Briefing note on HTA Cooperation and EU legislative initiative

Our specific asks

A. Avoid structural involvement EUnetHTA/New legislative initiative in IVDR/ MDR conformity assessment/ evidence requirements

1. Monitor very closely and **avoid structural involvement and defining IVDR/MDR evidence requirement to demonstrate "clinical benefits"** to respond to HTA specific evidence needs. This would risk to significantly increase the evidence requirement and would cause significant delay of CE certification of innovation, jeopardizing European patients to benefit from continuous and novel innovation especially by SME. The HTA Network called for this involvement to assist within the medical device conformity assessments, including development of relevant guidance for clinical evaluation. Likewise EUnetHTA include it as part of its 2018 work plan and initiated a workgroup and a meeting with notified bodies, competent authorities and the EC (see factual information). The EC project and future possible legislative initiative on EU HTA cooperation should instead recognize the differences of objectives between an HTA and the CE mark. We call on recognizing the specificity and strength of the European access model for medical technology and key role of IVDR/MDR. This should also be seen in the context of the FDA's new initiatives in support of more timely access to new innovation.

B. Build up a modern fit-for-purpose HTA cooperation

2. Support Medtech industry to be **out of scope of any new legislative proposal** as the current cooperation is not leading to meet EU and Member States objectives, nor is of value to the MedTech industry. For a cooperation support, building up a voluntary modern and fit-for-purpose HTA cooperation on the basis of the existing Cross Border Health Care Directive art. 15 for cooperation already defined. This allowing to develop a tailored approach for MedTech and proof of concept before developing additional legislation and avoid any impact to the IVDR/MDR.
   The resources that would be spent on a set-up of a permanent EU HTA cooperation under a new legislation should instead be allocated to the implementation of the IVDR/MDR.

3. Ensure the initiative **restrict its scope to supportive tools, methods** and if assessments are done to focus on **relative clinical effectiveness** and **exclude relative safety assessment** based on trial data leading to reporting inconclusive results as currently done. This creates confusion and uncertainty for decision makers, payers and patients. Instead what is needed is trust that safety is covered, and even reinforced, by the IVDR/MDR throughout the lifecycle. **This should be clearly**

formulated within a future EU Cooperation initiative by having the domain of safety out of scope of assessment by the EU HTA Cooperation. Instead safety need to be based upon the IVDR/MDR information.

4. Within the implementation of a cooperation, the selection of technologies assessed for a potential EU HTA cooperation should be based on the **potential value** they will bring to patient and health systems and therefore should focus on **transformative innovations**. Avoid selection of technologies to undergo HTA is based upon risk classes. Risk/ Benefit is already assessed under the IVDR/MDR and therefore there is no need to duplicate these efforts.

5. HTA for medtech should be conducted **at an appropriate time after market access**, where clinical effectiveness and real-world data are available. Conducting an HTA prior to allowing initial access leads to significant delays (years), hampers continuous innovation and makes Europe a less attractive region for innovation due to the lack of business predictability. The **principle of predictability** should be respected at all levels – not only for appropriate timing but also when developing methodologies or defining selection criteria and be done with appropriate stakeholder involvement.

In more detail concerns and proposals from the medtech industry[1]

1. Concern the current drive by EUnetHTA and HTA agencies towards the IVDR/ MDR.

In Joint Action 3, WP3 yearly Interim Report states that priorities for project year 2 will include "*Develop coordinated activities between the Competent Authorities, Notified Bodies and EUnetHTA (supported by the EU-Commission and in cooperation with stakeholders). The final aim is to* ***close the gap between requirements of clinical evaluations*** *for market authorization and for reimbursement*".
Linking CE-marking and HTA **jeopardises innovation to the benefit of patients and access to medical technology** due to sheer cost and time to market.

