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and the Environment
Ministry of Health, Welfare and Sport

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A market surveillance study

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Colophon

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Synopsis

Transcatheter aortic heart valves in Europe
A market surveillance study

Malfunctioning heart valves can be replaced by a prosthesis. In recent years, new techniques have been developed with less impact on patients, for example the use of a catheter to insert the prosthesis. The first of these ‘transcatheter aortic valve implantation devices’ (TAVI) became available in Europe in 2007. Since that time, more than 300,000 TAVIs have been implanted, and new generations of the devices have been developed.

As part of their market surveillance tasks, the Health and Youth Care Inspectorate (IGJ) commissioned RIVM to assess the technical documentation of five TAVI devices. None of the files contained items that were assessed as ‘insufficient’, and one file contained only ‘good’ or ‘almost good’ items. The other four files contained one to two items assessed as ‘moderate’.

In the file items “clinical evaluation” and “post-market surveillance data” some shortcomings were found with the implication that product safety and the safe use of the devices are insufficiently guaranteed with regard to these issues. Shortcomings in the file do not necessarily mean that the device is of insufficient quality. By maintaining complete and accurate files, manufacturers underpin the safety of their products for patients. Manufacturers are required to investigate carefully any shortcomings in their files, and to resolve these in order to comply with the regulations. Manufacturers have indicated that they are currently working to improve their files in order to comply with the new regulations on medical devices published in 2017.

Keywords: transcatheter aortic heart valve, product safety, technical documentation assessment

Publiekssamenvatting

Transkatheter aorta hartkleppen in Europa
Een onderzoek in het kader van markttoezicht

Slecht functionerende hartkleppen kunnen worden vervangen door een prothese. Hiervoor zijn de afgelopen jaren nieuwe technieken ontwikkeld die minder belastend zijn voor de patiënt, bijvoorbeeld het inbrengen van de prothese via een katheter. De eerste van deze zogeheten transkatheter aortaklep vervangende implantaten (TAVI) kwamen in 2007 beschikbaar in Europa. Sindsdien zijn wereldwijd meer dan 300.000 TAVI's geplaatst, en zijn de producten verder ontwikkeld.

Vanwege haar taak als toezichthouder heeft de Inspectie voor Gezondheidszorg en Jeugd (IGJ) het RIVM gevraagd de technische documentatie te beoordelen van vijf TAVI-producten. Geen van de dossiers bevatte onderdelen die onvoldoende waren, en één dossier had alleen maar onderdelen die goed of bijna goed waren. De andere vier dossiers hadden één tot twee onderdelen van middelmatige kwaliteit.

In de dossieronderdelen "klinische evaluatie" en "post-market surveillance" zijn enkele tekortkomingen gevonden waardoor de productveiligheid en een veilig gebruik van de producten onvoldoende zijn gegarandeerd op deze punten. Een tekortkoming in het dossier betekent niet direct dat het product minderwaardig is. Met volledige en correcte dossiers onderbouwen fabrikanten de veiligheid van het product voor de patiënt. Regelgeving vereist dat fabrikanten de tekortkomingen in hun dossiers zorgvuldig onderzoeken en oplossen. Fabrikanten geven aan dat zij hun dossiers momenteel verbeteren om te kunnen voldoen aan de nieuwe regelgeving voor medische hulpmiddelen uit 2017.

Kernwoorden: transkatheter aorta hartkleppen, productveiligheid, dossierbeoordeling

Contents

1 Introduction

The replacement of malfunctioning heart valves by a prosthesis using open heart surgery is a well-established procedure. However, patients at high risk of mortality during surgery are generally not eligible for this procedure [Iung, Baron et al. 2003; Bach, Siao et al. 2009]. Over the years, less invasive techniques have been developed like ministernotomy, minithoracotomy and transcatheter implantation. The first transcatheter aortic valve implantation devices (TAVI) became available in Europe in 2007. Since that time, more than 300,000 implantations have been performed worldwide [Puri, Chamandi et al. 2017]. The “first generation” transcatheter heart valves showed promising outcomes, however, various associated complications were observed. Therefore, several “second generation” transcatheter heart valves have been developed.

Regulators in Europe have been interested in the rapid developments occurring in the area of TAVI for some time. In the Netherlands, the Health and Youth Care Inspectorate (IGJ) regularly commissions RIVM to investigate a high risk medical product. In order to gain more insight on the state of affairs for TAVI in Europe, the Inspectorate commissioned RIVM to perform an investigation on TAVI. The investigation consists of the following parts:

1. Compiling an overview of transcatheter heart valves that are CE marked or in clinical investigations.
2. Literature research for available clinical data.
3. Assessment of technical documentation of selected TAVI devices available on the EU market.
4. Laboratory evaluation of selected biocompatibility parameters of the selected TAVI devices.

In this report, the results of part 3 are described. The following questions will be addressed:

- Do the technical files of the selected TAVI provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD) [European Commission, 1993+2007]?
- In case of shortcomings, do these lead to a concern for patient safety?

2 Assessment of technical documentation

In order to show compliance with the Medical Devices Directive (MDD) [European Commission, 1993+2007], manufacturers of medical devices have to compile a file with technical documentation.

From each manufacturer that had one or more CE-marked TAVI devices, as identified in part 1 of the investigation[1], the most recently CE-marked device was included in this investigation. The following manufacturers submitted the requested technical documentation: Abbott (product from recently acquired St Jude Medical), Boston Scientific Corporation (both a product from BSC and product from recently acquired Symetis), Edwards Lifesciences LLC, and Medtronic plc. JenaValve Inc was excluded because their product was no longer on the market at the start of the investigation. Direct Flow was excluded because the company was out of business. NVT GmbH did not want to cooperate; the German Competent Authority was asked to follow up on this. Thus, in total five products were included for assessment of the technical documentation.

A predefined selection of the technical documentation was requested from the manufacturers for assessment (see Annex 1). The method used for assessment of the documentation was adapted from previous investigations [Keizers et al., 2016, 2017; Van Drongelen et al., 2016; IGZ, 2013] and is described in detail in Annex 2.

