EUROPEAN COMMISSION

Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	23/03/2022
Notified Body number	0344
Internal CECP dossier #	2022-000213
Medical device type	The application concerns the Edwards SAPIEN 3 and Edwards SAPIEN3 Ultra transcatheter heart valves (THV) as well as the Edwards Commander Delivery System and accessories (Edwards eSheath Introducer Set and Crimper). SAPIEN 3 and SAPIEN 3 Ultra THV are balloon-expandable THVs with radiopaque cobalt-chromium frames, trileaflet pericardial tissue valves, and polyethylene terephthalate (PET) fabric skirts. The devices are designed to be delivered via transcatheter approaches to the target treatment site in the heart using the Edwards Commander Delivery System and accessories.
Intended purpose	The current MDR application is for the following additional intended purposes: - Failure of an aortic surgical bioprosthetic valve at any or all levels of surgical risk for open-heart surgery for both Edwards SAPIEN 3 THV and Edwards SAPIEN 3 Ultra THV - failure of an aortic transcatheter bioprosthetic or surgical mitral bioprosthetic valve in patients in patients at high or greater risk for open surgical for Edwards SAPIEN 3 Ultra THV
Risk class / type	☒ class III implantable ☐ class IIb ARMP
Screening step: medical field / competence area	Circulatory system

2 EXPERT DECISION AND OPINION

PART 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1 Decision of the screening experts

Date of decision	11/04/2022

Screening panel decision	
Is there intention to provide a scientific opinion?	☒ Yes ☐ No ☐ Insufficient information to reach a conclusion
In case the information was found insufficient to reach a conclusion: summary of reasons (see MRD Annex IX Section 5.1 point c)	
Not applicable	
Summary as to why there is intention to provide an opinion	
The devices analysed here have not CE mark for the two intended purposes: failure of an aortic surgical bioprosthetic valve at all surgical risks (only Edwards SAPIEN 3 Transcatheter Heart Valve system was CE Certified for use in patients at high or greater surgical risk, but not Edwards Ultra) and failure of an aortic transcatheter bioprosthetic or surgical mitral bioprosthetic valve. The clinical data to support the expanded indications for use come from 3 registries: PARTNER 2 and 3 AVIV and US STS/ACC TVT Registry studies. During follow up, severe health issues occurred as soon as in a 12 month follow up period – however the device is intended to be long-term-used in patients treated with the intended purposes. For the SAPIEN 3 Ultra, very limited data is available.	
Summary as to why there is *no* intention to provide an opinion	
Not applicable	
Any other comments	
Not applicable	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Novelty of device and/or of related clinical procedure
☐ No novelty: Neither device nor clinical procedure is novel ☐ Novelty: **Device** is novel

☒ Novelty: **Procedure** is novel

Short description of the novelty, including main dimension(s) of novelty

The SAPIEN 3 and 3 Ultra Systems are already used for deployment inside a failing aortic surgical bioprostheses. However, the novelty relies on the expansion of indications to other two procedures: 1) Failure of an aortic transcatheter bioprosthetic for all patients independently of surgical risk (not only high or greater surgical risk) and 2) failure of surgical mitral bioprosthetic valve in patients at high or greater risk for an opened surgical procedure. Also, it should be emphasized that the use of SAPIEN 3 Ultra is very limited an all settings.

Overall degree of novelty

Level of novelty:

☐ Low level *or*
☐ Medium level *or*
☒ High level

Uncertainties related to novelty

We have three scenarios:

1) In the case of failing aortic surgical bioprostheses, outcomes have been reported up to three years thus far. Longer valve durability in this setting is unknown. This is important when considering expanding indications to lower risk patients with higher life expectancies.

2) In cases of failing aortic thanscatheter bioprostheses, the evidence is even lower with lack of follow up data and extremely low sample size in the published studies.

3) In cases of failure of a surgical mitral bioprosthetic valve in patients at high or greater risk for open surgery, once again the number of patients treated is quite low and the reported outcomes lack long follow up.

