



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Mesh implants intended to treat patients with pelvic organ prolapse

Market survey and quality of technical documentation

RIVM letter report 2020-0154
B. Roszek et al.



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Colophon

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Synopsis

Mesh implants intended to treat patients with pelvic organ prolapse

Market survey and quality of technical documentation

Mesh implants intended to treat patients with pelvic organ prolapse (POP) can be implanted via two surgical approaches: via the abdomen (transabdominal) or via the vagina (transvaginal).

The Health and Youth Care Inspectorate requested RIVM to assess the technical documentation of mesh implants intended to treat patients with POP. First, RIVM investigated which mesh implants were used by physicians. Nine types of mesh implants used by physicians in the Netherlands in 2018 were assessed. Four of these are intended for implantation via the vagina and five for implantation via the abdomen. The nine mesh implants are produced by six different manufacturers.

RIVM has identified major or minor shortcomings in multiple parts of the technical documentation of all assessed products. An example of a major shortcoming is that the safety and performance are not adequately substantiated with data on the use of the product in humans. A minor shortcoming is for example the lack of an adequate description of the surgical procedure in the instructions for use in cases where it is indicated that physicians have to be trained to perform this type of surgery.

It is not clear whether the identified shortcomings could potentially damage a patient's health. Shortcomings in the technical documentation do not necessarily imply that the actual product is of insufficient quality. However, the safety and performance of the products have not been substantiated properly due to the shortcomings in the technical documentation. The regulatory system requires that manufacturers carefully investigate and resolve the shortcomings in their technical documentation. Manufacturers have indicated that they are improving the technical documentation based on the results of the assessment by RIVM. Some manufacturers have reported that they have been reaudited by their notified bodies and that their improved technical documentation is now compliant with European regulatory requirements. These audits took place after the RIVM assessment was completed.

Starting in May 2021, new European regulations for medical devices will apply. This means manufacturers will have to comply with additional and more strict requirements, also for the technical documentation.

Keywords: mesh implant, pelvic organ prolapse, market survey, assessment technical documentation

Publiekssamenvatting

Bekkenbodemmatjes

Marktverkenning en kwaliteit van technische documentatie

Bekkenbodemmatjes zijn implantaten waarmee verzakkingen van organen in het gebied van de bekkenbodem worden behandeld. Bekkenbodemmatjes kunnen op verschillende manieren geplaatst worden: via de buik (transabdominaal) en via de vagina (transvaginaal).

In opdracht van de Inspectie voor Gezondheidszorg en Jeugd (IGJ) heeft het RIVM de technische documentatie van bekkenbodemmatjes beoordeeld. Hiervoor heeft het RIVM eerst onderzocht welke bekkenbodemmatjes er door artsen werden geplaatst. De technische documentatie van negen typen bekkenbodemmatjes die artsen in 2018 in Nederland hebben geplaatst, zijn daarna beoordeeld. Hiervan zijn er vier bedoeld om via de vagina te worden geplaatst en vijf via de buik. De negen bekkenbodemmatjes zijn door zes verschillende fabrikanten gemaakt.

Het RIVM heeft in de technische documentatie van alle beoordeelde producten in meerdere onderdelen grote of kleine tekortkomingen gevonden. Een voorbeeld van een grote tekortkoming is dat de veiligheid en prestaties onvoldoende zijn onderbouwd met gegevens over het gebruik van het product in de mens. Een kleine tekortkoming is bijvoorbeeld dat een goede beschrijving van de operatie in de gebruiksaanwijzing ontbreekt, terwijl er wel staat dat een arts getraind moet zijn voor dit soort operaties.

Het is niet duidelijk of de gevonden tekortkomingen schadelijk zijn voor de gezondheid van de patiënt. Tekortkomingen in de technische documentatie hoeven niet te betekenen dat er iets mis is met het product. Wel is het zo dat de veiligheid en prestaties van de producten door de tekortkomingen in de technische documentatie niet goed zijn onderbouwd. Regelgeving vereist dat fabrikanten de tekortkomingen in hun technische documentatie zorgvuldig onderzoeken en oplossen. Fabrikanten geven aan dat zij naar aanleiding van de resultaten van de RIVM-beoordeling de technische documentatie aan het verbeteren zijn. Sommige fabrikanten hebben gemeld dat ze sindsdien opnieuw door hun *notified bodies* zijn geaudit en dat hun aangepaste technische documentatie nu voldoet aan de Europese wet- en regelgeving. Deze audits hebben plaatsgevonden nadat de RIVM-beoordeling was afgerond.

Vanaf mei 2021 gelden nieuwe Europese regels voor medische hulpmiddelen. Daardoor moeten fabrikanten zich aan meer en strengere regels houden, ook voor de technische documentatie.

Kernwoorden: bekkenbodemmatje, marktverkenning, verzakking bekkenbodem, beoordeling technische documentatie

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Summary

Pelvic organ prolapse (POP) affects 30-40% of women worldwide, and reduces their quality of life. Treatment options include reconstructive surgical procedures using surgical mesh implants. Previous investigations reported serious complications in patients with mesh surgery for POP. In this study mesh implants intended to treat POP in the Netherlands were investigated. The first part of the study was a market survey, providing an overview of mesh implants used in the Netherlands. The second part consisted of the assessment of technical documentation of mesh implants. There are two surgical approaches to treat POP using mesh implants: transvaginal and transabdominal implantation. In this study, mesh implants for both approaches were included. This study was performed by order of the Dutch Health and Youth Care Inspectorate.

The market survey showed that nine types of mesh implants from six manufacturers were used in the Netherlands in 2018. Some of the implants were available in different variants and two of the legal manufacturers were part of the same multinational company. From the total of nine mesh implants, four were intended for transvaginal implantation and five for transabdominal implantation.

The assessment indicated shortcomings in technical files of all included mesh implants. Therefore, full conformity with the requirements in the Medical Devices Directive (MDD) was not shown. The general description and the instructions for use (IFU) had no or minor shortcomings in all files. However, the file items risk analysis, biocompatibility, clinical evaluation and summary and analysis of post-market surveillance (PMS) data showed major shortcomings in most of the files. In a number of cases, updated versions of one or more file items were also assessed. Generally, improvements were seen in updated versions. Some, however not all, identified improvements resulted in a change from major shortcoming to minor shortcoming in the overall conclusion on a file item.

Shortcomings in the technical file do not necessarily mean that the device is of insufficient quality. However, the identified shortcomings mean that there are uncertainties about impact on patient safety. Analysis of the identified shortcomings showed that there is a potential impact on patient safety related to shortcomings in many of the file items.

All the shortcomings need to be adequately addressed by the manufacturers in order to better substantiate the quality and safety of their products as required in the regulatory system. The Inspectorate informed RIVM that manufacturers have indicated to be working on improvements in their technical documentation in order to comply with the requirements for the MDD. Some of the manufacturers have indicated that the improved technical documentation passed audits by their notified bodies and stated that their technical documentation is now compliant with European regulatory requirements. These audits took place after the RIVM assessment was completed.

Starting in May 2021, new European regulations for medical devices will apply. This means manufacturers will have to comply with additional and more strict requirements, also for the technical documentation.

1 Introduction

1.1 Background

Pelvic organ prolapse (POP) is the descent of one or more of the pelvic organs, i.e. uterus, vagina, bladder or bowel into or out of the vagina. It may affect the anterior (bladder), middle (uterus) or posterior (rectum, or back wall of the vagina) compartment. Although POP can affect women of all ages, it more commonly occurs in older women and affects 30-40% of women worldwide [1, 2]. The etiology of POP is complex and multifactorial and is linked to childbearing, obesity and advancing age [3]. POP is not life-threatening, but it reduces the quality of life for women [4].

There are several treatment options available for POP, depending on the severity of the symptoms and the severity of the prolapse in combination with age and health of the patient. For women with a mild degree of POP, conservative treatment options are lifestyle changes, pelvic floor physiotherapy and vaginal pessaries [5, 6]. If these treatment options do not work or if the prolapse and symptoms are very severe, surgery is a treatment option. A variety of reconstructive surgical procedures are available for these women, for instance native tissue repair and surgical mesh implantation. Scientific studies showed that native tissue repair has a failure rate of recurrent prolapse of 17-20% [3]. This resulted in embracing surgical mesh as treatment option for POP [3]. Surgery can be performed through the abdomen (transabdominal) or through the vagina (transvaginal) [1, 2, 7, 8].

A surgical mesh is a medical device that is permanently implanted to provide extra support when repairing weakened tissue. Surgical mesh can be used to treat patients for multiple different indications. Examples of indications are urine incontinence, hernia repair and POP. Recently RIVM provided an overview with seven of these indications [9]. Mesh material can be synthetic or biological. It can be non-absorbable, partially absorbable or absorbable [7, 8]. In the current report we focus on synthetic, non-absorbable or partially absorbable surgical mesh implants for treatment of POP.

Given that the use of surgical mesh implants in the treatment of POP had been shown to be associated with various adverse events, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) was asked to provide a scientific opinion on the health risks of mesh implants used in urogynaecological surgery. They outlined that clinical outcome following mesh implantation is influenced by material properties, product design, overall mesh size, route of implantation, patient characteristics, associated procedures (e.g. hysterectomy) and the surgeon's experience [10]. They also indicated that the implantation of any mesh for the treatment of POP via the vaginal route should only be considered in complex cases, in particular, after failed primary repair surgery [10]. In 2018, RIVM reviewed international literature on long-term complications of transvaginal mesh implants. The range of long-term complications

varied in the reviewed literature from 0-48%. The identified complications were primarily associated with products that were not available on the Dutch market in 2018 [11].