In short, a form was developed in order to enable a structured and uniform assessment of the technical documentation (see Annex 3). The form included technical documentation items (e.g. risk analysis), which were in turn subdivided into sub-items (e.g. risk control/mitigation). For every sub-item, presence of adequate information was assessed. The MDD, MEDDEV guidance documents and harmonised European standards as relevant were used as a basis for the assessment of the various (sub-)items. If adequate information was missing (a shortcoming), this was noted on the form. The overall conclusion per technical documentation item was based on the shortcomings identified, if any, and translated into a ‘good’, ‘almost good’, ‘moderate’ or ‘insufficient’ score based on the expert judgement of the assessors. In case all sub-items were adequately addressed, the technical documentation item was scored ‘good’. If shortcomings were identified with little or no potential impact on patient safety according to the expert judgement of the assessors, the technical documentation item was scored ‘almost good’. However, in case shortcomings were considered to have a potential impact on patient safety, the technical documentation item was scored ‘moderate’ or ‘insufficient’, as judged appropriate. To facilitate a consistent assessment, two assessors assessed the documentation independently. Assessment forms were

[1] http://www.rivm.nl/Onderwerpen/M/Medische_hulpmiddelen/Hartkleppen/Overview_of_transcatheter_heart_valve_systems_CE_marked_and_in_Clinical_Investigations

compared and any discrepancies were discussed and resolved for a final assessment.

After the assessment, the manufacturers were informed about the results and were given the opportunity to check on factual inconsistencies. In case a manufacturer was of the opinion that the assessment of a specific (sub-)item contained factual inconsistencies, the manufacturer was requested to either state where the specific information could be found in the original submitted documentation or provide additional documentation which contained the specific information. In the latter case, only documentation dated latest 10th May 2017, the date of initial information request, was considered.

The following paragraphs summarize the anonymized results of the technical documentation assessment, starting with an overview of the overall findings per transcatheter aortic valve system. The results reflect the assessment scores *after* processing of any additional information provided by the manufacturers. The subsequent paragraphs describe the findings per documentation item. The detailed results of the assessment of the technical documentation are presented in Table 4.1 (Annex 4). At the end of this chapter, an evaluation is given of the potential impact on patient safety of shortcomings found in the documentation.

2.1 Overall quality of the technical documentation

The overall results of the assessment are shown in Table 2.1. None of the technical documentation sets scored 'insufficient' for any item but also none of the sets scored entirely 'good' at all items. One documentation set had only 'good' or 'almost good' items, whereas the other four sets had one or two 'moderate' file items.

Table 2.1 Overview of the assessment of the technical documentation of TAVI systems

File item	TAVI1	TAVI2	TAVI3	TAVI4	TAVI5
Device description	Almost good	Good	Good	Good	Good
Instructions for use	Good	Good	Good	Good	Good
Risk analysis	Almost good	Moderate	Moderate	Almost good	Almost good
Biocompatibility	Good	Almost good	Good	Good	Almost good
Biological safety	Good	Good	Almost good	Good	Almost good
Clinical evaluation	Almost good	Good	Moderate	Moderate	Moderate
S&A PMS data	Good	Good	Good	Good	Moderate

Abbreviations:
PMS – post-market surveillance
S&A – summary and analysis
TAVI – transcatheter aortic valve implantation

2.2 Device description

The device description of four technical documentation sets complied with all aspects checked in the assessment. One file was considered

'almost good' due to a shortcoming in the description of any novel features. Features of the system such as valve and catheter delivery system were described in general, but no specific attention was paid to which of the features was novel. Therefore, it was not clear how this device differs from a previous generation of the TAVI system.

2.3 Instructions for use

No shortcomings were found in any of the instructions for use (IFU). IFU were submitted in Dutch and/or English. Indications, important aspects of the use (e.g. trained user), contraindications, and other transcatheter aortic valve-related topics were mentioned. Thus, all IFUs complied with the aspects checked in the assessment.

2.4 Risk analysis

All risk analyses had one or more shortcomings. One risk management plan was not submitted, although the manufacturer indicated that it was available. Nevertheless, several risk management issues that should be part of the plan were described in the provided risk management file and therefore the risk analysis of this device was scored 'almost good'. All risk analyses contained a date/version number and referred to the harmonised European standard on risk management for medical devices [EN ISO 14971, 2012]. Also the risk control/mitigation as well as the acceptability of residual risks were addressed in all cases.

Required general risk categories (see Annex 3, Attachment II), based on hazards derived from EN ISO 14971, were not fully addressed in three cases: information on 'Disposal and scrapping' of the medical device was missing.

The item 'Contraindications and TAVI-related risk topics' (see Annex 3, Attachment I) had shortcomings in two cases. In both cases, contraindications addressed in the IFU were not or only partially analysed in the risk analysis. Following the manufacturer's check on factual inconsistencies in the assessment by RIVM, both manufacturers indicated to incorporate the RIVM's feedback in future updates of the risk analysis documents. However, the outcome of the current assessment could not be changed on the basis of this statement and therefore the files of these two manufacturers were scored 'moderate' for risk analysis.

2.5 Biocompatibility

The EN ISO 10993 series of standards was used by all manufacturers. In general, the evaluation of the biocompatibility was properly performed, with only two shortcomings leading to 'almost good' scores. In both cases, shortcomings related to absence or limited information regarding 'any history of clinical use or human exposure data' and 'existing toxicology/biocompatibility data'. For example, only a standard operation procedure was submitted and no literature review regarding these aspects was submitted. However, all applicable biocompatibility tests were conducted and submitted. In all cases, the medical device passed all biocompatibility tests.

2.6 Biological safety

This item refers to management of biological safety aspects related to the use of animal tissue in medical devices, e.g. contamination by viruses or TSE agents, as described in the EN ISO 22442 series of standards. Two technical documentation files had a shortcoming in their description of the system for starting material record-keeping. This aspect is required for the traceability of any components from sources to the finished medical device. In both cases a general description was provided without details resulting in an 'almost good' score. All other aspects related to biological safety were covered in all files, i.e. a list of materials of animal origin, information on selection of sources, harvesting, processing, preservation, testing and handling of tissues of animal origin, process validation and, where applicable, information on conformity with Commission Regulation (EU) No 722/2012 [European Commission, 2012] was ensured.