1.2 Possible negative clinical / health impact resulting from novelty

Potential feared complications resulting from novelty to consider for **aortic valve-in-valve procedures** include **coronary artery obstruction and patient- prostheses mismatch**. Displacement of the existing bioprosthetic tissue during aortic valve-in-valve procedures can result in coronary obstruction with rates ranging from 0.6-2.3%. Coronary obstruction is associated with a high mortality rate and has been shown to occur more frequently, four- to six-fold higher, in valve-in-valve procedures than in native aortic valve replacement procedures. In relation to patient- prostheses mismatch, rates of severe patient-prostheses mismatch following aortic valve-in-valve procedures ranged from 24.6-58.4%. Among the SAVR literature, patient-prostheses mismatch has been shown to be associated with negative outcomes, such as reduced improvement in symptoms and functional class, reduced improvement in coronary flow reserve, and increased risk of cardiac events and heart failure.

In the field of **mitral bioprosthetic valve failure**, valve in valve has been associated with **left ventricular outflow tract (LVOT) obstruction**, as leaflets of the pre-existing bioprosthesis are stented open when the new transcatheter valve is inserted, thereby creating a “neo” LVOT. Left ventricular outflow tract

obstruction in transcatheter mitral valve procedures is not uncommon and can result in hemodynamic instability that requires urgent alcohol septal ablation, with the risk of AV block development, pacemaker implantation and arrhythmias.

In conclusion, the overall degree of novelty for the new indications are high, but major possible health impacts are present: increased cardiac mortality and morbidity.

Estimated* severity of clinical and/or health impact

* This can entail uncertainty. Not only *known* clinical / health impacts but also *possible* ones (conceivable uncertainties, hazards, risks) should be taken into account but need to be supported by a scientific, clinical or technical reasoning. Uncertainties need to be described.

Severity of clinical/health impact:

☐ No clinical or health impact
☐ Minor clinical or health impact
☐ Moderate clinical or health impact
☒ Major clinical or health impact

Uncertainties related to clinical/health impact

With respect to new indications for use for Valve in Valve, available data of the **aortic valve-in-valve** experience derives from the PARTNER 2 and 3 Aortic VIV Registry and TVT Registry Data AVIV. In PARTNER 2 Valve-in-Valve Registry (J Am Coll Cardiol. 2017;69(18):2253-2262), at 30 days, all-cause mortality was 2.7%, stroke was 2.7%, major vascular complication was 4.1%, conversion to surgery was 0.6%, coronary occlusion was 0.8%, and new pacemaker insertion was 1.9%. In the PARTNER 3, the implantation was successful in all patients and no procedures were aborted or converted to SAVR. At one year, however, the rate of reintervention was 6.25% in the PARTNER 3 AVIV trial, and 2.0% in the TVT Registry AVIV.

Limited data is available with SAPIEN 3 Ultra.

The results of the **mitral valve-in-valve experience (Mitral ViV from the TVT Registry)**, limited 12-month follow-up, show that the implantation was successful in 97.3% of patient subjects and 0.6% procedures were aborted and 0.8% procedures were converted to open heart surgery. At 30 days, all-cause mortality was 5.0%; at one year, all-cause mortality was 16.6%. Cardiac mortality was 2.0% at 30 days and 3.9% at one year.

Uncertainties arise from the missing long-term course in the three scenarios. Also importantly, in the case of aortic valve-in-valve procedures, it is documented the difficulty to access the coronary tree and an increased risk of PCI failure in cases of acute coronary syndromes.

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to

a) Component(s)
b) Source material(s)
c) Impact on health in case of failure of the device

2.1 Information received from Secretariat:	☐ Yes ☒ No

2.2 Other information available to experts:	☐ Yes ☒ No

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment *(if information is available, it will always be provided by the expert panel secretariat)*	
3.1 Information received from secretariat?	☐ Yes ☒ No

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☐	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☐ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☒	**Circulatory system**	☒ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☐ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
☐	**Neurology**	☐ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices
☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	23/05/2022
Expert panel name	Circulatory system
Sub-group of expert panel	Prosthetic heart valves and devices for heart valve repair