The transabdominal surgical approach for mesh implantation can be carried out via laparotomy, conventional laparoscopy or robotic-assisted laparoscopy. Recently, Le Teuff *et al.* reported that the incidence of complications was similar comparing transvaginal mesh and transabdominal mesh. This included post-operative complications and complications one year post-operative [12]. In a recent Dutch investigation, van Zanten *et al.* showed a low mesh exposure rate in robot-assisted transabdominal pelvic floor surgery for POP [13]. Surgeon's experience is one of the factors that influence clinical outcome following mesh implantation [10] and thus complication rates are partly dependent on the surgeon's experience. Surgeon's experience and training differ among different countries. Therefore complication rates can vary among different countries. The exact complication rate of transvaginal and transabdominal mesh implantation in the Netherlands is not known.

Surgical mesh implanted to treat patients with POP can cause serious complications like infection, mesh shrinkage, chronic pain, including dyspareunia, exposure and erosion into other organs [3]. This has led to new international guidelines for the use of mesh implants that are more stringent [3, 6, 10]. In 2017, the European Association of Urology (EAU) and the European Urogynaecological Association (EUGA) published a paper with a consensus statement [3]. They indicate that it is clear that vaginally implanted mesh for POP is associated with increased risks and its use should be restricted to experts in specialised departments and to a special group of patients or approved clinical research. Furthermore, that the use of transabdominal mesh should also be restricted to specialist practice although the associated risk is considered more acceptable. In their conclusion, however, no distinction is made between surgical approaches: 'synthetic mesh for POP should be used only in complex cases with recurrent prolapse in the same compartment and restricted to surgeons with appropriate training, working in multidisciplinary referral centres' [3]. In addition, importantly, it is emphasised that patients should be adequately informed regarding the potential success rates and mesh-related adverse events compared with non-mesh alternatives, and should be engaged in the decision-making process [3].

1.2 Mesh implants in the Netherlands

In 2009 and 2010, the Dutch Health Care Inspectorate, currently the Dutch Health and Youth Care Inspectorate (hereafter Inspectorate) received and analysed incident reports concerning transvaginal mesh implants for the treatment of POP. In 2011, the Inspectorate started an investigation, and media attention in December 2012 led to an increase in reports to the Inspectorate regarding serious complications experienced by patients after receiving a transvaginal mesh implant. The Inspectorate published a report urging caution regarding the use of transvaginal mesh implants [14]. Since 2013, the number of reports received by the Dutch Inspectorate on transvaginal mesh implant complications has decreased.

After the publication of the Inspectorate's report in 2013, the Netherlands Society of Obstetrics and Gynaecology (NVOG) took several measures to improve transvaginal mesh implantation. They implemented a multidisciplinary guideline, and introduced specific indications for the treatment with the purpose of decreasing the number and severity of complications following transvaginal mesh implantation [15, 16]. The NVOG stated that the surgeon's experience is important and that therefore every surgeon would need to perform at least 10 transvaginal mesh implantations per year [15, 16].

For a medical centre that performs mesh surgery (transvaginal and/or transabdominal), the NVOG documents included a recommendation that at least two urogynaecology specialists or subspecialists competent in performing mesh surgery are available. The NVOG documents stated additional requirements for transvaginal mesh surgery, however did not provide specific indications or requirements on surgeon's experience for transabdominal mesh surgery [15, 16]. Given that the EAU and the EUGA made no distinction with regard to the surgical approach in the conclusion of their recent consensus paper [3], it was not clear whether the NVOG guideline still reflected current insights. The NVOG implemented a new guideline in December 2020 [17]. In the updated NVOG guideline no distinction is made between transabdominal and transvaginal mesh surgery with regard to requirements on surgeons experience.

The NVOG also has requirements and recommendations for facilities where mesh surgery is performed, and requires that all transvaginal and transabdominal mesh implants, together with any mesh-related complications are registered in a central NVOG system [15, 16, 17]. Unfortunately, not all surgical mesh implanted in patients with POP in the Netherlands are currently recorded in such a registry. Therefore the exact number and type of mesh implanted to treat patients with POP is not known. All surgeries can only be identified in the personal medical files of every patient available in the handling hospital. Only medical doctors treating these patients have access to these medical files. In 2019, RIVM reported on the number of transvaginal mesh reimbursement claims in 2015, 2016 and 2017. Per year 272 to 368 transvaginal mesh implants were provided. This number was based on reimbursement claims of the Dutch Healthcare Authority [18]. Recently, NVOG performed a survey in which all Dutch hospitals were asked to participate. The number of respondents is not known, but NVOG informed RIVM that participating hospitals reported that 172 transvaginal mesh were implanted in 2018 in the Netherlands¹. NVOG also performed a survey in which all Dutch hospitals were asked to participate concerning transabdominal mesh. NVOG informed RIVM that 72 hospitals responded to this survey, reporting that 600 transabdominal mesh were implanted in 2019.

1.3 Mesh implants in other countries

Like in the Netherlands, in recent years also in France a relatively small number of vigilance reports were filed at the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) [19]. Several countries (for instance USA, Australia, Ireland and the UK) have

¹ NVOG, Werkgroep Bekkenbodern (WBB) Nieuwsbrief November 2019

reported that mesh implants for POP continue to cause complications [20-24]. USA and Australia have taken transvaginal mesh implants off their market. In several countries, the use of surgical mesh implants for the transvaginal treatment of POP is under examination or restriction through measures taken by their national authorities [19]. For example, the Australian Government Department of Health, Therapeutic Goods Administration (TGA) determined that the risks to patients from implantation of transvaginal mesh to treat POP outweigh the potential benefits and the supply of these products is no longer allowed [23]. In contrast to transvaginal mesh implant procedures, transabdominal mesh implant procedures are still allowed to be performed in several of these countries (e.g. UK, USA and Australia) [20-24].

1.4 Current study

The Dutch Inspectorate is entrusted with market surveillance and law enforcement of medical devices and their use, in order to address the greatest risks for patient safety and their early identification. In order to gain more insight on the state of affairs for mesh implants used to treat POP in the Netherlands, the Inspectorate commissioned RIVM to perform a study. This study included both transvaginal and transabdominal mesh implants used to treat POP. Slings used to treat stress urinary incontinence and abdominal implants used to treat rectal prolapse were not included in this study. This study included the assessment of technical documentation requested by the Inspectorate in 2018 and 2020.

1.4.1 *Background information current study*

RIVM identified major shortcomings in the technical documentation of the two transvaginal mesh implants that were on the Dutch market November 1st 2019. Therefore, RIVM decided to notify the Inspectorate ahead of the full report. In February 2020, a summary of the assessment of the technical documentation sets of these two transvaginal mesh implants was reported to the Inspectorate and published by RIVM [25]. Subsequently, the Inspectorate published their position on this [26] and NVOG followed their position. Since then, transvaginal mesh implant surgery is recommended to be performed only in a clinical research setting subject to the Medical Research Involving Human Subjects Act (WMO) [27]. As the next step, RIVM assessed the technical documentation of the four transabdominal mesh implants that were on the Dutch market November 1st 2019 and identified major shortcomings. Assessment of the technical documentation identified major and minor shortcomings. Since, the mesh implants were still on the Dutch market November 1st 2019, RIVM decided to notify the Inspectorate ahead of the full report. In May 2020, RIVM reported a summary to the Inspectorate on the assessment of the technical documentation sets of these four transabdominal mesh implants. In the current full report, the overall results of the assessment of technical documentation of these transvaginal and transabdominal mesh implants are described, together with the results of three mesh implants that were withdrawn from the Dutch market earlier in 2019.

1.5 Aim of the study

The aim of this study was to investigate mesh implants intended to treat POP in the Netherlands. This study consisted of the following parts:

1. Market survey to compile an overview of mesh implants used in the Netherlands.
2. Assessment of technical documentation of selected mesh implants.

Part one

Regarding the market survey, the following question was addressed:

- Which transvaginal and transabdominal synthetic mesh implants are being used to treat POP in the Netherlands?

Part two

Regarding the assessment of technical documentation of selected mesh implants, the following questions were addressed:

- Do the technical files of the selected mesh implants provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD) [28]?
- In case of shortcomings, do these lead to a concern for patient safety?

1.6 Guide to reading the report

In chapter 2, the results of the market survey are presented, as well as the products selected for technical file assessment. Chapter 3 describes the results of the assessment of the technical files and the potential impact on patient safety. In chapter 4, the general conclusions are presented.

2 Market survey

To investigate which mesh implants, intended to treat patients with POP, are applied in the Netherlands, NVOG was contacted to obtain contact details of two experts in the Netherlands in 2018. These experts provided information of mesh implantation to treat patients with POP. In addition, information showed that the transvaginal approach to treat patients with POP was performed in a limited number of Dutch hospitals in 2018. Detailed information regarding Dutch hospitals where the transabdominal approach to treat patients with POP was performed was missing. Therefore, RIVM contacted NVOG for contact information of urogynaecologists working in hospitals where patients with POP are treated with transvaginal mesh implantation. RIVM sent a short questionnaire to these urogynaecologists in 2018. The questionnaire included the following questions:

- Which surgical mesh implants (include brand names and manufacturers), intended to treat patients with POP, do you implant?
- Which material are the surgical mesh implants made of: non-absorbable or partly-absorbable?
- Is the surgical mesh implanted transabdominally or transvaginally?

RIVM received responses from urogynaecologists working in eight hospitals. All these urogynaecologists used transvaginal and transabdominal mesh implants.

Subsequently, web searches (www.google.com) were conducted to identify information regarding the mesh products that were implanted in the Netherlands in 2018. This information included: the surgical route, mesh material, absorbability, material density, fixation methods and specifications. In general, information was obtained using websites of the manufacturers.

Table 2.1 and Annex 1 show an overview of all transvaginal and transabdominal mesh identified in the questionnaire. Several mesh products have been withdrawn from the market worldwide in 2019. These surgical mesh implants were used in 2018. In addition to this overview of mesh implants, one hospital reported that Parietene light (Parietex; manufacturer: Covidien/Medtronic) was used to treat patients for POP. This surgical mesh was not included in this study, because this surgical mesh is intended to be used for hernia repair.

Table 2.1 Overview of surgical mesh implants used to treat POP in the Netherlands in 2018.