2.7 Clinical evaluation

The clinical evaluation is an extensive item in the technical documentation file and comprises 13 sub-items (see Annex 3, item 4.4). The reference document for clinical evaluation is the MEDDEV guidance document on this topic [European Commission, 2016]. One technical documentation file complied with all aspects checked in the assessment. Four files each had one shortcoming. Three of them resulted in a 'moderate' score for this documentation item and one in 'almost good'.

A shortcoming was found for the choice of clinical data types, in particular in relation to the use of the equivalence principle. In case the characteristics of two medical devices are similar to a large extent (i.e. equivalent), it can be assumed that there would be no clinically significant difference in their safety and performance. Consequently, the so-called equivalence principle can be used, which means the clinical data of one device can be used in the clinical evaluation of the other device without conducting a new clinical investigation. This principle can only be used if literature provides strong evidence. In addition, clinical, technical, and biological characteristics of the two products should be included in the demonstration of equivalence according to the MEDDEV guidance document on clinical evaluation [European Commission, 2016]. In this case, the technical equivalence was not fully demonstrated. In particular, it was not substantiated whether added components in the design of the medical device could trigger clinically significant differences in the safety and performance of the medical device.

Two other shortcomings were related to inconsistency of medical device literature and the IFU with clinical data. In particular, not all exclusion criteria as mentioned in the clinical evaluation report were used to define contraindications for inclusion in the IFU.

The fourth shortcoming was found for the safety and performance claims, which were not clearly expressed. Specific claims should be included. The indications for use, contraindications and warnings were mentioned, however, these are not formulated as claims. The manufacturer did not elaborate on this aspect when the opportunity was

given to check on factual inconsistencies in the assessment. Therefore, the item was scored ‘almost good’.

2.8 Summary and analysis of post-market surveillance data

The summary and analysis of the post-market surveillance (PMS) data of four technical documentation sets complied with all aspects checked in the assessment. In one case, a shortcoming was found related to the sources used for collecting PMS data. In particular, only complaints were taken into consideration. Other, more proactive sources, e.g. expert user groups, post-market clinical follow-up studies, literature reviews, implant registries, and experience with similar devices made by the same or other manufacturers should also be used.

2.9 Potential impact of findings on patient safety

This paragraph analyses whether the findings described above potentially affect patient safety. Shortcomings in the technical documentation could imply that product safety and safe use of the device are insufficiently guaranteed. This in turn could have impact on patient safety. On the other hand, the impact of shortcomings could be counterbalanced by available information in other parts of the file, the file could be poorly maintained while the device is of high quality, or the manufacturer could have omitted to provide crucial parts of the documentation. Thus, while it is important that the technical documentation is providing all the necessary information in the correct section of the file, shortcomings in the file do not necessarily have impact on patient safety.

Device description and Instructions for use
The shortcoming in the device description, absence of the description of any novel features, is not considered to have impact on patient safety. The instructions for use did not contain shortcomings in any of the technical file documentations.

Risk analysis
For the risk analysis, the most frequently observed shortcoming was the absence of addressing disposal/scrapping of the medical device, which is considered to have no direct impact on patient safety. Not analysing risks related to contraindications and precautions potentially has impact on patient safety because measures to mitigate these risks could be missed. However, given the fact that the contraindications and precautions are provided to the experienced user, the potential impact is expected to be limited.

Biocompatibility
The shortcoming for biocompatibility in two technical documentation files was caused by not performing a literature review. A literature review is important as a first step in a biological evaluation [EN ISO 10993-1, 2009]. This is required in order to take account of the existing knowledge and the generally acknowledged state of the art, regarding the evaluation of biocompatibility of particular products. Furthermore, the review is used to prevent unnecessary animal tests being performed. However, in all cases, a standard set of tests was performed according to applicable standards (EN ISO 10993-series) and the results

did not indicate problems. Consequently, in these cases the potential impact on patient safety of not performing the literature review is counterbalanced by the data from testing and thus a negligible impact on patient safety is expected.

Biological safety
In two files only a general description of their traceability system was provided. A system for record-keeping allowing traceability from sources of starting materials, e.g. animal tissues, to the finished medical device is important. In case of unexpected adverse events, it is necessary to be able to trace all devices produced from the same source. If this is not possible, it potentially has an impact on patient safety. Since a system was present in both cases, and the other aspects related to biological safety, e.g. detailed information regarding materials of animal origin, process validation and conformity to the TSE Regulation (where applicable) were covered, potential impact on patient safety is expected to be very limited.

Clinical evaluation
In one clinical evaluation substantiation of the technical equivalence was limited. Insufficient substantiation of the equivalence principle potentially has an impact on patient safety. On the other hand, using a combination of the equivalence principle – i.e. using data obtained with a (partially) equivalent device – and data obtained from studies with manufacturer's own device (direct clinical evidence), can also provide the necessary full data set. It is not clear from the technical documentation file which clinical data were obtained from studies with the manufacturer's own device, and which data from other devices were included based on equivalence. Therefore, it cannot be determined whether direct clinical evidence could counterbalance the potential impact on patient safety posed by the limited substantiation of equivalence. Thus, this shortcoming is judged to have potential impact on patient safety.

Another shortcoming was a discrepancy between exclusion criteria in the clinical investigation and contraindications in the IFU. Exclusion criteria shape the intended patient population by defining which types of patients need to be excluded from a clinical investigation. Contraindications in the IFU indicate patient characteristics, e.g. comorbidities, in which case the device should not be used. For patients with characteristics corresponding to the exclusion criteria from the clinical investigation, benefit and risk of using the device have not been evaluated, and thus a contraindication is considered appropriate. Therefore, all exclusion criteria mentioned in the clinical investigation should be mentioned as contraindication in the IFU, which was not the case in this technical documentation file. Using a device in a category of patients which were excluded from the clinical investigation could lead to an inferior performance and unexpected complications. Therefore, this shortcoming is judged to have potential impact on patient safety.

PMS data
Using complaints as the only source for PMS led to a shortcoming for one technical documentation file. Other sources, especially (pro)active ones, should be used to obtain more comprehensive PMS data. Not

using such sources means missing the opportunity to improve the functionality and safety of the medical device. Therefore, this shortcoming is judged to have potential impact on patient safety.