2.2 Summary of expert panel opinion

- **Device description:** Edwards Sapien 3 and Sapien 3 Ultra are balloon-expandable biological valves composed of a cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate inner and outer fabric skirts. They were primarily developed to be implanted in the native aortic valve ring, to treat native aortic valve stenosis. The products were developed with a catheter delivery system allowing minimally invasive implantation (transvascular percutaneous implantation or minimally invasive surgical implantation). The principal action is to replace the dysfunctional native valve and restore valve physiology. The use of percutaneous balloon-expandable biological valves has been extended to the treatment of dysfunctional prosthetic biological valves (surgical and percutaneous) in several different heart valve positions. In this setting, both devices are implanted inside the ring of the dysfunctional prosthetic valve, restoring valve physiology.
- **Novelty:** The novelty of the current application relates to changes to the intended purpose (new indications for use): 1) Failure of an aortic surgical bioprosthetic valve at any or all levels of surgical risk for open-heart surgery for Edwards Sapien 3 and Edwards Sapien 3 Ultra; 2) Failure of an aortic transcatheter bioprosthetic or surgical mitral bioprosthetic valve in patients in patients at high or greater risk for open-heart surgery for Edwards Sapien 3 Ultra.
- **Adequacy of clinical evidence assessment by the notified body:** The NB has accurately reported the clinical evidence submitted by the manufacturer which consisted of clinical investigations on the devices (either sponsored or not sponsored by the company) together with a clinical literature review. Some shortcomings of the submission could have been highlighted in the NB's assessment. In particular, although the quality of clinical investigations is reasonable, no formal critical evaluation of the results was presented in the CER, especially with regard to the limited follow-up of patients. Moreover, the completeness of the literature review is questionable since the search period upper limit was December 2019. Overall, more updated follow-up data from clinical investigations, and a more updated literature review may have contributed to improving clinical evidence generation.
- **Sufficiency of clinical evidence:** The panel's view is that the NB has not precisely assessed whether the clinical evidence provided by the manufacturer was sufficient in terms of amount and quality. This is of particular importance since the clinical data related to one of the indications (namely aortic THV-in-SV[1]) are limited to one single-arm, multicentre, registry with follow-up only reported at 12 months to date. For Edwards SAPIEN 3 Ultra, the manufacturer has presented a claim for a

[1] SV: Surgical Valve

technical, biological, and clinical equivalence to SAPIEN 3, which was accurately reviewed by the NB. A longer-term follow-up is planned as part of the PMCF plan.

- **Adequacy of benefit-risk determination:** The panel's view is that benefit-risk determination as assessed by the NB is not fully adequate when considering the current state of the art, namely surgical reintervention, in low/intermediate patients with dysfunctional or failing aortic bioprostheses.
- **Consistency of clinical evidence with purpose / medical indication(s):** The panel agrees with the NB that the clinical evidence submitted by the manufacturer does match the medical indications under assessment. Although the clinical data suggest an acceptable benefit/risk balance, whether this constitutes sufficient clinical evidence is debatable owing to the limitations of the submitted clinical data.
- **Consistency of clinical evidence with PMCF plan:** The panel considers that the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan is reasonable, however, more emphasis on the shortcomings of the PMCF may have been underlined.
- **Overall conclusions and recommendations on clinical evaluation** (full details in 2.4):

⇒ The first indication is "Failure of an aortic surgical bioprosthetic valve at any or all levels of surgical risk for open-heart surgery (assessed for Edwards Sapien 3 and Sapien 3 Ultra)"

Patients at high or greater risk for open-heart surgery: it seems reasonable to accept the same indication for Sapien 3 Ultra based mainly on biological and technical equivalence data.

Patients with intermediate or low risk for open-heart surgery: owing to the shortcomings of the submitted evidence, the panel considers that the benefit/risk balance of Sapien 3 valves for this sub-population is not sufficiently supported by evidence in terms of amount and quality. Therefore, the panel does not support the extension of the indication of the valves to this setting. The panel recommends that more prolonged follow-up from AVIV is reported and that additional studies are conducted so as to confirm the external validity of the first registry.