Manufacturer	Name of the medical device	Surgical approach
A.M.I. GmbH	BSC Mesh ²	Transvaginal
BD/C.R. Bard Inc ³	Alyte® Y-Mesh Graft ¹	Transabdominal
BD/C.R. Bard Inc ³	Nuvia™ SI Single-Incision Prolapse Repair System ^{1, 4}	Transvaginal
Coloplast A/S	Restorelle® DirectFix™ ^{1, 5}	Transvaginal
Coloplast A/S	Restorelle® M L XL	Transabdominal
Coloplast A/S	Restorelle® Y	Transabdominal
Ethicon LLC ⁶	GYNECARE GYNEMESH™ PS Nonabsorbable PROLENE™ Soft Mesh	Transabdominal
Johnson & Johnson Int	ARTISYN™ Y-Shaped Mesh ⁷	Transabdominal
Promedon SA	Calistar S ⁸	Transvaginal

¹ These mesh implants were withdrawn from the Dutch market earlier in 2019.

² November 2019: Notified body temporarily restricted CE certificate of BSC Mesh. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for BSC Mesh.

³ BD (Becton, Dickinson and Company) acquired C.R. Bard Inc in 2017.

March 2019: BD announced the removal of its Women's Pelvic Organ Prolapse and Stress Urinary Incontinence Mesh Devices from the European market.

⁴ Nuvia™ SI Single-Incision Prolapse Repair System consisted of an anterior and posterior repair system.

⁵ Restorelle® DirectFix™ consisted of Restorelle® DirectFix™ Anterior and Restorelle® DirectFix™ Posterior. In May 2019, Coloplast A/S stopped selling Restorelle® DirectFix™.

⁶ Ethicon LLC is a Johnson & Johnson subsidiary.

⁷ ARTISYN™ Y-Shaped Mesh is a partly absorbable mesh.

⁸ March 2020: Notified body temporarily restricted CE certificate of Calistar S. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for Calistar S.

Disclaimer: This information is obtained from urogynaecologists, the Inspectorate and publicly available websites.

3 Assessment of technical documentation

In order to show compliance with the MDD [28], manufacturers of medical devices have to compile a file, including all relevant technical documentation, for example on items such as risk analysis, design verification and validation, and post-market surveillance. A selection of seven technical documentation items, hereafter called technical documentation set, was requested by the Inspectorate from the manufacturers for assessment (see Textbox 1 and Annex 2).

CE-marked gynaecological mesh implants for the treatment of POP, that were on the Dutch market in 2018, were included in this assessment. The manufacturers and their mesh implants are shown in Table 2.1.

The method used for assessment of the documentation was adapted from previous assessments [29-31] and is described in detail in Annex 3.

In short, a form was developed in order to enable a structured and uniform assessment of the technical documentation sets (see Annex 5). The form included technical documentation items (e.g. risk analysis), which were subdivided into sub-items (e.g. risk control/mitigation). For every sub-item, presence of adequate information was assessed. The MDD, MEDDEV guidance documents, harmonised European standards and state-of-the-art (EN) ISO standards as relevant, and specific scientific opinions and guidelines from professional medical societies were used as a basis for the assessment of the various (sub-)items [10, 15, 16, 28, 32-36]. If adequate information was missing, this was noted on the form as a shortcoming. To facilitate a consistent assessment, two assessors assessed the documentation independently. Assessment forms were compared and any discrepancies were discussed and resolved, leading to a combined assessment.

After this 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 originally submitted documentation or to provide additional documentation, which contained the specific information. In the latter case, only technical documentation that existed at the time of the initial request was taken into consideration. Two assessors reviewed the response of the manufacturer, assessed the (additional) technical documentation and finalized the assessment.

Textbox 1.

By order of the Inspectorate, RIVM assessed specified parts of the technical documentation (see Annex 2 for more details) of selected mesh implants intended to treat POP.

Requested technical documentation items:

1. Device description
2. Instructions for use
3. Risk management plan and risk analysis
4. Chemical composition
5. Biocompatibility
6. Clinical evaluation
7. Summary and analysis of post-market surveillance data

In December 2018, the Inspectorate requested technical documentation of all selected mesh implants and ordered RIVM to assess the technical documentation (Annex 4). RIVM performed the assessment and manufacturers were given the opportunity to check on factual inconsistencies. The response of the manufacturers was reviewed by RIVM and the assessments were finalized.

In January 2020, the Inspectorate requested the latest 'Clinical evaluation' of two transvaginal mesh implants and asked RIVM to assess the latest 'Clinical evaluation'. Manufacturers were not given the opportunity to check on specific factual inconsistencies of the assessment, however, they were given the opportunity to check on factual inconsistencies of the entire current report. In February 2020, a summary of the assessment of the technical documentation sets of two transvaginal mesh implants that were on the Dutch market November 1st 2019 was reported to the Inspectorate and published [25]. This assessment included the technical documentation requested in 2018 and the latest 'Clinical evaluation' requested in 2020.

In February 2020, the Inspectorate requested the latest technical documentation of 'Instructions for use (IFU)', 'Risk analysis', 'Clinical evaluation' and 'Summary and analysis of post-market surveillance data' of a set of transabdominal mesh implants. The Inspectorate asked RIVM to assess the latest technical documentation. Manufacturers were not given the opportunity to check on specific factual inconsistencies of the assessment, however, they were given the opportunity to check on factual inconsistencies of the entire current report. In May 2020, a summary on the assessment of the technical documentation sets of transabdominal mesh implants that were on the Dutch market November 1st 2019 was reported to the Inspectorate. This assessment included the technical documentation requested in 2018 and in 2020.

The Inspectorate has indicated that manufacturers and notified bodies are currently working to address the identified shortcomings at their request.

The following sections of this report summarize the results of the assessment of the technical documentation sets. A summary of the overall conclusions on shortcomings of file items requested in 2018 per mesh implant is given in section 3.1 in terms of major, minor or none. A file item can contain multiple shortcomings. Whether to qualify the combined shortcomings in a file item as major or as minor was based on expert judgment by the assessors. Important considerations to decide that the shortcomings were major include the amount and type of missing information and the potential impact on patient safety of the shortcoming. The detailed conclusions of the assessment of each technical file item per mesh implant are presented in Annex 6. The subsequent sections 3.2-3.8 summarise the findings per file item. In section 3.9, the assessment of the clinical evaluation for two transvaginal mesh implants requested in 2020 by the Inspectorate is compared to the assessment of document versions requested in 2018. In section 3.10, the assessment of the file items IFU, risk analysis, clinical evaluation, and summary and analysis of post-market surveillance (PMS) data, of four transabdominal mesh implants requested in 2020 are compared to the assessment of versions requested in 2018. In section 3.11, an evaluation is made of the potential impact on patient safety of shortcomings found in the technical documentation. A summary of the assessment of technical documentation are provided in section 3.12.

3.1 Overall quality of the technical documentation 2018

The overall results of the assessment of the technical documentation requested in 2018 are shown in Table 3.1. The files had major shortcomings in three up to five file items and minor shortcomings in one up to three file items. Five technical documentation sets had major or minor shortcomings in all file items. Four technical documentation sets had one or two file items without any shortcoming. Examples of identified shortcomings for each file item are listed below.

Table 3.1 Summary of the assessment of technical documentation sets of gynaecological mesh implants requested by the Inspectorate in December 2018.

Mesh (manufacturer)	Overall conclusion on shortcomings in file items						
	Device description	IFU	Risk analysis	Chemical composition	Biocompatibility	Clinical evaluation	S&A PMS data
<i>Transvaginal approach</i>							
BSC (A.M.I.)	None	Minor	Major	Major	Major	Major	^a
Calistar S (Promedon)	None	Minor	Major	Major	Major	Major	Major
Nuvia SI (BD)	Minor	Minor	Major	Major	Major	Major	Minor
Restorelle DirectFix (Coloplast)	Minor	Minor	Major	Minor	Major	Major	Major
<i>Transabdominal approach</i>							
Alyte (BD)	Minor	Minor	Major	Major	Major	Major	Major
ARTISYN (Johnson & Johnson)	None	Minor	Major	None	Major	Major	Major
GYNEMESH PS (Ethicon)	None	Minor	Major	None	Major	Major	Minor
Restorelle M L XL (Coloplast)	Minor	Minor	Major	Minor	Major	Major	Major
Restorelle Y (Coloplast)	Minor	Minor	Major	Minor	Major	Major	Major

Abbreviations:

IFU – instructions for use

S&A PMS – summary and analysis of post-market surveillance

^a Not assessed; the manufacturer did not provide documents dating before the deadline of the initial request by the Inspectorate despite repeated requests from the Inspectorate.

3.2 Device description

The device description of four technical documentation sets complied with all aspects checked in the assessment. Five technical documentation sets had minor shortcomings. Examples of identified shortcomings are:

- No separate section with a general device description as required in the MDD. The information was scattered over multiple file items;
- Lack of information when to use the various designs of the mesh when more than one design was available. It appeared that choosing the appropriate mesh depends on the preference and experience of the surgeon;
- No details on the geometry, i.e. physical dimensions of the different parts of a mesh;
- Insufficient description of a key functional element of the mesh;
- No information on the knitting pattern of the mesh.

3.3 Instructions for use

All instructions for use (IFU) were submitted in English and four IFUs also in Dutch. Considering the education levels of the users, both languages are considered acceptable. Contraindications and mesh-related risk topics were mentioned in all IFUs. However, minor shortcomings were identified in all IFUs. Examples of identified shortcomings are:

- The submission of a non-current version of the IFU, i.e. a version from 2014, while a version from 2015 was referred to in another file item;
- The IFUs of mesh implants with different designs or variants from the same manufacturer were identical with regard to the indications for use and the surgical procedure. More information is needed to allow an understanding when to use which design, and how this affects the surgical procedure;
- No specific or only brief surgical instructions for a particular mesh were included. It was always indicated that the mesh implants have to be implanted by trained and/or experienced surgeons. However, more specific instructions should be included to aid even trained surgeons with specific aspects of the mesh to be used;
- For the transvaginal mesh implants, no reference to recommendations from the relevant SCENIHR opinion [10] and/or specific professional (national) guidelines was included in any IFU. These documents recommend the use of transvaginal mesh implants only when other surgical options are not feasible.