2.10 Conclusions assessment of technical documentation

The content of the technical documentation varied between the included products. None of the technical documentation sets scored ‘insufficient’ for any item, but also none of the sets scored entirely ‘good’ at all items. Although it is important that the technical documentation is providing all the necessary information, shortcomings in the file do not necessarily mean that the device is of insufficient quality. An analysis of the shortcomings showed that the potential impact of most shortcomings on patient safety can be considered negligible or limited. However, the shortcomings related to the clinical evaluation and the post market surveillance data could imply that product safety and safe use of the devices concerned are insufficiently guaranteed.

Given the fact that the quality and safety of medical devices is required to be substantiated by the information in the files according to the regulatory system for medical devices, this outcome should be reason for manufacturers to carefully consider and resolve the shortcomings in order to substantiate the quality and safety of their medical devices. Several manufacturers have indicated they are continuing to improve their files during the transition they are currently making to compliance with the recently published new regulation for medical devices [European Commission, 2017]. Two of the main changes this regulation includes, are strengthening the requirements for clinical evaluation and post-market surveillance.

3 Conclusion

In this study, we have assessed the technical files from five manufacturers marketing transcatheter heart valves in Europe. All technical documentation files contained a number of shortcomings. The potential impact on patient safety is expected to be limited for most shortcomings. However, all the shortcomings need to be adequately addressed by the manufacturers in order to substantiate the quality and safety of their products as required in the regulatory system. To arrive at this over-all conclusion, two questions were addressed as described below.

Do the technical files of the selected TAVI provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD)?
All technical files showed two or more shortcomings, and thus full conformity with the MDD was not shown. None of the technical documentation sets had ‘insufficient’ items and one had only ‘good’ or ‘almost good’ items. The other four sets had one to two ‘moderate’ file items.

In case of shortcomings, do these lead to a concern for patient safety?
The regulatory system for medical devices depends to a large extent on the quality of the submitted technical documentation. Therefore, any shortcomings in that documentation could imply that product safety and safe use of the device are insufficiently guaranteed. However, shortcomings in a technical documentation file do not necessarily mean that the device is of insufficient quality. An analysis of the shortcomings in the technical documentation showed that the potential impact of most shortcomings on patient safety can be considered negligible or limited. However, the shortcomings related to the clinical evaluation and the post-market surveillance data could imply that product safety and safe use of the devices concerned are insufficiently guaranteed. Manufacturers should carefully consider and resolve the shortcomings in order to substantiate the quality and safety of their medical devices as required in the regulatory system.

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Annex 1: Checklist for Dutch request transcatheter heart valve implantation systems

1. Device description

The device description should cover the following elements:

a) a general description including its intended use/purpose;
b) the intended patient population and medical condition treated and other considerations such as patient selection criteria;
c) the mode of action;
d) the risk class and applicable classification rule according to MDD 93/42/EEC, Annex IX;
e) an explanation of any novel features;
f) a description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it;
g) a description or complete list of the variants of the device;
h) a general description of the key functional elements:
   - its parts/components,
   - its composition,
   - its functionality;
i) labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams;
j) a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body;
k) the relevant CE mark certificate(s) issued by the notified body, e.g. EC Design Examination Certificate Directive 93/42/EEC on Medical Devices, Annex II (4).

2. Instructions for use

The instructions for use of the device as described in essential requirement 13, including requirements 7.5 and 9.1 (MDD 93/42/EEC, Annex I).[1]

[1] For the purpose of the investigation, the instructions for use should be the ones associated with the medical device as marketed in the Netherlands; if the device is currently not marketed in the Netherlands, at least an English version should be provided.

3. Risk management plan and risk analysis

This documentation should contain a full report (NOT a summary) of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. Preferably, this risk analysis should be based on recognised standards, be consistent with the manufacturer's risk management plan, and be in English. For this investigation, the documentation should include:

a) The risk management plan;
b) The risk analysis, containing the following elements:
   - date/version number;
   - reference to any standards used, e.g. EN ISO 14971;

- all hazard categories (for example: Table Annex E of the current standard EN ISO 14971) identified or, appropriately, declared not applicable;
- estimates of associated risk;
- risk control, i.e. control measures that are consistently described in line with essential requirement 2 (MDD 93/42/EEC, Annex I);
- (overall) justification/acceptability of residual risks in relation to anticipated benefits;

c) the risk management report, ensuring that the risk management plan is appropriately implemented, residual risks are acceptable and appropriate methods are in place to obtain relevant production and post-production information.

4. Product verification and validation – relevant parts for this investigation;

4.1. General

The documentation should summarise the results of verification and validation studies undertaken to demonstrate conformity of the device with the essential requirements that apply to it. For this investigation, the information should cover the following items:

a) biocompatibility (see 4.2);
b) biological safety (see 4.3);
c) clinical evaluation (see 4.4);
d) where no testing has been undertaken, the documentation should incorporate a rationale for that decision.

4.2. Biocompatibility

Detailed information should be included on:

a) a structured biological evaluation programme including documented, informed decisions that assess the advantages/disadvantages and relevance of
   i. the physical and chemical characteristics of the various candidate materials;
   ii. any history of clinical use or human exposure data (including data in published literature);
   iii. any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites (including data in published literature);
   iv. the selection of appropriate tests;
b) the tests conducted;
c) standards applied;
d) protocols (“standard operating procedures”) of the in vitro and in vivo studies conducted;
e) analysis of data;
f) summary of results and conclusion.

4.3 Biological safety (for devices using animal tissue or their derivatives)

Substantiation of the choices made in relation to the bullet points below shall include reference to existing data in published literature where possible. Detailed information should be included on:

a) a list of all materials of animal origin used in the device and a justification for their use;

b) detailed information concerning the selection of sources, the harvesting, processing, preservation, testing and handling of tissues, cells and substances of animal origin;
c) process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents; where such procedures would lead to unacceptable degradation of a device/material, substantiation why other risk control measures are sufficient;
d) description of the system for record-keeping to allow traceability from sources to the finished device;
e) where applicable, information on how conformity with the requirements of the Commission Regulation (EU) No 722/2012 has been ensured.