⇒ The second indication is "Failure of an aortic transcatheter bioprosthetic or surgical mitral bioprosthetic valve in patients who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator) (assessed only for Edwards Sapien 3 Ultra)"

Considering the previous approval of Edwards Sapien 3, the panel agrees with the NB that it seems reasonable to accept the same indication for Edwards Sapien 3 Ultra based mainly on biological and technical equivalence data.

2.3 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the notified body (CEAR)[2]
1. Overall opinion on the NB's assessment of the adequacy of the manufacturer's clinical evaluation report
The assessment of the clinical evaluation report (CER) by the NB has included a section relevant to the clinical literature review (section D), and one relevant to the clinical investigations on the devices (namely SAPIEN 3 and SAPIEN 3 Ultra [for which a claim of equivalence to SAPIEN 3 was made]). The panel has identified potential shortcomings in the literature review conducted by the manufacturer that could have been highlighted by the NB. Electronic databases were searched for articles published between 01 January 2018 and 31 December 2019. For an evolving field such as transcatheter bioprostheses, the literature search may have deserved an update before the completion of the CER (noted to be March 2021). As of the time of the present opinion (May 2022), the panel notes that several relevant papers published over the last two years have not been reported in the review (for example Sa M, et al. JACC Cardiovasc Interv 2021;14:211-220; Deharo P, et al. J Am Coll Cardiol 2020;76:489-499; Tam DY, et al. JACC Cardiovasc Interv 2020;13:765-774.). It is unexpected that the manufacturer chose to interrogate cvPipeline and Amedeo as additional databases to Pubmed, since the formers appear very uncommon, compared to the more widespread database such as Embase, or Web of Science. Last, while the NB judged that inclusion/exclusion criteria were acceptable, the panel considers these criteria were not specified with sufficient details. In light of these comments, the panel's view is that the completeness of the literature review is questionable. With regards to the clinical investigations, the NB has adequately summarised the main characteristics of studies, consisting of clinical registries. However, the CER did not include a critical evaluation of the results, and this could have been pointed out in the CEAR. In the CEAR, the panel found no discussion on the quality of these registries, especially with regard to internal and external validity. As previously indicated, two devices SAPIEN 3 and SAPIEN 3 Ultra, from the same manufacturer, were assessed by the NB. For SAPIEN 3 Ultra, the manufacturer has claimed equivalence to SAPIEN 3, which was assessed by the NB in the CEAR. SAPIEN 3 and SAPIEN 3 Ultra are composed of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate inner and outer fabric skirts. The leaflets are treated according to the same process. Both devices currently use the same accessories, namely the same delivery system, balloon, introducer sheath and crimper. Design improvements were introduced to reduce the risk of paravalvular leakage. In summary, SAPIEN 3 Ultra is identical in design to SAPIEN 3, with the only exception being the outer skirt component and its attachment to the frame. The outer skirts for both valves are made from the same material; however, the material is [redacted] on SAPIEN 3 and [redacted] on SAPIEN 3 Ultra. [redacted]

[2] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

[redacted] The placement of the skirt on SAPIEN 3 Ultra is [redacted] on the frame than on SAPIEN 3. Resulting in a higher sealing skirt by 40% and a 50% increase in the area of contact with the native anatomy. [redacted]

The Sapien 3 Ultra was approved by the U.S. Food and Drug Administration in late 2018 and obtained an expanded indication to treat low-risk patients in 2019. This new valve was initially introduced along with a dedicated Delivery System, which was designed to allow the valve to be crimped directly onto the deployment balloon, eliminating the need for valve alignment and reducing the number of procedural steps as well as with a dedicated sheath, which had a reduced profile of 14 F across all valve sizes. However, reports of burst balloons during some implantation procedures using the new delivery system, which resulted in a few cases of vascular injury, bleeding, and the need for surgical intervention, led the Food and Drug Administration to issue a Class I recall for the delivery system in August 2019[3]. Following this recall, the new delivery system and the sheath were replaced by previous-generation accessories.