3.4 Risk analysis

Although the EN ISO 14971 standard was used by all manufacturers, the overall conclusion on the risk management documentation was that it contained major shortcomings in all cases. Examples of identified shortcomings – not all major by itself – are:

- No (specific) risk management plan available;
- Not all general hazard categories as derived from EN ISO 14971 were addressed in the risk analysis (see Attachment II in Annex 5);
- Contraindications and their related risks were not analysed;
- Risk estimation before mitigation was missing. Risk estimation before and after mitigation allows insights into the effect of the mitigation action;
- Risk control was not in line with essential requirement 2 of the MDD, as risk reduction as far as possible was not adequately substantiated or it was not clear how risk reduction as far as possible was achieved (e.g. whether a change in design was considered);
- Acceptability of residual risks in relation to the benefit was insufficiently substantiated;
- The link between risk management and PMS was not adequately shown.

3.5 Chemical composition

Major shortcomings were found in four technical documentation sets and minor shortcomings in three sets. In two sets, the chemical composition

was sufficiently described. Examples of identified shortcomings – not all major by itself – are:

- Limited information on the chemical specification of the final product or of the raw materials, e.g. molecular weight of the polypropylene was missing;
- No details of the chemical specification of accessories;
- No preparation protocol of the mesh.

3.6 Biocompatibility

Although the EN ISO 10993 series of standards were used by all manufacturers, the overall conclusion on the evaluation of the biocompatibility in all technical documentation sets was that it contained major shortcomings. Examples of identified shortcomings – not all major by itself – are:

- Limited chemical, physical or mechanical characterisation of the mesh was included;
- Only a general statement of the long history of use of polypropylene in implants was included, with limited or no reference to literature;
- Existing toxicology and biocompatibility data were used from other mesh implants with different physical and/or mechanical characteristics. Manufacturers' claims of comparability lacked adequate substantiation for the extrapolation of data from one product to another;
- Only standard toxicity endpoints, as specifically mentioned in ISO 10993, were considered. No additional testing related to specific aspects of the mesh was considered; tissue in-growth, which has been advocated as an advantage of ultralight weight mesh implants, could be an example of such specific aspects;
- Implantation tests were performed on products with different geometry and shape, without proper justification; this includes using suture material instead of mesh material. ISO 10993-6 indicates that physical characteristics, such as geometry and shape, can influence tissue response. For tests using extracts, this could be considered less relevant. However, for tests using the actual mesh material, e.g. implantation testing, this should be considered;
- Insufficient justification was given on the selection of the control sample, implantation site (type of tissue), type of experimental animal, and the duration of the implantation period;
- Protocols for testing were not submitted;
- Either no summary of results was included or the overall analysis was limited and results were only summarized per endpoint as "acceptable".

3.7 Clinical evaluation

For all documentation sets, the overall conclusion on the clinical evaluation report (CER) was that it contained major shortcomings. Examples of identified shortcomings – not all major by itself – are:

Structured overview on all relevant clinical data

- The CER used for initial market approval was often not included, although it was specifically requested. In addition, several

manufacturers used a system of “updated” versions of the CER, in which a new version of the CER was covering only the period since the previous version. The most recent version did not provide a complete overview of all relevant literature and other clinical data. Summarised descriptions of the clinical data as discussed in previous versions of the CER and conclusions on the complete clinical data set were usually lacking;

- A family of transabdominal mesh implants was covered by one CER, without clear and structured stratification of the clinical data between the different designs. Another manufacturer covered mesh implants intended for transabdominal as well as transvaginal application in the same CER, again without stratification.

Choice of clinical data types

Several CERs were not in line with the insights on the clinical data needed according to the relevant European guidance document [32].

Examples of shortcomings are:

- Clinical data were collected in a non-structured manner;
- Clinical data were included from cases where the mesh implants were used outside the indications for use;
- Mainly or only publications with a low level of evidence were used, such as case reports, case series, and abstracts of conference proceedings;
- Data were used from other mesh implants claimed to be equivalent, without adequate substantiation of such equivalence, see also below;
- Limited number of publications were used.

Safety and performance

- No (clinical) safety and performance claims were included in most CERs. The following topics were indicated as claims in the reports assessed: description of the intended use and indication for use, promotional claims, or descriptive text on product design, or preclinical performance. A clear description of (quantitative) clinical safety and performance claims is needed for adequate safety and performance analysis;
- Safety data, e.g. adverse events and complaints, as well as performance data, e.g. clinical and patient-reported outcomes, were included, but no analyses were performed on the acceptability of such data. As no safety and performance claims (thresholds) were indicated in the CER, no comparisons were made to such thresholds. This hampered the assessment of the appropriateness of the conclusions of the safety and performance analyses;
- Safety and performance were only discussed on a high level, without presenting safety data or discussion;
- Most safety and performance information was related to other mesh implants than the subject mesh. The subject mesh and other mesh implants were part of a product family;
- Treatment of POP using native tissue repair was not always included for comparison.

Equivalence

In case equivalence was claimed, adequate substantiation was lacking.

Examples of such inadequate substantiations are:

- Data from a flat mesh were used for a Y-shaped mesh. It was claimed in a response from the manufacturer that only data were used from cases where it was self-cut and sewn into a Y-shaped mesh. In the CER this was not clear for all data included. Moreover, constructing a Y-shaped mesh from a flat mesh was not considered a reproducible process, thus still undermining the claim of equivalence;
- Differences in physical and mechanical mesh properties, for instance pore size, density, thickness, stiffness, pull-out strength, knitting pattern, or shape were indicated but not discussed or a short statement was made that differences were not relevant.

Post-market clinical follow-up (PMCF)

- PMCF was not deemed necessary by the manufacturer; sufficient medium and long term safety and performance were considered to be demonstrated based on a small number of publications, including non-scientific papers;
- PMCF was not deemed necessary by the manufacturer as sufficient clinical data were considered to be available, especially for the "equivalent" device. However, the claimed equivalence was insufficiently substantiated;
- PMCF was not mentioned or discussed;
- The information on PMCF in the CER and the PMCF Report was mostly, but not entirely, the same. For example, additional details were provided on the US Food and Drug Administration (FDA) ordered PMS study, indicating patient enrolment since 2014. Neither in the CER, nor in the PMCF Report results of this study were described, although it was mentioned that results have been provided to the FDA in May 2018. A manufacturer managed registry was being set up, but no data were yet available.

Clinical benefit, summary and appraisal, change in benefit/risk ratio, conclusions

- Clinical benefit was not addressed or the discussion on clinical benefit was insufficient;
- A summary of the clinical data was not provided or limited;
- Appraisal was not performed;
- Benefit/risk ratio was not addressed;
- Conclusions focussed only on the identification of new unanticipated risks or negative trends;
- No conclusion was provided on the performance of mesh implants;
- Conclusions were limited to clinical data from the time period covered by the updated version of the CER. Conclusions should cover all available data as discussed in previous versions of the CER, plus the additional data from the update;
- Conclusions were described in a high level manner or contained only high level statements without sufficient underlying analysis.

3.8 Summary and analysis of post-market surveillance data

The summary and analysis of the post-market surveillance (PMS) data of six technical documentation sets showed major shortcomings. Minor shortcomings were identified in two technical documentation sets, including one set that did not include a separate technical documentation item. Instead, the manufacturer indicated that these data were included in the CER. Hence, the assessment was based on information in the CER. Also, one manufacturer did not submit the summary and analysis of PMS data dating before the deadline of this assessment. Therefore, the summary and analysis of PMS data of this particular mesh was not assessed. Examples of identified shortcomings – not all major by itself – are:

- No summary of PMS data was present. Only the number of complaints received was mentioned, with the remark that “none of all complaints involved any situation that could affect the safety of the patients”;
- Limited number of PMS sources, mainly complaints were used;
- No adequate analysis of PMS data was included. Criteria for the necessity to take action with regard to the frequency of complications were not provided;
- The results of periodic analyses, including decisions made and actions assigned, were not present;
- The argumentation that PMCF is not necessary was not sufficiently substantiated;
- The PMCF plan contained only limited PMCF activities.

3.9 Assessment of updated clinical evaluations of transvaginal mesh implants

In addition to the technical file items requested in 2018, the Inspectorate requested the current CERs of two transvaginal mesh implants in January 2020. These two transvaginal mesh implants were still on the Dutch market November 1st 2019. These updated CERs were also assessed by RIVM. The overall conclusion on these updated CERs was that they still contained major shortcomings, as was the overall conclusion for those requested in 2018 (Table 3.2). Although part of the sub-items of the CERs had identical shortcomings, a number of sub-items were improved. However, the shortcomings were not always fully resolved. In the text underneath, the updated CER always refers to the CER requested in 2020.

Table 3.2 Comparison of the assessment of the clinical evaluation of transvaginal gynaecological mesh implants requested by the Inspectorate in 2018 and 2020.

Mesh (manufacturer)	Overall conclusion on shortcomings in CER	
	Requested in 2018	Requested in 2020
BSC (A.M.I.) ¹	Major	Major
Calistar S (Promedon) ²	Major	Major

¹ November 2019: Notified body temporarily restricted CE certificate of BSC Mesh. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for BSC Mesh.

² March 2020: Notified body temporarily restricted CE certificate of Calistar S. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for Calistar S.

Examples of improvements in updated CERs (requested in 2020) are provided below.

Choice of clinical data types

- In one of the CERs requested in 2018, a very basic literature search was conducted, not in line with the relevant MEDDEV guidance document. In the updated CER (requested in 2020), a comprehensive literature search was performed, more in line with a systematic approach. However, it was limited to a period of 5 years ending almost two years before the date of the CER and appraisal was lacking. It contained very few references of a low level of evidence related to the subject mesh, and also included data from which the relevance was less clear (e.g. on mesh implants constructed from materials different from the subject mesh).