4.4 Clinical evaluation

The documentation should contain the clinical evidence that demonstrates conformity of the device with the essential requirements that apply to it. The clinical evaluation report should contain the following elements:

a) the proprietary name of the medical device and any code names assigned during device development;
b) identification of the manufacturer of the medical device;
c) description of the medical device and its intended application;
d) intended therapeutic indications;
e) safety and performance claims made for the medical device;
f) context of the evaluation;
g) choice of clinical data types, i.e. clinical data used for the evaluation can be published scientific literature, clinical investigation(s), or a combination of scientific literature and clinical investigations(s);
h) description of clinical follow-up;
i) safety analysis of the medical device, including serious adverse events that occurred;
j) performance analysis of the medical device;
k) summary of the clinical data and appraisal;
l) consistency of medical device literature and instructions for use with clinical data;
m) conclusions.

More information on the contents of the clinical evaluation report is available in MEDDEV 2.7/1 and on the website of the International Medical Device Regulators Forum (www.imdrf.org).

5. Summary and analysis of PMS data

The submitted documentation should contain a PMS report of the last four years, or the period since introduction on the market if less than four years, containing the following elements:

a) summary of PMS data, including specification of the frequency of separate adverse events, complaints, side effects, complications, and description of other experiences related to the use of the product;
b) sources used to obtain PMS data;
c) analysis of PMS data;
d) actions taken based on the analysis of PMS data.

Annex 2: Method of the assessment of technical documentation

Identification and selection of manufacturers and devices
Identification of the manufacturers was performed by RIVM based on scientific literature and web searches. Of manufacturers having CE-marked TAVI systems, the latest TAVI generation was selected for inclusion in the investigation.

Technical documentation requested
IGJ requested a relevant part of the technical documentation of the selected TAVI systems from the accompanying manufacturers in order to assess the information and report on the assessment anonymously in an RIVM letter report. With the letter requesting the technical file, a checklist was enclosed which described details on the items to be submitted (see Annex 1). The checklist was developed by RIVM and was largely based on the Summary Technical Documentation (STED) from the Global Harmonisation Task Force[2], modified in some places to fit better with the requirements of the MDD. It was decided for this study that the information requested was directly related to the TAVI systems and not related to the procedures of the manufacturers (e.g. the PMS procedure). The following information was requested from the manufacturers:

- Device description
- Instructions for use (IFU)
- Risk management plan and risk analysis
- Product verification and validation – relevant parts for this investigation:
  - General
  - Biocompatibility
  - Biological safety (for devices using animal tissue or their derivatives)
  - Clinical evaluation
- Summary and analysis of post-market surveillance (PMS) data.

Following receipt, the documentation was checked for completeness and any missing documentation was requested once more by IGJ.

Assessment method
An assessment form (see Annex 3) was developed in order to enable a structured and uniform assessment of the documentation sets.
For each section of the checklist from Annex 1, a file item was included and for each item a set of sub-items was listed (largely based on the sub-items listed in the STED). The MDD, the MEDDEV guidance document 2.7.1/Rev4 on clinical evaluation and harmonised European standards as relevant were used as a basis for the assessment of the

[2] The Global Harmonization Task Force (GHTF) was the predecessor of the current International Medical Device Regulators Forum (IMDRF). IMDRF aims to accelerate international medical device regulatory harmonization and convergence. GHTF final documents are still current and can be accessed on the IMDRF website. As the work of IMDRF progresses, these documents will be reviewed and published as IMDRF documents. For more information, see http://www.imdrf.org/index.asp.

particular (sub-)items on risk management (EN ISO 14971), biocompatibility (EN ISO 10993 series) and biological safety (EN ISO 22442 series). In general, the assessment was based on the presence or adequate description of each particular sub-item in the documentation. Only the shortcomings were noted in the assessment form.

The device description was mainly used as background information for the assessment. For the IFU, it was checked whether specific TAVI-related risks (see Annex 3, Attachment I) were mentioned. For the assessment of the risk analysis, it was checked whether these TAVI-related risks were addressed as well as whether general hazard categories (see Annex 3, Attachment II), as derived from the harmonised standard for risk management of medical devices [EN ISO 14971, 2012] were covered. For the item product verification the documentation should summarise the results of verification and validation studies undertaken to demonstrate conformity of the device with the essential requirements that apply to it. For this investigation, the information should at least cover the following items: biocompatibility, biological safety and clinical evaluation. For biocompatibility, it was checked whether appropriate tests were performed. The biological safety of the medical device was checked because of the presence of materials from animal tissue or their derivatives and the associated risks. It should be demonstrated that the biological risk is minimized. For the clinical evaluation, a list of TAVI-related topics to be covered was drawn up and checked (see Annex 3, Attachment III). For the summary and analysis of PMS data it was checked whether PMS was adequately performed.

To facilitate consistent assessment, two assessors assessed the documentation independently. Assessment forms were compared and any discrepancies were discussed and resolved for a final assessment. This method has also been used for previous investigations on metal-on-metal hip implants, silicone breast implants, blood glucose meters and dermal fillers.

Quality of technical documentation items
Using expert judgement of the RIVM, the overall conclusion for the technical documentation items was obtained based on the shortcomings in relation to the potential impact of the finding on patient safety.
If the shortcoming had no relation to patient safety or was more of an ‘administrative’ nature according to the expert judgement of the assessors, the conclusion was ‘almost good’. If there was a relation to patient safety the conclusion was ‘moderate’. If there were several shortcomings related to patient safety the conclusion was ‘insufficient’. Items scored ‘good’ if every sub-item was adequately addressed and no shortcomings were observed.

Manufacturer’s check on factual inconsistencies
Manufacturers received the result of the assessment of the requested file items in the attached assessment form. In case the manufacturer was of the opinion that the assessment contained factual inconsistencies, he was given the opportunity to respond and point out these inconsistencies before the assessment was made final.