Since then, the Sapien 3 Ultra has been widely used in the US and European markets. The manufacturer provided evidence mainly focused on the use of SAPIEN 3 and SAPIEN 3 Ultra in the particular context of valve-in-surgical valve intervention. A more recent paper expands the evidence on the same clinical setting (Valve-in-Surgical-Valve With SAPIEN 3 for Transcatheter Aortic Valve Replacement Based on Society of Thoracic Surgeons Predicted Risk of Mortality. Circ Cardiovasc Interv. 2021 May;14(5):e010288). However, to better understand the relative performance of both valves, one should take into account additional data suggesting an equivalent performance regarding procedural success rate, all-cause mortality, stroke, major bleeding, or permanent pacemaker implantation but with a significant reduction in both mild and moderate/severe paravalvular leakage with SAPIEN 3 Ultra.

SAPIEN 3 Ultra is the fourth generation of THV from the manufacturer's product line. All designs/versions are and/or have been CE certified under MDD with the exception of the expanded intended use for Valve in Valve (ViV). Namely, SAPIEN 3 and SAPIEN 3 Ultra are intended for use in patients requiring heart valve replacement for any surgical risk class. The manufacturer supports the expanded intended ViV uses for Sapien 3 Ultra with the demonstration of biologic/technical and clinical equivalence of SAPIEN 3 Ultra to SAPIEN 3 per MDCG 2020-5[4]. Both devices are deployed in the same manner (balloon inflation), using the same delivery system. Additionally, the conditions of use are the same; both valves are used in the same environment, in the same patient populations, by physicians who have received training from the manufacturer. Edwards designed and is the legal manufacturer of both devices and has access to all specifications. The NB states that the devices are equivalent in accordance with Section 3 of Annex XIV of Regulation (EU) 2017/745 including technical, biological, and clinical characteristics and the demonstration of equivalence and access to data is compliant with the applicable requirements of the MDR.

[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=174655

[4] https://ec.europa.eu/health/system/files/2020-09/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en_0.pdf

Considering the biological, technical, and clinical evidence, the panel agrees to assume clinical equivalence between SAPIEN 3 and SAPIEN 3 Ultra, regarding procedural success rate, complication rate, and major clinical outcomes. Available evidence supports a significant reduction of paravalvular leakage occurrence with SAPIEN 3 Ultra, which may positively impact mid and long-term clinical outcomes. This opinion is consistent with that of the NB.

2. Opinion on the NB's assessment of the sufficiency of the clinical evidence provided by the manufacturer

In section H of the CEAR, the NB was asked to assess whether the clinical data provide sufficient clinical evidence to "*demonstrate compliance with the relevant general safety and performance requirements, to support the intended purpose, the claims, and the information in the IFU and SSCP, as well as to indicate if unanswered questions regarding the device under evaluation were remaining*".

According to Regulation (EU) 2017/745, the sufficiency of clinical evidence has to be assessed in terms of amount and quality.

For SAPIEN 3, the panel's opinion is that the assessment is not fully adequate since neither the amount nor the quality of clinical evidence have been discussed.

The NB's statement on the matter only indicates that long-term follow-up for valve-in-valve is limited, which suggests that the clinical evidence could be deemed as insufficient.

In terms of amount, the panel's opinion is that the clinical data available to support the benefit-risk assessment of the use of aortic THV-in-SV in low- and intermediate-risk patients is currently limited to a prospective single-arm registry with 97 patients who underwent the procedure and no follow-up data beyond 12 months at the date of the submission. While the panel agrees with the NB's assessment, within the CEAR, that "*the results are in line with previous reports of aortic ViV procedures*", it considers the question on whether the present clinical evidence is of sufficient amount could have been more elaborated.

Similarly, although the panel has not identified major methodological issues, the quality of clinical evidence provided by a prospective, single-arm, registry could have been more questioned, especially since the clinical evaluation report should include a critical evaluation of all clinical investigations results.