PMCF

- In one of the CERs (requested in 2018), PMCF was not described or discussed. In the updated CER (requested in 2020), PMCF was considered necessary and two PMCF studies were waiting for approval of the ethical committee.

Equivalence

- For both mesh implants the clinical evaluation has been performed based mainly on clinical data from other products, without adequate substantiation of equivalence in the previous or the updated CER;
- For one mesh implant, the CER requested in 2018 did not contain any substantiation. The updated CER (requested in 2020) listed an appendix on equivalence assessment in the table of contents, however, the appendix was not present. Discussion on equivalence or comparison with other mesh implants was not included or referred to in the main text;
- For the other mesh, in both versions of the CER, a comparison with other products was made on a number of relevant aspects as required in the relevant guidance document [32]. In the CER requested in 2018, the mesh implants were claimed to be “very similar” despite a number of differences that were not debated. In the updated CER, part, but not all, of the differences were acknowledged, equivalence was not claimed. However, the data of the compared mesh implants were still used for the clinical evaluation of the subject mesh.

3.10 Assessment of updated technical documentation items of transabdominal mesh implants

The technical documentation sets of four transabdominal mesh implants requested in 2020 were assessed and compared with the technical documentation sets requested in 2018 (Table 3.3). These four transabdominal mesh implants were still on the Dutch market November 1st 2019. Current versions of the items IFU, risk analysis, clinical evaluation and summary and analysis of PMS data were requested by the Inspectorate. Not for every included item a new version was available. In comparison to the technical documentation requested in

December 2018, the overall conclusions on some file items were changed from major to minor shortcomings, while others remained the same despite the fact that improvements were observed (Table 3.3). In the text below, updated always refers to documentation requested in 2020.

Table 3.3 Comparison of the assessment of technical documentation of transabdominal gynaecological meshes requested by the Inspectorate in 2018 and 2020.

Mesh (manufacturer)	Overall conclusion on shortcomings in file items								
	IFU		Risk analysis		Clinical evaluation		S&A PMS data		
	Requested in								
	2018	2020	2018	2020	2018	2020	2018	2020	
ARTISYN (Johnson & Johnson)	Minor	Minor ¹	Major	Major	Major	Major	Major	Major	Minor
GYNEMESH PS (Ethicon)	Minor	Minor ¹	Major	Major	Major	Major ¹	Minor	Minor	Minor
Restorelle M L XL (Coloplast)	Minor	Minor ¹	Major	Minor	Major	Major	Major	Major	Major
Restorelle Y (Coloplast)	Minor	Minor ¹	Major	Minor	Major	Major	Major	Major	Major

Abbreviations:

IFU – instructions for use

S&A PMS – summary and analysis of post-market surveillance

¹ Documentation requested in 2018 and 2020 was identical, indicated by same version and date.

Examples of improvements in updated technical documentation items (requested in 2020) are provided below.

IFU

The IFUs requested in 2018 and 2020 were identical, as indicated by same identification of the version of the IFU and the same date of the IFU. Thus, the overall conclusion on the IFUs did not change and all IFUs had minor shortcomings.

Risk analysis

Improvements in the risk analysis were observed in all four cases. For two transabdominal meshes, some sub-items of the risk analysis improved but this did not change the overall conclusion, i.e. major shortcomings remained for these risk analyses. However, for the other two transabdominal meshes, the overall conclusion of the risk analysis was changed from major to minor shortcomings. Examples of improvement are:

- A risk management plan was submitted instead of a template for a risk management plan. However, the plan did not differentiate between the different designs of the various transabdominal meshes it was covering. Different designs could lead to specific risks, e.g. in manufacturing and surgical procedure, which should be identified in the plan;
- Risk estimation before risk mitigation as well as post-mitigation was shown in the risk analysis;

- A common shortcoming for the technical documentation (requested in 2018) was insufficient substantiation that the risks had been reduced as far as possible although statements indicating this were included. This shortcoming was resolved for two of the products.

Clinical evaluation

For one mesh, the same CER was submitted in 2018 and in 2020. The remaining three CERs were more recent. Although some improvements were identified, shortcomings were basically the same or the improvements did not resolve the earlier identified shortcomings.

Examples of improvements are:

- An increased number of publications was used for the safety and performance analysis. However, all of the data on the subject device had the lowest level of evidence, and part of it was related to off-label use. Another part of the data was related to a different mesh implant, of which the equivalence was not sufficiently substantiated;
- In the CER requested in 2018, it was stated that PMCF was not needed. In the updated CER (requested in 2020) it was indicated that additional PMCF activities have been planned to verify the long term safety and performance of the mesh. However, data from these activities were not yet available.

Summary and analysis of PMS data

The summary and analysis of PMS data of two updated technical documentation sets (requested in 2020) showed major shortcomings. In one case the improvements in the in 2020 requested technical documentation sets resulted in a change in the overall conclusion from major to minor shortcomings. For the fourth product, the overall conclusion remained that the documentation had minor shortcomings.

Examples of improvement are:

- The number of sources used to obtain PMS data was increased;
- In two cases, the earlier documentation indicated no need for PMCF, while PMCF activities were planned in the updated version (data not yet available).

3.11 Potential impact of findings on patient safety

This paragraph describes whether the identified shortcomings 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, or the file could be poorly maintained while the device is of high quality. 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

The shortcomings in the device description, such as scattered information in the files and limited information on several aspects of the mesh implants, are not considered to have potential impact on patient safety.

Instructions for use

Although the shortcomings for the IFU were not considered to be major, some of these shortcomings could influence the correct use of the mesh implants and could therefore potentially impact patient safety.

RIVM did not receive the latest version of one of the IFUs. If this is also the case for the users, this could mean that the users do not have the latest information on the appropriate use of the mesh or on all identified residual risks. Limited information on the use of different designs or on surgical procedures to be followed could hamper the correct application of mesh implants. For trained surgeons, the potential impact on patient safety is considered limited.

Recommendations on the use of transvaginal mesh implants only when other surgical options are not feasible, are included in specific (national) professional clinical guidelines, as well as in an opinion of the European scientific committee SCENIHR [10, 15, 16]. Not referring to this in the IFU could mean that this recommendation is insufficiently included in the deliberations on the treatment between the surgeon and the patient. In relation to this, given the current insights into the risk-benefit of transvaginal mesh implants, manufacturers should consider modifying the indications for use of their products based on these guidelines.

Risk analysis

For the risk analysis, a frequently observed shortcoming was inadequate substantiation that all risks had been reduced as far as possible. For example, considering a modification of the design, which is the mandatory first risk control option in the MDD, was often not described in the risk analysis. If the design could be improved, this could have a potential positive impact on patient safety.

On the other hand, not addressing all general hazard categories as derived from the harmonised standard, or insufficiently substantiating the acceptability of residual risks in relation to the benefit has a potential negative impact on patient safety.

Also not adequately showing the link between PMS and the risk analysis has potential impact: during PMS new risks may be detected. If these new risks are not fed back into the risk analysis adequately, risk reduction will not be pursued.

Not analysing risks related to contraindications potentially has impact on patient safety, because measures to mitigate these risks could be missed. However, given the fact that the contraindications are provided to an experienced user through the IFU, the potential impact is expected to be limited.

Chemical composition

If detailed information on the chemical composition is not available, adequate quality control on the raw materials might not be possible, leading to potential variation in material properties. This could impact the effect of the mesh implants in the patients, and thus patient safety.

Information on the chemical composition is also essential for the biocompatibility evaluation.

Biocompatibility

In a number of cases, existing data were used from other mesh implants with different physical characteristics, for example shape, without proper justification. This is especially relevant in relation to the implantation tests that are performed with the actual material, rather than extracts. As also indicated in the ISO standard for implantation testing [36], such characteristics can influence tissue response. Furthermore, if the choices for important parameters in these tests, like the implantation site and the duration of implantation, have not been substantiated in relation to the product and its intended use, it is uncertain whether the most relevant data are available. This could have potential impact on patient safety. If test protocols are not submitted, assessors have no insight which choices were made.

The ISO standards require that additional testing besides the standard endpoints is considered, in relation to specific aspects of the implant. It is uncertain whether the lack of such considerations could have impact on patient safety. This is also the case for just generally stating the long history of use of polypropylene in implants, with limited or no reference to literature.

The lack of an overall analysis and summary of results becomes especially important if one or more test results could imply potential toxicity. This was not observed in the submitted files. However, these had shortcomings, as explained above.

Clinical evaluation

Clinical data are the basis for a clinical evaluation. An adequate amount of data relevant for the device and its intended use with an acceptable level of evidence are needed for a reliable clinical evaluation. The shortcomings identified in relation to this can have a potential impact on patient safety. A specific example is when manufacturers use the data from a different device. Such data can only be used to analyse safety, performance and clinical benefit when the devices are equivalent. If the equivalence is not adequately substantiated, this reduces the reliability of the clinical evaluation. The same applies to cases where the data for mesh implants with different designs and/or different intended use are combined in one CER without a proper stratification.

An issue in relation to the data encountered with several manufacturers was that they use a system in which a new version of the CER is covering only the period since the previous version of the CER. The most recent version did not provide a complete, or even summarised overview of all relevant literature and other clinical data from previous CERs. Therefore, the basis for conclusions in the CER on safety, performance and benefit-risk was not clear. The analysis and the conclusion should cover all available data, not just the new data presented in the CER update. Depending on the total data set the manufacturer has available in the different versions of the CER, this may or may not have a potential impact on patient safety.

When good clinical data are available, a proper analysis of safety and performance with sufficient detail needs to take place. The clinical benefit and the benefit-risk ratio have to be specifically addressed. The absence of safety and performance claims (for example on adverse

events or patient-reported outcomes) hampers the assessment of the appropriateness of conclusions on safety and performance. The shortcomings identified in relation to this could have a potential impact on patient safety.