➔ **Proposal**

A complementary approach should be pursued. An efficient **CE marking regime as reinforced by the IVDR/MDR ensures the safety, performance and clinical benefit** of IVDs and medical devices within a regulatory framework. **HTA could add further value by informing subsequent decision making** (i.e. post-CE marking) about funding, reimbursement and/or population to benefit of use of CE-marked products.

[1] MedTech Europe full position: http://www.medtecheurope.org/sites/default/files/resource_items/files/MTE_Position%20Paper_EU%20HTA%20collaboration_March2017.pdf

HTA, which is relevant for a very limited range of medtech, aims to inform a different set of decisions than those addressed by the regulatory process. For instance, HTA considers relative effectiveness, cost-effectiveness, economic impact, organisational impact, and other effects of technologies within specific timeframes and contexts. Safety should not be assessed outside the CE marking process laid down in the IVDR/MDR and any potential legislative frame should ensure this is avoided.

HTA Cooperation initiatives should not impact in particular with regards to:

- Conformity assessment
- Premarket evaluation
- Notified bodies
- Setting evidence requirements / programs on safety, performance or clinical utility.

HTA cooperation should instead:

- keep its scope limited to facilitating cooperation of Member States;
- develop tools supporting cooperation, such as defining unmet needs, horizon scanning, methodologies that are appropriate and tailored to the specificities of medtech;
- be carried out at the appropriate time after the CE mark is granted.

2. Concern: the new legislation on HTA cooperation could include medical technology in its scope.

A new legislation would come on top of the new regulatory frameworks for MDs and IVDs that are currently being implemented, would create possible links and would **not contribute to achieving the Commission's policy objectives** as required by the Better Regulation agenda.

➔ **Proposal**

The role that HTA currently plays in the needed healthcare reforms **differs significantly between pharmaceuticals and medical technologies**. While HTAs of innovative medicines typically inform decisions about pricing and reimbursement, the same is not true for medical technologies, where a strategic link between assessment and decision to award the value created is missing in many Member States.

A voluntary HTA cooperation is already possible on the basis of the Directive on the application of Patients' rights in Cross-border healthcare (9 March 2011) – Article 15. If any future HTA cooperation is put in place it should be implemented within the **existing legal framework**, through a voluntary engagement of Member States, based on processes and methodologies that are appropriate and tailored to the specificities of medical technologies. There is no need for a new legislation which is unlikely to comply with the Better Regulation agenda. Investment in eg. methodologies and other tools can be funded thought RTD (as currently planned for methodologies).

3. Concern: on implementation, the new legislation on HTA cooperation could lay down rules for the selection of technologies to be assessed on the basis of high risk – namely IIb and above or other risk based classification (eg. product going through scrutiny).

We believe that this position could be based on the research project AdvanceHTA and from some initial suggestion from HTA agencies. A risk-based selection process would focus on technologies where safety, performance, clinical utility are already addressed by the IVDR/MDR.

➔ **Proposal**

MedTech Europe suggests HTA cooperation to use clear and predictable criteria for the choice of technologies, seeking technologies of most value to address unmet needs and to focus on "**transformative innovations**", namely solutions that:
1. address high unmet patient/citizen and/or societal and health care systems' needs; and
2. require significant structural and/or organisational change to deliver their benefits.
These criteria should guide the cooperating HTA agencies in selecting only products for assessment based on their **value** rather than risk, which will direct resources to where they will make the biggest difference.

4. Concern: HTA for medical technologies would be conducted at market entry

Assessments at market entry would not capture the true effectiveness and full value of the product and jeopardize IVDR/MDR by an additional legal framework at time of obtaining CE mark.

➔ **Proposal**

MedTech Europe recommends HTA to be conducted at an **appropriate timing**. HTA cooperation should identify the best time(s) to conduct HTA within the life-cycle of the different technologies, which may include the use of **real world evidence** by taking contextual factors into consideration, understanding the differing care pathways and diagnostic information, and the learning curve of professionals or patients using the new technology.