A careful and detailed critical appraisal of the clinical data would be particularly important in the setting of valve-in-valve in low and intermediate-risk patients for open-heart surgery. Specific challenges/risks pertaining to the placement of a THV within a surgical heart valve should be considered:

a) Coronary obstruction is a well-documented complication. The Valve in Valve International Data Registry (VIVIDR) or Global VIV Registry has reported a frequency of coronary artery obstruction of 3.5%, which is higher than the incidence of coronary obstruction from a native valve procedure. A common mode of obstruction is due to the bioprosthetic leaflets being pushed outwards by the THV, thereby coming into direct contact with the coronary ostia or the sinotubular junction overlying the ostia. Other factors, which should also raise the possibility of potential coronary obstruction are low lying coronary ostia; specific SHV design with leaflets outside the stent frame (trifecta, mitroflow); bulky bioprosthetic valve leaflets; stentless valves; high implantation of a THV.
b) Intra-procedural migration and embolization of THV during VIV procedure, due to suboptimal sizing and positioning have been reported in the literature.
c) High residual gradients are an Achilles heel of aortic VIV procedures. The VIVIDR reported an incidence of high gradients (mean gradient >20 mmHg) in 28% of cases and these were

predominantly with balloon-expandable valves. Data suggest that post-procedural high residual gradients impact mid and long-term durability.

3. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

The panel is generally in the agreement that the benefits and risks of the devices under assessment have been adequately assessed against the clinical data submitted by the manufacturer. These data consist of one prospective, multi-center, single-arm registry with a limited sample size (aortic THV-in-SV/ THV in low- and intermediate-risk), sponsored by the manufacturer, and one larger prospective, multi-center, single-arm, public, registry (aortic THV-in-SV/THV in high-risk patients [outside the scope of this opinion] and mitral THV-in-SV in high-risk/inoperable patients).

When considering alternative treatments in low-to intermediate-risk patients, which include surgical reoperation, the NB has emphasized the potential advantages of THV over surgery in terms of reduced risk due to its minimally invasive nature.

However, the panel is of the opinion that the NB has not sufficiently counterbalanced these advantages against the shortcomings of the presented clinical data.

Indeed, while it can be admitted that the short-term risk that carries surgical reoperation is higher than after valve-in-valve THV in patients at low-to-intermediate risk, redo surgery after dysfunctional or failing bioprostheses has a proven benefit and a demonstrated durability in the mid-to long term.

Conversely, to date, there is no available data to confirm the sustained benefit and durability of valve-in-valve THR beyond 12 months in the context of low-to-intermediate risk patients. Moreover, for SAPIEN 3 Ultra, no clinical investigation has been conducted, although the claim of biological/technical and clinical equivalence to SAPIEN 3 appears reasonable as indicated in the previous section.

Overall, the panel's opinion is that benefit-risk determination as assessed by the NB is not fully adequate when considering the current state of the art in low/intermediate patients with dysfunctional or failing aortic bioprostheses. This concern does not apply to mitral valve-in-valve in patients at high or greater risk, which is a more established option.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

The panel agrees with the NB that the clinical evidence submitted by the manufacturer does match the indications assessed as part of the CECP. Indeed, the TVT Registry has included high-risk patients who underwent aortic valve-in-valve and mitral valve-in-valve, whereas the other prospective, multi-center, single-arm registry (AVIV study) did specifically include low to intermediate-risk patients who underwent aortic THV-in-SV/ THV. The NB has commented further that it is not appropriate to randomize patients to replacement of valve by surgical means or to withhold replacement.

The panel agrees that a study comparing valve-in-valve versus medical treatment alone could be considered unethical.

However, whether a study randomizing patients between valve-in-valve or redo surgery would be inappropriate can be a matter of debate in light of the advantages and shortcomings of each strategy (*Borger M, et al. Repeat Aortic Valve Surgery or Transcatheter Valve-in-Valve Therapy: We Need a Randomized Trial. J Am Coll Cardiol. 2020 Aug, 76 (5) 500–502).* This comparison would be particularly relevant in low and intermediate-risk patients for open-heart surgery. Important issues, such as

coronary access and obstruction, significant residual gradients, and mid to long-term durability are crucial to adequately assess the risk-benefit profile of valve-in-surgical valve.

5. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The PMCF plan was reviewed by the NB in section F of CEAR. Overall, it has comprehensively described the process by which the clinical data associated with the devices under assessment (SAPIEN 3, SAPIEN 3 Ultra, together with the delivery system and accessories) will be collected and evaluated in the post-market phase.

PMCF plan consists of a specific study sponsored by the manufacturer that was initiated in 2018, and the continuation of the TVT registry.

The specific study will be carried out on the newer generation of THV (SAPIEN 3 Ultra) and enable a period of 5 year-follow-up post-procedure for 200 enrolled patients. Although the panel agrees with the NB's assessment that the study's plan is appropriate and includes relevant primary and secondary endpoints, it is not clear if the study will enrol patients benefiting from valve-in-valve THR. Moreover, the population of this study will be at intermediate or greater risk for open surgical therapy. Therefore, the panel considers that the present study will provide additional data of limited relevance within the scope of aortic THV-in-SV/ THV in low- and intermediate-risk patients.

It appears that the TVT registry will provide valuable information in the context of the above-mentioned population, though the maximal duration of follow-up after implantation is not clearly reported. In the NB's assessment, the conduct of the literature review to complement clinical data at the post-market stage was also noted. However, the claim of a systematic review by the manufacturer was not challenged by the NB, especially with regard to the nature of the database that will be interrogated.

Overall, the panel considers that the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan is reasonable, however, more emphasis on the shortcomings of the PMCF may have been underlined.

2.4 Overall conclusions and recommendations

⇒ First indication**: Failure of an aortic surgical bioprosthetic valve at any or all levels of surgical risk for open-heart surgery (assessed for both Edwards Sapien 3 and Sapien 3 Ultra)**

- Patients at high or greater risk for open-heart surgery: considering the previous approval of Sapien 3 in this setting, the panel agrees with the NB that it is reasonable to accept the equivalence of Sapien 3 Ultra to Sapien 3 according to the three criteria (clinical, technical, biological).

- Patients at low to intermediate risk for open-heart redo surgery:

- Based on the submitted evidence within the CER, the NB has considered that the clinical benefits of Sapien 3 valves in this setting outweigh the risks, and therefore that transcatheter valve-in-valve procedures could provide another treatment option for patients who would otherwise undergo a new surgery.
- The panel has the following major concerns:
    - The benefit-risk balance of Sapien 3 valves is only supported by one specific clinical registry (AVIV). Another source of clinical investigations includes a registry not specific to this target of patients.
    - The main source of evidence (AVIV registry) consists of data based on a population of only 97 treated patients. Even though the rate of all-cause death or all stroke at 12 months (primary endpoint) was low (2.1%), the fact that these results are based on a single study with limited sample questions the generalisability of the findings.
    - Equally important, no follow-up data beyond 12 months are reported as of May 2022, which appears notably insufficient to establish mid to long-term effectiveness and safety.
    - Conversely, for these types of patients, the current state of the art is represented by redo surgery for which long-term effectiveness is well-validated.
- Conclusions and recommendations:
    - The panel considers that the benefit/risk balance of Sapien 3 valves for this sub-population is not sufficiently supported by evidence in terms of amount and quality.
    - Based on the currently submitted data, the panel does not support the extension of indication of the valves to this setting.
    - The panel recommends that more prolonged follow-up from AVIV is reported (especially as the database extract was last performed in August 2020) and that additional studies are conducted so as to confirm external validity of the first registry.

⇒ Second indication: **Failure of an aortic transcatheter bioprosthetic or surgical mitral bioprosthetic valve in patients who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator) (assessed for Edwards Sapien 3 Ultra only).**

Considering the previous approval of Edwards Sapien 3, the panel agrees with the NB that it seems reasonable to accept the same indication for Edwards Sapien 3 Ultra based mainly on biological and technical equivalence data. The clinical data is sparse for both products in this setting. However, the data points towards safe and effective acute results and this often are the only therapeutic option for

severe and complex patients. Mid and long-term results should be accessed accurately by the manufacturer.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[5]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.
Not applicable

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions
There were no divergent positions. A consensus was reached.

Please indicate how many of the experts of the panel or sub-group had divergent views
Not applicable

[5] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.