitinol stent**	**Coil A**
Full biocomp per ISO 10993	**Established biocomp**	**Established biocomp**	**Established biocomp**

The Stent Materials are not the same => Equivalent ?

Evaluation of the Performance and Safety of an Intracranial Endoluminal Stent Following Implantation in a Rabbit Saccular Aneurysm Model

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Outcome ?

- Study synopsis: The purpose of this nonclinical GLP study was to evaluate the safety, biological and technical performance of an intracranial endoluminal braided chrome cobalt stent (D01) coupled with a coil. The test article was compared to a commercially available stent (D02 or D03) after implantation into the right subclavian artery (RSCA) up to 26 weeks in a Rabbit Saccular Aneurysm Model
- Technical outcome : No RSCA perforation, occlusion, or stenosis was observed during implantation, No acute thrombus formed on the delivery system during the surgical procedure, Safety outcome :no relevant differences between the test and control stents in terms of local tissue effects (endothelialization, medial compression, intimal hyperplasia, vascular stenosis, etc.).
- Performance/Usability outcome : mean aneurysm occlusion percentage achieved was similar at 26 weeks, trackability, visibility of coil and stent markers, expandability and reliability of delivery were judged equivalent by surgeon

Conclusion :

Should we then do a Human study ??? Can this comparator be considered D02 ??

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We should remember …

- These Technical, Biological, Clinical characteristics shall be similar to such an extent that there would be no clinically significant difference in the clinical performance and safety of the *device….*
- Is the CoCr stent different or equivalent to the Nitinol Stent ??

- Scientific demonstration of Clinically relevant data to address Safety and Performance RISKS and cover clinical PERFORMANCE to support the BENEFIT / RISK ratio

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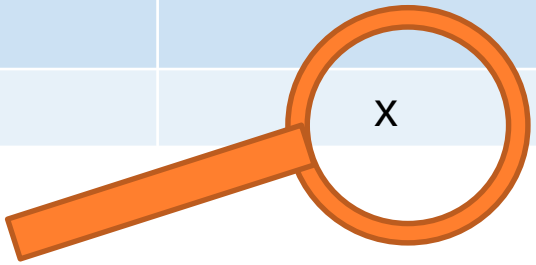
In the end …

	DO1	DO2	No data
Risk 1		x	
Risk 2	x		
Technical claim 1	x		
Technical claim 2		x	
Clinical Claim 1		x	
Clinical Claim 2			x



If a Human exposure is the only route => Clinical Investigation
Otherwise => non clinical study (*in vitro*, bench test, *in vivo*)

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Clinical Evaluation Report-stage IV-

Rev 3

- General details
- Description of the device and its intended application
- Intended therapeutic and/or diagnostic indications and claims
- Context of the evaluation and choice of clinical data types
- Summary of the clinical data and appraisal
  - Data analysis
  - Performance
  - Safety
- Product Literature and Instructions for Use
- Conclusions

Rev 4

- Executive summary
- Clinical Evaluation Scope
- Clinical background, state of the art
- Device under evaluation
  - Type of evaluation
  - Demonstration of equivalence
  - Data generated/held by manufacturer
    - Pre-clinical data
    - Clinical data
  - Data from literature
  - Summary and appraisal
  - Analysis of the clinical data
    - Safety
    - Acceptability of benefit/risk profile
    - Performance
    - Acceptability of Side effects
- Conclusions
- Date of Next Clinical Evaluation
- Dates and signatures
- Evaluator Qualifications

MEDDEV and MDR changes – Take Away

- The bar is being raised significantly
- Increase in clinical investigations is inevitable
- Shift to larger and longer studies than in the past
- Greater scrutiny and transparency of investigation results
- More difficult to use literature from “equivalent devices” in lieu of clinical investigations – especially for Class III and implants
- Clinical evaluation **planning** is critical in determining which safety and performance specifications and claims can be demonstrated in bench, laboratory and animal studies, and which will require clinical investigations
- CER is no longer the last piece of the puzzle to finalize last day before submitting Tech file …

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Steps to Compliance

- Verify NB Expectations to Conversion to New MEDDEV
  - Timelines and expectations may vary somewhat amongst the NBs
- Prepare a Quality Plan that addresses steps planned to attain compliance
  - Gap analysis between MEDDEV and company procedures
    - Take into account instructions to NBs in MEDDEV
  - Present at management review
  - Ensure the necessary interfaces between systems are defined
  - Plan for update of applicable procedures
  - Implementation Plan for New CERs
  - Plan for update of existing CERs
  - Plan for training all impacted staff – clinical, engineering, quality, marketing
- Keep abreast of additional changes to MEDDEV 2.7.1 and other MEDEVs during transition to new MDR


thank you
danke
謝謝
gracias
merci
obrigado
dziękuję
bedankt
teşekkür ederim
go raibh maith agat
sukriya
kop khun krap
terima kasih
grazie
arigatô
dakujem
mauruuru
hvala
sagolun
tapadh leat
mochchakkeram
ngiyabonga
спасибо
рахмат
Баярлалаа
dank je
gracias
merci
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