After a device is placed on the market, the manufacturer needs to continue clinical safety and performance evaluation in the long term and in a broader population. If no adequate PMCF takes place, new clinical insights can be missed, which could potentially have impact on patient safety.

Summary and analysis of PMS data

One identified shortcoming was using complaints as the only source for PMS. 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. The same argument also applies for mesh implants where only limited PMS sources were used.

Not performing an adequate analysis of the available PMS data could lead to incorrect assessment of changes in the benefit/risk ratio or missing opportunities for improvement. This could lead to delayed or no actions to improve the functionality and safety of the medical device. Therefore, this shortcoming is judged to have potential impact on patient safety.

3.12 Summary of the assessment of technical documentation sets

The quality of the technical documentation sets varied between the included mesh products. The general description and the IFU had no or minor shortcomings in all files of the various mesh implants. However, the file items risk analysis, biocompatibility, clinical evaluation and summary and analysis of PMS data showed major shortcomings in most of the files.

For part of the technical documentation sets, updated versions of one or more technical documentation items were also assessed. Generally, the updated versions showed improvements in sub-items. This did, however, not always lead to a change in the overall conclusion with regard to the quality of the technical documentation item.

It should be noted that the overall conclusion "major shortcomings" does not discriminate between documentation with multiple shortcomings and documentation with fewer shortcomings, that still lead to the qualification "major shortcomings". For example, a clinical evaluation based on a limited amount of clinical data from other devices without any substantiation of equivalence and hardly any analysis of the data gets the conclusion "major shortcomings". On the other hand, a clinical evaluation based on a larger amount of data, all related to the subject device, can still get the qualification "major shortcomings" if the analysis of the data needs to be improved.

It is important that the technical documentation is providing all the necessary information to show conformity with the regulatory requirements. Shortcomings in the documentation do not necessarily mean that the device is of insufficient quality, or that patient safety is at stake. However, the identified shortcomings mean that patient safety is

not sufficiently guaranteed by the technical documentation. An analysis showed that there is a potential impact on patient safety related to shortcomings in many of the file items.

Given this, and the fact that the safety and performance of medical devices are 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 better substantiate the quality and safety of their medical devices. The Inspectorate informed RIVM that several manufacturers are currently working to address the identified shortcomings in order to comply with the requirements for the MDD.

4 Conclusion

POP can affect women of all ages. It more commonly occurs in older women and affects 30-40% of women worldwide. POP is not life-threatening, however, it does reduce the quality of life for women with this condition. Several treatment options are available for POP, including reconstructive surgical procedures using surgical mesh implants. Previous investigations showed that surgical mesh implanted to treat patients with POP can cause serious complications.

The NVOG has requirements that all transvaginal and transabdominal mesh implants, together with any mesh-related complications are registered in a central NVOG system. Currently, not all surgical mesh implanted in patients with POP in the Netherlands are recorded in such a registry. Well maintained registries are important for the collection of real world data on the safety and performance of mesh implants.

In this study, we have compiled an overview of surgical mesh implants intended to treat POP, as used in Dutch hospitals in 2018. We have assessed the technical documentation sets from six manufacturers marketing mesh implants for POP in the Netherlands at that time. All technical documentation files contained a number of major and/or minor shortcomings. Mesh implants that were on the Dutch market November 1st 2019 were prioritised and RIVM decided to notify the Inspectorate about the results ahead of the full report. Summaries of the assessments of the technical documentation sets of the two transvaginal mesh implants (published in February 2020) and the four transabdominal mesh implants that were on the Dutch market November 1st 2019, were reported to the Inspectorate ahead of the full report. The assessment showed shortcomings in the technical files of all included mesh implants. Therefore, full conformity with the requirements in the MDD was not shown. Although shortcomings in the technical documentation do not necessarily mean that the device is not safe, in many cases shortcomings in a particular file item were found to have a potential impact on patient safety. All the shortcomings need to be adequately addressed by the manufacturers in order to better substantiate the quality and safety of their products as required in the regulatory system. To arrive at this over-all conclusion, three questions were addressed as described below.

Which transvaginal and transabdominal synthetic mesh implants are being used to treat POP in the Netherlands?

A total of nine surgical mesh implants from six manufacturers were identified to be used in the Netherlands in 2018. Five of these were transabdominal mesh implants and four were transvaginal mesh implants. Some of them had more than one variant, e.g. with different sizes or for anterior, respectively posterior repair.

Do the technical files of the selected mesh implants provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD)?

All technical files contained three or more file items with major and one or more file items with minor shortcomings. Therefore, full conformity with the requirements in the MDD was not shown.

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. Any shortcoming 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 or unsafe. An analysis of the shortcomings in the technical documentation showed that there is a potential impact on patient safety of shortcomings in many of the file items. Manufacturers should carefully consider and resolve the shortcomings in order to better substantiate the quality and safety of their medical devices as required in the regulatory system. The Inspectorate indicated that manufacturers are currently working on improvements in their technical documentation in order to comply with the requirements for the MDD. Some of the manufacturers have indicated that the improved technical documentation passed audits by their notified bodies and stated that their technical documentation is now compliant with European regulatory requirements. These audits took place after the RIVM assessment was completed.

Recently, a new regulation for medical devices was published [37]. The date of application of this regulation is May 26th 2021. It will then replace the MDD [28]. This is the regulatory framework under which the mesh implants were placed on the market. The new regulation is strengthening the requirements on medical devices and on the technical documentation. This includes strengthened requirements for risk management, clinical evaluation and PMS. In light of these strengthened requirements, update of all technical documentation sets is considered necessary.

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Annex 1: Characteristics of surgical mesh implants used to treat POP in the Netherlands in 2018.

Manufacturer	Name of the medical device	Surgical approach	Material	Absorbability	Material density	Fixation possibilities	Specifications	Reference
A.M.I. GmbH	BSC Mesh ¹	Trans-vaginal	Poly-propylene	Non-absorbable	ultra-lightweight 21 g/m ²	Bilateral sacrospinous fixation with A.M.I. i-Stitch device. The i-Stitch facilitates the attachments of sutures that are difficult to reach without extensive dissection, e.g. the medio-cranial aspect of the sacrospinous ligament. Uterine cervix suspension (illustration in brochure: 2 sutures for apical suspension).	Porosity 93%; hexagonal mesh structure; surface area of material surrounding the vaginal wall is small: 3 cm ² of the implant has direct contact with the vagina (uterine cervix suspension); u-shaped mesh (2 arms).	[38]
BD/C.R. Bard Inc ²	Alyte® Y-Mesh Graft	Trans-abdominal	Poly-propylene	Non-absorbable	17,67 g/m ² (anterior/posterior) and 35,55 g/m ² (sacrocolpopexy)	No Information	Pore size: 2,78 x 1,33 mm (anterior/posterior) and 1,96 x 1,06 mm (sacrocolpopexy). Thickness: 0,29 mm (anterior/posterior) and 0,40 mm (sacrocolpopexy). Mesh size: 5 x 27 cm	[39], [40]
BD/C.R. Bard Inc ²	Nuvia™ SI Single-Incision Prolapse	Trans-vaginal	Poly-propylene	Non-absorbable	No information	4 point fixation (anterior) and 2 point fixation (posterior)	No information	[41]

Manufacturer	Name of the medical device	Surgical approach	Material	Absorbability	Material density	Fixation possibilities	Specifications	Reference
	Repair System							
Coloplast A/S	Restorelle® DirectFix™ Anterior, Restorelle® DirectFix™ Posterior ³	Trans-vaginal	Poly-propylene Smart-mesh® technology	Non-absorbable	No information	Digitex® suture delivery system, StatTack or AbsorbaTack fixation technologies. Digitex can be used with non-absorbable polypropylene sutures, absorbable polydioxanone sutures or absorbable polyglycolic sutures, and sutures sizes 0-0 or 2-0. Single incision fixation. Sutures anterior procedural technique (with Digitex): apex, bilateral SSL, bilateral AT, bladder neck. Variations in use occur due to individual technique and patient anatomy.		[42, 43] [44]
Coloplast A/S	Restorelle® M, Restorelle® L, Restorelle® XL	Trans-abdominal	Poly-propylene	Non-absorbable	Ultra-lightweight	Digitex® suture delivery system, StatTack or AbsorbaTack fixation technologies.	NL & UK website: size not indicated in centimetres, only M and XL. Indicated for anterior and posterior repair. US website: size Restorelle M Flat Mesh 15x10 cm, Restorelle XL Flat Mesh 30x30 cm, Restorelle L Flat	[45, 46] [47]

Manufacturer	Name of the medical device	Surgical approach	Material	Absorbability	Material density	Fixation possibilities	Specifications	Reference
							Mesh 24x8 cm. Indicated for sarcocolpopexy for surgical treatment of vaginal vault prolapse. FDA 510(k) Summary (2013-08): Restorelle M and Restorelle XL are indicated for use as a bridging material for sacrocolposuspension and/or sacrocolpopexy (laparotomy, laparoscopic, or robotic approach). Where surgical treatment for vaginal vault prolapse is warranted. Both are designed for the treatment of apical vaginal prolapse.	
Coloplast A/S	Restorelle® Y	Trans-abdominal	Poly-propylene	Non-absorbable	No information	No information	NL & US website: size Restorelle Y 24x4 cm and 27x4 cm. IFU US/CA version (2016-03): Restorelle Y is indicated for use as a bridging material for sacrocolposuspension/sacrocolpopexy (i.e. abdominal placement via laparotomy, laparoscopic, or robotic approach) where surgical	[48, 49]