Two kinds of factual inconsistencies were considered:

- The manufacturer submitted information but it did not appear to be taken into account for a specific file item or sub-item. The manufacturer was requested to specify the name of document and page number(s);
- The appropriate documentation to cover a specific item of the assessment did exist at the time, but was not submitted. As the investigation was based on the situation at the moment of the submission request, any documentation dating from after 10 May 2017, the date of the request for the technical documentation items, was not taken into consideration during the re-assessment.

Annex 3: Assessment form

	Medical device code				
	Notified body (code and name)				

1	**Device description**	**Shortcomings**	**Reference**	**Version**	**Date**
1.a	General description, including intended use / purpose				
1.b	Intended patient population and medical conditions treated and other considerations such as patient selection criteria				
1.c	The mode of action and delivery approach				
1.d	The risk class and applicable classification rule according to MDD 93/42/EEC, Annex IX				
1.e	An explanation of any novel features				
1.f	A description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it				
1.g	A description or complete list of the variants of the device				
1.h	A general description of the key functional elements: its parts / compartments; its composition and its functionality				
1.i	Labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts / components, including sufficient explanation to understand the drawings and diagrams				
1.j	A description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body				
1.k	The relevant CE mark certificate(s) issued by the notified body, e.g. EC Design Examination Certificate Directive 93/42/EEC on Medical Devices, Annex II (4)				
		Conclusion:			

2	IFU	Shortcomings	Reference	Version	Date
2.a	Indications for use				
2.b	Important aspects of the use of the TAVI (trained user)				
2.c	Contraindications and TAVI-related risk topics (attachment I)				
2.d	IFU in Dutch or English				
		Conclusion:			

3	Risk analysis	Shortcomings	Reference	Version	Date
	This documentation should contain a full report (NOT a summary) of the risks identified during the risk analysis process and how these risks have been controlled to an acceptable level. Preferably, this risk analysis should be based on recognised standards, be consistent with the manufacturer's risk management plan, and be in English. For this investigation, the documentation should include:				
3.a	Risk management plan				
3.b	The risk analysis, containing the following elements:				
	Dated / version number risk analysis;				
	Reference to any standards used, e.g. EN ISO 14971;				
	All hazard categories cf EN ISO 14971 (see attachment II) identified or, appropriately, declared not applicable;				
	Contraindications and TAVI-related risk topics addressed (attachment I);				
	Estimates of associated risk;				
	Risk control, i.e. control measures that are consistently described in line with essential requirement 2 (MDD 93/42/EEC, Annex I);				
	Acceptability of residual risks addressed in relation to anticipated benefits				
3.c	Conclusions: the risk management report, ensuring that the risk management plan is appropriately implemented, residual risks are acceptable and appropriate methods are in place to obtain relevant production and post-production				

	information				
		Conclusion:			

4	**Product verification and validation – relevant parts for this investigation**	**Shortcomings**			
4.1	*The documentation should summarise the results of verification and validation studies undertaken to demonstrate conformity of the device with the essential requirements that apply to it. For this investigation, the information should cover the items 4.2 / 4.3 and 4.4.*				
	Where no testing has been undertaken, the documentation should incorporate a rationale for that decision.				

4.2	**Biocompatibility**	**Shortcomings**	**Reference**	**Version**	**Date**
4.2.a	*A structured biological evaluation program including documented, informed decisions that assess the advantages / disadvantages and relevance of*				
	i. the physical and chemical characteristics of the various candidate materials;				
	ii. any history of clinical use or human exposure data (including data in published literature);				
	iii. any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites (including data in published literature);				
	iv. the selection of appropriate tests				
4.2.b	Tests conducted				
4.2.c	Standards applied (ISO 10993-series)				
4.2.d	Protocols of the in-vitro and in-vivo studies conducted				
4.2.e	Analysis of data				
4.2.f	Summary of results and conclusions				

		Conclusion:			

4.3	**Biological safety**	**Shortcomings**	**Reference**	**Version**	**Date**
	Substantiation of the choices made in relation to the bullet points below shall include reference to existing data in published literature where possible. Detailed information should be included on:				
4.3.a	A list of all materials of animal origin used in the device and a justification for their use				
4.3.b	Detailed information concerning the selection of sources, the harvesting, processing, preservation, testing and handling of tissues, cells and substances of animal origin				
4.3.c	Process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents; where such procedures would lead to unacceptable degradation of a device / material, substantiation why other risk control measures are sufficient				
4.3.d	Description of the system for record-keeping to allow traceability from sources to the finished device				
4.3.e	Where applicable, information on how conformity with the requirements of the Commission Regulation (EU) No 722/2012 has been ensured				
		Conclusion:			

4.4	**Clinical evaluation**	**Shortcomings**	**Reference**	**Version**	**Date**
	The documentation should contain the clinical evidence that demonstrates conformity of the device with the essential requirements that apply to it. The clinical evaluation report should				

	contain the following elements:				
4.4.a	The proprietary name of the medical device and any code names assigned during device development				
4.4.b	Identification of the manufacturer of the medical device				
4.4.c	Description of the medical device and its intended application				
4.4.d	Intended therapeutic indications				
4.4.e	Safety and performance claims made for the medical device				
4.4.f	Context of the evaluation				
4.4.g	Choice of clinical data types, i.e. clinical data used for the evaluation can be published scientific literature, clinical investigation(s), or a combination of scientific literature and clinical investigations(s)				
4.4.h	Description of clinical follow-up				
4.4.i	Safety analysis of the medical device, including serious adverse events that occurred				
4.4.j	Performance analysis of the medical device				
4.4.k	Summary of the clinical data and appraisal				
4.4.l	Consistency of medical device literature and instructions for use with clinical data (see attachment III)				
4.4.m	Conclusions				
		Conclusion:			

5	**Summary & analysis of PMS data**	**Shortcomings**	**Reference**	**Version**	**Date**
	The submitted documentation should contain a PMS report of the last four years, or the period since introduction on the market if less than four years, containing the following elements:				
5.a	Sources used to obtain PMS data				
5.b	Summary of PMS data, including specification of the frequency of separate adverse events, complaints, side effects, complications, and				

	description of other experiences related to the use of the product				
5.c	Analysis of PMS data and conclusions				
5.d	Actions taken based on the analysis of PMS data				
		Conclusion:			