Conclusion

Today, HTA assessments are most often not fit-for-purpose and does not inform decisions such as use or reimbursement and uptake decisions. Until this is clarified, we firmly believe that the medtech sector (IVD and medical devices) should remain out of scope of additional new legislation on HTA cooperation, as this will not lead to Better Regulation. On the contrary, by including medtech in its scope, this legislation risks to create unjustifiable overlaps with the IVDR/MDR, which risk 'second-guessing' the intended goals possibly adding an extra layer of evidence demands that significantly delay access. This is the opposite of what we

see in other markets eg. the US, where efforts are made to accelerate access with new programs being put in place.

For HTA and HTA cooperation to be of true value, it needs to be seen in the context of other instruments and fit within a future value-based access model. A voluntary cooperation is the most appropriate option and is already facilitated by the existing Cross Border Healthcare Directive. We call for medtech to be explicitly out of scope of any forthcoming HTA Cooperation legislation and for the work done to be enabled by a voluntary cooperation on HTA focusing on common unmet needs.

Factual information

1. On our concern that HTA Cooperation seeks to define the evidence requirements for the IVDR/ MDR

The HTA-N (Network of Member States) Paper on Strategy for EU Cooperation on Health Technology Assessment[2] **explicitly calls for Synergy between HTA and Regulatory[3] issues**.
"*For medical devices, synergies should be explored in relation to the Medical Devices legislation. This may include:*

- *Supporting initiatives for more transparency of scientific data, including clinical data, generated in the regulatory sector,*
- *Assisting medical device conformity assessments, including development of relevant guidance for clinical evaluation of specific types of medical device and in IVDs,*
- *Conducting early dialogues/scientific advice with developers of technologies (pre-market access),*
- *Designing studies that could meet requirements for post market clinical follow-up, including evaluation of registries and coverage with evidence schemes*."

"*To implement the principles outlined above the Network:*

- *Calls upon technology developers to engage in early dialogue and scientific advice processes involving both regulators and HTA bodies.*
- *Commits to developing further links with bodies responsible for conformity assessment of Medical Devices, within the framework of relevant legislation and relevant working/expert groups at EU and international level.*
- *Calls on the Commission to facilitate exchange of information with the Network, as appropriate. For example, when implementing relevant legislative and non-legislative measures which can contribute to strengthening synergies between regulators and HTA bodies. Such synergies may be found for medical devices in clinical investigations and evaluation and post-marketing clinical follow up*".

[2] https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf
[3] "In this context "regulatory" should be understood as covering also the conformity assessment procedures with Notified Bodies necessary for placing medical devices on the market."

2. **HTA Reports under EUnetHTA have safety assessment in their scope, which created uncertainty. These are produced by a handful of countries and the findings have limited to no impact.**

Detailed examples

1. EUnetHTA Assessment of Mitra-clip[4], September 2015, 3-7 years after CE mark

Conclusion after 23.000 patients: *"The available evidence **did not allow any final statement to be reached on the relative effectiveness and safety** of transcatheter implantable devices for mitral valve repair in adults with moderate-to-severe and severe chronic MR. As recognised by most of the authors, comparative analyses with longer durations of follow-up are believed necessary to clarify the benefits–harms ratio of the 3 procedures.*

Two of the devices assessed, NeoChord DS1000 and CARILLON® Mitral Contour System® , can be considered still at an early stage of development and show small levels of diffusion. Different is the MitraClip® case that is not at early stages, counting around 23,000 patients implanted worldwide before results from studies comparing the MitraClip therapy to its claimed comparator (i.e. optimal medical therapy) have been published.