Manufacturer	Name of the medical device	Surgical approach	Material	Absorbability	Material density	Fixation possibilities	Specifications	Reference
							treatment for vaginal vault prolapse is warranted.	
Ethicon LLC ⁴	GYNECARE GYNEMESH™ PS Nonabsorbable PROLENE™ Soft Mesh	Trans-abdominal	Poly-propylene, identical to PROLENE™	Non-absorbable	42,38 g/m ²	The fixation technique and products used should follow current standard care. It is recommended that sutures, staples, or other appropriate fixation devices be placed at least 6,5 mm from edge of the mesh.	Mesh size: 10 x 15 cm and 25 x 25 cm. Thickness 0,42 mm. Pore size: 2,47 x 1,68 mm	[50, 51] [52]
Johnson & Johnson Int	ARTISYN™ Y-Shaped Mesh	Trans-abdominal	Poly-propylene and poly-glecaprone-25	Partially absorbable	No information	The fixation technique and products used should follow current standard care. When fixating with sutures or other mechanical fixation devices, a safe distance from the edge of the mesh of not less than 1 cm must be maintained.	Mesh size: 27 x 5 cm	[53, 54]
Promedon SA	Calistar S ⁵	Trans-vaginal	Poly-propylene	Non-absorbable	16 g/m ² at central area	TAS (Tissue Anchoring System) anchors with sutures for fixation to sacrospinous ligaments. Anterior fixation arms: fixation to obturator muscle. Retractable insertion guide designed for the placement of the anchors. Retractable insertion guide designed for	Differential elasticity at longitudinal and transversal axis; reinforcement for De Lancey Level I & II; two polypropylene attachment arms and three TAS anchors with their corresponding sutures;	[55, 56]

Manufacturer	Name of the medical device	Surgical approach	Material	Absorbability	Material density	Fixation possibilities	Specifications	Reference
						the placement of the anterior attachment arms of the implant. Knot pusher.	highly porous polypropylene mesh.	

¹ November 2019: Notified body temporarily restricted CE certificate of BSC Mesh. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for BSC Mesh.

² BD (Becton, Dickinson and Company) acquired C.R. Bard Inc in 2017.

March 2019: BD announced the removal of its Women’s Pelvic Organ Prolapse and Stress Urinary Incontinence Mesh Devices from the European market.

³ In May 2019, Coloplast A/S stopped selling Restorelle® DirectFix™.

⁴ Ethicon LLC is a Johnson & Johnson subsidiary.

⁵ March 2020: Notified body temporary restricted CE certificate of Calistar S. In September 2020, temporary restriction was removed after audit by notified body of updated technical documentation for Calistar S.

Annex 2: Checklist for Dutch request gynaecological mesh implants

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 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. Chemical composition/product specification

Detailed information should be included on:

- a) identify of raw materials (including chemical name);
- b) chemical specification of raw materials;
- c) list of suppliers of raw materials;
- d) preparation protocol of the mesh;
- e) chemical specifications of the mesh, including underlying documentation on requirements of the mesh and the methods of analysis;
- f) medical substance, if applicable.

4.3. 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, mechanical and chemical characteristics of the medical device and its materials of construction;
 - ii. any history of clinical use or human exposure data (including data in published literature);
 - iii. any existing toxicology and other biocompatibility data on product and component materials, breakdown products and metabolites (including data in published literature). For all data, applicability to the relevant device should be shown;
 - iv. the selection of appropriate tests;
- b) the tests conducted;
- c) standards applied;
- d) protocols ("standard operating procedures") of the physical and chemical characterisation, as well as in vitro and in vivo biological evaluation studies conducted;

- e) analysis of data as gathered with the protocols under d);
- f) summary of results and conclusion.

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) alternative devices or treatments;
- f) safety and performance claims made for the medical device;
- g) context of the evaluation;
- h) 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). These data should be supplemented with data from the post-market phase, if applicable;
- i) description of post-market clinical follow-up;
- j) safety analysis of the medical device, including serious adverse events that occurred;
- k) performance analysis of the medical device;
- l) summary of the clinical data and appraisal;
- m) consistency of medical device literature and instructions for use with clinical data;
- n) conclusions, including possible changes to the benefit-risk ratio and comparison with alternative treatments or devices.

The documentation should contain the evidence on which the initial market authorization was based and the update of this information based on data collected following placing on the market of the product, e.g. but not limited to PMCF and PMS.

More information on the contents of the clinical evaluation report is available in MEDDEV 2.7/1 revision 4, June 2016.

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, PMCF, patient-reported outcomes and data related to explanted devices;
- b) sources used to obtain PMS data;
- c) analysis of PMS data, including trends, suitable indicators and threshold values, substantiated decision whether any action (e.g. FSCA) is necessary;
- d) actions taken based on the analysis of PMS data.

Annex 3: Method of the assessment of technical documentation

Identification and selection of manufacturers and devices

For the identification of manufacturers and mesh implants used for the treatment of POP, information was used from an RIVM questionnaire sent to urogynaecologists performing transvaginal mesh surgery affiliated to Dutch hospitals. Urogynaecologists were asked which mesh (brand name and manufacturer) they implanted. The survey resulted in an overview of manufacturers and their CE-marked gynaecological mesh implants for the treatment of POP, that had been used in Dutch hospitals in 2018. All listed mesh implants were selected for the assessment of technical documentation (Table 2.1).

Request of technical documentation and manufacturer's check on factual inconsistencies

In December 2018, the Inspectorate requested a relevant part of the technical documentation of the selected mesh implants from the accompanying manufacturers (see Annex 4 for a copy of the letter). With the letter requesting the technical documentation, a checklist was enclosed which described details on the items to be submitted (see Annex 2). The checklist was developed by RIVM and was largely based on the Summary Technical Documentation (STED) from the Global Harmonisation Task Force², modified in some places to better fit with the requirements of the MDD. The following information was requested from the manufacturers:

- Device description;
- Instructions for use;
- Risk management plan and risk analysis;
- Product verification and validation – relevant parts for this investigation:
 - General;
 - Chemical composition/product specification;
 - Biocompatibility;
 - Clinical evaluation;
- Summary and analysis of PMS data.

Following receipt, the technical documentation set was checked for completeness by RIVM and the manufacturer was asked by the Inspectorate to provide any missing documentation. The submitted documentation was accepted for assessment if dated on or before the deadline of the initial request.

In October 2019, manufacturers received the results of the assessment. For more information on the method of assessment see below. In case a manufacturer was of the opinion that the assessment of a specific (sub-)

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>.

item contained factual inconsistencies, the manufacturer was requested to either state where the specific information could be found in the originally submitted documentation or to provide additional documentation which contained the specific information and was dated on or before the deadline of the initial request. Upon reviewing the manufacturer's response, the assessment of the technical documentation set requested in 2018 was finalized.

In January 2020, the Inspectorate requested the most recent CERs of two transvaginal mesh implants. In February 2020, the Inspectorate requested recent technical documentation of four transabdominal mesh implants. The following information was requested:

- Instructions for use;
- Risk management plan and risk analysis;
- Clinical evaluation;
- Summary and analysis of PMS data.

Following receipt, the check for completeness was performed. Manufacturers were not given the opportunity to check whether the assessment of the technical documentation set requested in 2020 contained factual inconsistencies. Manufacturers were given the opportunity to check whether the full report contained factual inconsistencies.

Method of assessment

RIVM developed an assessment form (see Annex 5) in order to enable a structured and uniform assessment of the documentation sets. For each section of the checklist from Annex 2, a file item was included. For each of these items, 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, harmonised European standards and state-of-the-art (EN) ISO standards as relevant were used as a basis for the assessment of the particular (sub-) items on risk management and biocompatibility [28, 32-36].

The device description was mainly used as background information for the assessment. For the IFU, it was checked whether specific mesh-related risks (see Annex 5, Attachment I) were mentioned. For the assessment of the risk analysis, it was checked whether these mesh-related risks were addressed as well as whether general hazard categories (see Annex 5, Attachment II), as derived from the harmonised standard for risk management of medical devices were covered [33]. 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 assessment, the information should at least cover the following items: chemical composition, biocompatibility, and clinical evaluation. For chemical composition, it was checked whether chemical product specifications of raw materials and the mesh were described. For biocompatibility, it was checked whether the evaluation was performed in line with the standards. For the clinical evaluation, a list of mesh-related topics to be covered was drawn up and checked (see Annex 5, Attachment III). For the summary

and analysis of PMS data it was checked whether PMS was adequately performed.

To facilitate a consistent assessment, two assessors assessed the (additional) documentation and reviewed the manufacturer's response independently. Assessment forms were compared, any discrepancies were discussed and resolved, and forms were finalized. This method has also been used for previous assessments, such as silicone breast implants, dermal fillers, and transcatheter aortic valves [29-31].

Quality of technical documentation items

In general, the quality of the technical documentation was based on the presence or adequate description of each particular sub-item. Only a shortcoming was noted in the assessment form. Several sub-items are associated with patient safety, while for other sub-items, such a link is not the case. Using expert judgement of the RIVM assessors, the overall conclusion (indicated by no/minor/major shortcomings) for the technical documentation items was obtained. Important considerations to decide that the shortcomings were major include the amount and type of missing information and the potential impact on patient safety of the shortcoming.

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 study was based on the situation at the moment of the submission request, any documentation dating from after deadline of the initial request for the technical documentation items was not taken into consideration during the re-assessment.



Annex 4: Request of the Inspectorate

> Return address Postbus 2518 6401 DA Heerlen

<Name manufacturer>

Sent by email

Date 20 December 2018
Subject Request for technical documentation

Stadsplateau 1
3521 AZ Utrecht
Postbus 2518
6401 DA Heerlen
T 088 120 5000
www.igj.nl

Information
<Name Inspector>

Our reference
<Reference number>

Dear Sir/Madam,

The Dutch Health and Youth Care Inspectorate (Inspectorate) is the competent authority for the European Directive on Medical Devices 93/42/EEC in the Netherlands. As such the Inspectorate is charged with the surveillance and law enforcement of this Directive.

According to the information known to the Inspectorate your company markets mesh implants to treat pelvic organ prolapse in the Netherlands. By request of the Inspectorate, the National Institute for Public Health and Environment (RIVM) will perform a study on mesh implants.