Attachment I

Contraindications and risks based on literature for TAVI

	IFU	RA
1. Contraindications		
Left ventricular or atrial thrombus		
Vascular conditions (stenosis, tortuosity, calcification)		
Congenital aortic stenosis or unicuspid or bicuspid aortic valve		
Inability to tolerate anti-platelet / anti-coagulant therapy		
Active systemic infection (sepsis or endocarditis)		
Hypersensitivity to contrast agents that cannot be premedicated		
Hypersensitivity to e.g. aspirin, all thienopyridines, heparin, nickel, titanium, tantalum, bovine-derived materials or poly-urethanes		
Non-valvular aortic stenosis		
Presence of mitral or aortic bioprothesis		
Evidence of intracardial mass or vegetation		
Coronary artery disease / untreated clinically significant coronary artery disease requiring revascularization		
Severe deformation of chest		
Significant aortic disease		
Severe ventricular dysfunction with ejection fraction < 30% or 20%		
Cerebrovascular events (stroke / CVA / TIA) < 6 months		
Hypertropic cardiomyopathy with or without obstruction (HOCM)		
Recent emboli		
Patient refusing blood transfusion		
Pregnancy		
Creatine clearance < 20 ml/min		
Uncontrolled atrial fibrillation		
Renal failure therapy		
Previous aortic mechanical valve replacement		

	IFU	RA
2. Complications / side effects / adverse events		
Stroke / CVA / TIA		
Death (all-cause / cardiovascular mortality)		
Vascular complications (major / minor complications)		
Bleeding (life-threatening / major / minor bleeding)		
Pacemaker implantation		
Myocardial infarction (peri-procedural MI (<72 h after index procedure), spontaneous MI (>72 h after index procedure))		
Acute kidney injury (stage 1, 2 or 3) / renal failure		
Allergic reaction / hypersensitivity / inflammation		
Infection		
Severe allergic reaction (anaphylactic shock)		
Cardiac arrhythmias		
Haemolysis		
Prosthetic valve dysfunction - regurgitation		

Prosthetic valve dysfunction - stenosis
Prosthetic valve dysfunction - thrombosis
Endocarditis
Pulmonary embolism
Thrombosis
Haemodynamic instability
Device embolisation (valve or delivery system components)
Coronary obstruction
Conversion to open surgery
Unplanned use of cardiopulmonary bypass
Ventricular septal perforation
Cardiac tamponade (evidence of a new pericardial effusion associated with haemodynamic instability)
Valve malpositioning (valve migration, valve embolization, ectopic valve deployment)

	IFU	RA
3. Operational specifications		

Principles of operation / specific instruction for implanting
Intended device delivery approach
Specific instructions for device preparation
Expected device lifetime
Shelf-life
Shipping / storage limits
Sterility
Visibility under fluoroscopy or other imaging modalities
Warnings regarding handling and implanting the device
Crush / force resistance
Instruction for re-sterilisation method / max number (if applicable)
Magnetic resonance safety

	IFU	RA
4. Risk factors, other than side effects		

Virus, BSE or other transmissible agent
Embolization of debris
Bio-incompatibility
Package opened or damaged
Paravalvular leak
Inability to complete implant procedure
Unintended anatomical interactions
Plastic deformation of prosthesis support structure
Prosthesis is prematurely deployed

Attachment II

This appendix provides a selection of categories of risks and subsequent examples, and is based on hazards described in the standard EN ISO 14971:2007, corrected 2012 Medical devices – Application of risk management to medical devices.

Biological hazards	

- Contamination with bacteria
- Contamination with viruses
- Contamination with endotoxins
- Re- or cross infection

Biocompatibility	

- Allergencity / irritancy
- Cytotoxicity
- Acute systemic toxicity
- Animal implantation

Chemical hazards	

- Acids and alkalis
- Residues, e.g. cleaning
- Contaminating agents
- Manufacturing additives or adjuvants
- Corrosion

Use error	

- Use by unskilled / untrained personnel
- Inadequate equipment
- Inadequate implantation / procedure
- Inadequate patients
- Mismatch

Hazardous phenomena linked to inadequate labelling	

- Incomplete instructions for use
- Inadequate description of performance characteristics
- Inadequate specification of intended use
- Inadequate disclosure of limitations

Hazardous phenomena linked to inadequate operating instructions	

- Inadequate specification of accessories to be used with the medical device
- Incompatibility of consumables / accessories / other medical devices
- Inadequate specification of pre-use checks
- Over-complicated (operating) instructions

Hazardous phenomena linked to insufficient warnings about	

- Of complications / side effects
- Of single-use medical devices

Incomplete requirements	

- Inadequate specification of:
  - design parameters
  - performance requirements
  - end of life

Manufacturing processes	
- Insufficient control of changes to manufacturing processes - Insufficient control of materials / materials compatibility information - Insufficient control of manufacturing processes - Insufficient control of subcontractors	
Transport and storage	
- Inadequate packaging - Contamination or deterioration - Inappropriate environmental conditions	
Environmental factors	
- Physical, e.g. heat, pressure, time - Chemical, e.g. corrosions, contamination - Mechanical, e.g. accidental mechanical damage	
Cleaning, disinfection and sterilization	
- Lack / inadequate specification for, validated sterilization procedures, if applicable cleaning / disinfection - Inadequate conduct of cleaning, disinfection and sterilization	
Disposal and scrapping	
- No or inadequate information provided	
Formulation	
- (Bio)degradation - Inadequate warning of hazards associated with incorrect formulations	
Potential for use errors triggered by design flaws, such as	
- Missing instructions for use - Ambiguous or unclear device state - Ambiguous or unclear presentation of settings, measurements or other information	
Failure modes	
- Unexpected loss of mechanical integrity - Deterioration in function (e.g. change in resistance to flow) as a result of ageing - Loss of sterility	

Attachment III
Clinical evaluation of TAVIs

1. Indications	

Patients with aortic valve insufficiency (regurgitation)
Patients with symptomatic severe (native / calcific) aortic stenosis who are considered high surgical risk
Patients with symptomatic severe (native / calcific) aortic stenosis who are considered intermediate surgical risk
Patients with previously implanted failing aortic surgical bioprosthesis