*Ongoing studies on CARILLON® Mitral Contour System® and MitraClip® will, in the near future, **help to determine whether they are more effective and/or safe** than the comparators. For NeoChord DS1000, thorough research, including controlled trials, needs to be conducted to determine whether this device is more effective and/or safe than the comparators, and to verify how long the effects of the treatment remain."*

2. EUnetHTA Assessment of Sutures [5] , March 2017, 13 years after CE mark

"*All the clinical data assessed in this report are related to triclosan-coated sutures. No published clinical studies on chlorhexidine-coated sutures have been identified. A statistically significant benefit of triclosan-coated sutures in reducing the risk of total incisional SSIs was demonstrated in our SR/MA, based on moderate quality RCTs data. Comparisons with other antimicrobial sutures are needed, since we did not find any published clinical studies despite the fact that chlorhexidine-coated sutures are already on the market. All studies should be designed as an RCT with the SSI outcome defined according to CDC criteria and sub-specified as superficial, deep and organ space SSIs. The **relative safety of triclosan-coated sutures could not be confirmed** due to a **lack of reporting of AEs in RCTs and non-RCTs included in our assessment. The same is true for chlorhexidinecoated***

[4] http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/news-attachments/wp5-sb-15_transcatheter_implantable_dvices_for_mitral_valve_repair.pdf

[5] http://www.eunethta.eu/sites/default/files/OTCA02_Antibacterial%20coated%20sutures%20for%20the%20prevention%20of%20abdominal%20SSI_0.pdf

sutures because no clinical studies were found during our literature search. *Ten years after the launch, the manufacturer Ethicon has not been contacted by any regulatory body concerning the use of IRGACARE®† MP on Plus Sutures*."

Total overview of HTA reports on findings in EunetHTA JA2 and JA3

PILOT	COMPANIES	CE MARK	FINDINGS
Duodenal-jejunal bypass sleeve for the treatment of obesity	GI Dynamics	3 yrs	Insufficient evidence
Renal denervation systems for treatment-resistant hypertension	St Jude Medical Boston Scientific Covidien Medtronic Recor Biosense Webster (JnJ)	1 yr 1 yr 1 yr 1 yr 1 yr -	The published data suggest that RDN is a safe procedure in the short to medium term. However, because safety was not considered the main endpoint, it can not be dismissed that some complications were not adequately reported.
Biodegradable stents for benign refractory oesophageal stenosis	ELLA-C	7 yrs	Insufficient evidence
Balloon Eustachian tuboplasty for the treatment of Eustachian tube dysfunction	Spiggle and Theis Acclarent (JnJ)	3 yrs -	Despite promising results, due to a lack of high quality data no definite conclusions can be drawn as to whether BET is effective in the treatment of ETD
Implantable devices for the treatment of mitral valve regurgitation	Abbott Vascular Cardiac Dimensions Neochord	7 yrs 4 yrs 3 yrs	Available evidence insufficient to reach final statement on relative effectiveness and safety. Check if long term effects remain New technology unclear more/less safe
Mechanical thrombectomy in acute ischaemic stroke	Styker DePuy Synthes (JnJ)	5 yrs 3 yrs	The evidence presented in this pilot assessment suggests that mechanical thrombectomy is of benefit, but insufficient evidence in

			many areas

PAST ASSESMENTS	COMPANIES	CE MARK	FINDINGS
2016 Wearable cardioverter-defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac arrest in patients at risk	ZOLL Medical Corporation	2011 (latest model)	Insufficient evidence
2017 Antibacterial-coated sutures versus non-antibactareial coated sutures for the prevention of abdomina, superficial and deep, surgical site infections (SSI)	Ethicon, Johnson & Johnson International	2004 (first issued)	Scope: effectiveness and safety. Statistical significant benefit of triclosan-coated sutures in reducing risk of total incisional SSI based on moderate quality RCT. Relative safety could not be confirmed.
2017 Repetitive transcranial magnetic stimulation for treatment resistant major depression	Neurosoft Magstim Mag&More MagVenture Neurostar Neuronetics	2009/2015 N/A N/A N/A 2012 N/A	Scope: effectiveness and safety. Body evidence indicates rtms is generally safe and well tolerated. Current evidence not sufficient to prove if rtms is as effective and safe as ECT.