2. Contraindications	

Left ventricular or atrial thrombus
Vascular conditions (stenosis, tortuosity, calcification)
Congenital aortic stenosis or unicuspid or bicuspid aortic valve
Inability to tolerate anti-platelet / anti-coagulant therapy
Active systemic infection (sepsis or endocarditis)
Hypersensitivity to contrast agents that cannot be premedicated
Hypersensitivity to e.g. aspirin, all thienopyridines, heparin, nickel, titanium, tantalum, bovine-derived materials or poly-urethanes
Non-valvular aortic stenosis
Presence of mitral or aortic bioprothesis
Evidence of intracardial mass or vegetation
Coronary artery disease / untreated clinically significant coronary artery disease requiring revascularization
Severe deformation of chest
Significant aortic disease
Severe ventricular dysfunction with ejection fraction < 30% or 20%
Cerebrovascular events (stroke / CVA / TIA) < 6 months
Hypertropic cardiomyopathy with or without obstruction (HOCM)
Recent emboli
Patient refusing blood transfusion
Pregnancy
Creatine clearance < 20 ml/min
Uncontrolled atrial fibrillation
Renal failure therapy
Previous aortic mechanical valve replacement

3. Safety and performance	

Stroke / CVA / TIA
Death (all-cause / cardiovascular mortality)
Vascular complications (major / minor complications)
Bleeding (life-threatening / major / minor bleeding)
Pacemaker implantation
Myocardial infarction (peri-procedural MI (<72 h after index procedure), spontaneous MI (>72 h after index procedure))
Acute kidney injury (stage 1, 2 or 3) / renal failure
Allergic reaction / hypersensitivity / inflammation

Infection
Severe allergic reaction (anaphylactic shock)
Cardiac arrhythmias
Haemolysis
Prosthetic valve dysfunction - regurgitation
Prosthetic valve dysfunction - stenosis
Prosthetic valve dysfunction - thrombosis
Endocarditis
Pulmonary embolism
Thrombosis
Haemodynamic instability
Device embolisation (valve or delivery system components)
Coronary obstruction
Cardiac tamponade
Bio-incompatibility
Amount of contrast dye
Hospital length of stay
Magnetic resonance safety

4. Device and procedural success	

Device success
Procedural success

Annex 4: Results of the assessment of technical documentation

Table 5.1 Overview of the assessment of technical documentation of TAVI systems after the manufacturer's check on factual inconsistencies – Where shortcomings were found, this is indicated with sh.

File item	TAVI 1	TAVI 2	TAVI 3	TAVI 4	TAVI 5
Device description					
General description, including intended use / purpose					
Intended patient population and medical conditions treated and other considerations such as patient selection criteria					
The mode of action and delivery approach					
The risk class and applicable classification rule according to MDD 93/42/EEC, Annex IX					
An explanation of any novel features	sh				
A description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it					
A description or complete list of the variants of the device					
A general description of the key functional elements: its parts / compartments; its composition and its functionality					
Labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts / components, including sufficient explanation to understand the drawings and diagrams					
A description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body					
The relevant CE mark certificate(s) issued by the notified body, e.g. EC Design Examination Certificate Directive 93/42/EEC on Medical Devices, Annex II (4)General description					
IFU					
Indications for use					
Important aspects of the use of the TAVI (trained user)					
Contraindications and TAVI-related risk topics (attachment I)					
IFU in Dutch or English					
Risk analysis					
Risk management plan	sh				
Dated / version number risk analysis					
Reference to any standards used, e.g. EN ISO 14971					
All hazard categories cf EN ISO 14971 (see attachment II) identified or, appropriately, declared		sh		sh	sh

not applicable					
Contraindications and TAVI-related risk topics addressed (attachment I)		sh	sh		
Estimates of associated risk					
Risk control, i.e. control measures that are consistently described in line with essential requirement 2 (MDD 93/42/EEC, Annex I)					
Acceptability of residual risks addressed in relation to anticipated benefits					
Conclusions: the risk management report, ensuring that the risk management plan is appropriately implemented, residual risks are acceptable and appropriate methods are in place to obtain relevant production and post-production information					
Biocompatibility					
The physical and chemical characteristics of the various candidate materials					
Any history of clinical use or human exposure data (including data in published literature)		sh			sh
Any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites (including data in published literature)		sh			sh
The selection of appropriate tests					
Tests conducted					
Standards applied (ISO 10993-series)					
Protocols of the in-vitro and in-vivo studies conducted					
Analysis of data					
Summary of results and conclusions					
Biological safety					
A list of all materials of animal origin used in the device and a justification for their use					
Detailed information concerning the selection of sources, the harvesting, processing, preservation, testing and handling of tissues, cells and substances of animal origin					
Process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents; where such procedures would lead to unacceptable degradation of a device / material, substantiation why other risk control measures are sufficient					
Description of the system for record-keeping to allow traceability from sources to the finished device			sh		sh
Where applicable, information on how conformity with the requirements of the Commission Regulation (EU) No 722/2012 has been ensured					
Clinical evaluation					
The proprietary name of the medical device and any code names assigned during device development					
Identification of the manufacturer of the medical					

device					
Description of the medical device and its intended application					
Intended therapeutic indications					
Safety and performance claims made for the medical device	sh				
Context of the evaluation					
Choice of clinical data types, i.e. clinical data used for the evaluation can be published scientific literature, clinical investigation(s), or a combination of scientific literature and clinical investigations(s)				sh	
Description of clinical follow-up					
Safety analysis of the medical device, including serious adverse events that occurred					
Performance analysis of the medical device					
Summary of the clinical data and appraisal					
Consistency of medical device literature and instructions for use with clinical data (see attachment III)			sh		sh
Conclusions					
Summary and analysis of PMS data					
Sources used to obtain PMS data					sh
Summary of PMS data, including specification of the frequency of separate adverse events, complaints, side effects, complications, and description of other use-related experiences of the product					
Analysis of PMS data and conclusions					
Actions taken based on the analysis of PMS data					

Abbreviations:
IFU – instructions for use
PMS – post-market surveillance
TAV – transcatheter aortic valve
TAVI – transcatheter aortic valve implantation

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