Request for technical documentation

Part of this study involves an assessment of the technical documentation of mesh products for the treatment of pelvic organ prolapse. Therefore, we request you to follow the steps below and provide the following information to the Inspectorate by e-mail to _Die_nstpostbusIGJMedischetechnologie@igj.nl (please note the underscore _ at the beginning of the address).

1. After receipt of this letter: please provide the contact details (including name, e-mail address and telephone number) of the person who will be in charge of handling our request on behalf of your company on **January 7th, 2019** at the latest;
2. Additionally, please include an overview of the product names / types of the marketed mesh implants and distributors in/for the Netherlands;
3. Start collecting the documentation for the product(s) mentioned below, according to the attached checklist. Please, mark the documents as 'confidential' and provide them in such a format that it clearly refers to the items as listed in the attached checklist, in order to prevent misinterpretation during assessment.

The request under item 3 concerns your product(s): **<product name(s)>**.

In the week of January 7th, 2019 and after receipt of the contact details of the person in charge of our request, we will send this contact person information on how to provide us with the documents by secured

means. In order to be able to start the assessment in time, we kindly request you to forward the information before, but no later than **January 21st, 2019**.

Please note that additional documentation may be requested, if information is considered to be incomplete or assessment of provided information indicates a need for more information.

Upon finalisation of the assessment, I will inform you regarding the findings concerning your product(s). The results of this study will be published by RIVM in a publicly available report.

If you have any questions regarding this letter or study, please do not hesitate to contact me at the letter head address or at:
_DienstpostbusIGJMedischetechnologie@igj.nl.

Yours sincerely,

<Signing and name inspector dep. of Medical Technology>

Enclosure(s): Documentation required

Annex 5: Assessment form

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

1	Device description	Shortcomings	Reference
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		
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:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

2	IFU	Shortcomings	Reference
2.a	Indications for use		
2.b	Important aspects of the use of the mesh (trained user)		
2.c	Contraindications and mesh-related risk topics (Attachment I)		
2.d	IFU in Dutch or English		
	Reference to SCENIHR opinion and/or Dutch guideline regarding the use of meshes only when other surgical options are not feasible		
		Conclusion:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

3	Risk analysis	Shortcomings	Reference
	<i>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:</i>		
3.a	Risk management plan		
3.b	Risk analysis, containing the following elements:		
	Date / version number risk analysis;		
	Reference to any standards used, e.g. EN ISO 14971;		
	All hazard categories of EN ISO 14971 (Attachment II) identified or, appropriately, declared not applicable;		
	Contraindications and mesh-related risk topics addressed (Attachment I);		
	Adequate estimation 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 (RMR), 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:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

4	Product verification and validation – relevant parts for this investigation	Shortcomings	Reference
4.1	<i>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.</i>		
	Where no testing has been undertaken, the documentation should incorporate a rationale for that decision.		
4.2	Chemical composition / Product specifications	Shortcomings	Reference
4.2.a	Identity of raw materials (including chemical name)		
4.2.b	Chemical specification of raw materials		
4.2.c	List of suppliers of raw materials		
4.2.d	Preparation protocol of the mesh		

4	Product verification and validation – relevant parts for this investigation	Shortcomings	Reference
4.2.e	Chemical specifications of mesh, including underlying documenta-tion on requirements of the mesh and the methods of analysis		
4.2.f	Medicinal substance, if applicable		
		Conclusion:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

4.3	Biocompatibility	Shortcomings	Reference
4.3.a	<i>A structured biological evaluation program including documented, informed decisions that assess the advantages / disadvantages and relevance of</i>		
	i. the physical, mechanical and chemical characteristics of the medical device and its materials of construction;		
	ii. any history of clinical use or human exposure data (including data in published literature);		
	iii. any existing toxicology and other biocompatibility data on product and component materials, breakdown products and metabolites (including data in published literature). For all data, applicability to the relevant device should be shown;		
	iv. the selection of appropriate tests		
4.3.b	Tests conducted		
4.3.c	Standards applied (ISO 10993-series)		
4.3.d	Protocols ("standard operating procedures") of the physical and chemical characterisation, as well as the in vitro and in vivo biological evaluation studies conducted		
4.3.e	Analysis of data as gathered with the protocols under d)		
4.3.f	Summary of results and conclusion		
		Conclusion:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

4.4	Clinical evaluation	Shortcomings	Reference
	<i>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:</i>		
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	Alternative devices or treatments		
4.4.f	Safety and performance claims made for the medical device		

4.4	Clinical evaluation	Shortcomings	Reference
4.4.g	Objective of the CER clearly documented		
4.4.h	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). These clinical data should be supplemented with data from the post-market phase, if applicable		
4.4.i	Description of post-market clinical follow-up		
4.4.j	Safety analysis of the medical device, including serious adverse events that occurred		
4.4.k	Performance analysis of the medical device		
4.4.l	Summary of the clinical data and appraisal		
4.4.m	Consistency of medical device literature and instructions for use with clinical data (Attachment I & III)		
4.4.n	Conclusions, including possible changes to the benefit-risk ratio and comparison with alternative treatments or devices.		
	State of the art addressed?		
	Equivalence used for CER? Has the equivalence been adequately substantiated, see also MEDDEV 2.7/1 rev 4		
	Comparison with other devices documented?		
	Risks addressed consistently throughout relevant documents (Attachment I)?		
	Literature: same device / same indications / patient population if other devices included		
	Clinical benefit addressed?		
		Conclusion:	

Manufacturer	
Medical device (code – name – type of mesh)	
Notified body (code – name)	

5	Summary & analysis of PMS data	Shortcomings	Reference
	<i>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:</i>		
5.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 device, PMCF, patient-reported outcomes and data related to explanted devices		
5.b	Sources used to obtain PMS data		
5.c	Analysis of PMS data, including trends, suitable indicators and threshold values, substantiated decision whether any action (e.g. FSCA) is necessary		
5.d	Actions taken based on the analysis of PMS data		
	Actions taken adequate in relation to deficiencies observed?		
	PMCF part of PMS?		
		Conclusion:	

Attachment I

Contraindications and risks based on literature for mesh (x = addressed)

Note: this is not an exhaustive list of contraindications and risks

	IFU	RA	CER
1. Contraindications			
<ul style="list-style-type: none"> - Pregnant women, women that are considering / planning future pregnancy - Potential of future / for further growth (e.g. infants, children, adolescents) - Patients undergoing anticoagulant therapy - Patients with known sensitivity or allergy to polypropylene products - Presence of known or suspected cancer of the vagina, cervix, or uterus - (Active / pre-existing / latent) Systemic or local infection, especially genital or related to the urinary tract - Blood coagulation disorder - Renal insufficiency and upper urinary tract obstruction - Autoimmune connective tissue disease - Any pathology that would limit blood supply and compromise healing (e.g. decreased blood supply to organs due to treatments such as radiation therapy, chemotherapy) - Any pathology, including known or suspected uterine pathology, which would compromise implant placement - Pathology of soft tissue into which the mesh is to be placed - Patients with pre-existing conditions that pose an unacceptable surgical risk - Planned intraoperative or accidental opening of the gastrointestinal tract - Mesh should be used with precaution in diabetic women 			
2. Complications / side effects / adverse events			
<ul style="list-style-type: none"> - Abscess - Adhesion formation - Allergy, hypersensitivity or other immune reaction - Bladder damage - Bleeding, including haematoma, haemorrhage - Bowel damage - Contracture - Discomfort - Fistula formation - Granulation tissue formation - Infection / potentiation of existing infection - Inflammation - Mesh exposure, erosion or extrusion - Mesh migration - Necrosis - Nerve damage - Pain 			

- Pain during intercourse (dyspareunia)
- Painful urination (dysuria)
- Recurrent prolapse
- Reoperation / resurgery
- Scarring / vaginal scarring
- Seroma
- Ureteral obstruction
- Urethra damage
- Urinary incontinence (stress urinary incontinence, urge incontinence)
- Urinary retention / obstruction
- Vaginal wall damage
- Vessel damage
- Voiding dysfunction
- Wound dehiscence

	IFU	RA	CER
3. Operational risks			

- Missing information on intended device delivery approach
- Insufficient specification of all relevant dimensions
- Inadequate device preparation
- Disregard of expected device lifetime
- Use beyond expiry date
- Inadequate adherence to shipping / storage conditions
- Warnings regarding handling and implanting the device
- Inadequate or missing instruction for re-sterilisation method / max number (if applicable)
- Incompatibility with physiological environment in which it is intended to function

	IFU	RA	CER
4. Risk factors, other than side effects			

- Bio-incompatibility
- Adverse reaction to breakdown product of absorbable materials (if applicable)
- Package opened or damaged
- Inability to complete implant procedure
- Unintended anatomical interactions

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. The list of examples is not exhaustively (x = addressed).

Biocompatibility	
<ul style="list-style-type: none"> - Allergenicity / irritancy - Sensitization - Cytotoxicity - Carcinogenicity 	
Chemical hazards	
<ul style="list-style-type: none"> - Acids and alkalis - Residues, e.g. cleaning - Contaminating agents - Manufacturing additives or adjuvants 	
Use error	
<ul style="list-style-type: none"> - Use by unskilled / untrained personnel - Inadequate equipment - Incorrect instrument operation 	
Hazardous phenomena linked to inadequate labelling	
<ul style="list-style-type: none"> - 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	
<ul style="list-style-type: none"> - Inadequate specification of accessories to be used with the medical device - Inadequate specification of pre-use checks - Over-complicated (operating) instructions 	
Hazardous phenomena linked to insufficient warnings about	
<ul style="list-style-type: none"> - Of complications / side effects - Of reuse of single-use medical devices 	
Incomplete requirements	
<ul style="list-style-type: none"> - Inadequate specification of: <ul style="list-style-type: none"> • design parameters • performance requirements • end of life 	
Manufacturing processes	
<ul style="list-style-type: none"> - 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	
<ul style="list-style-type: none"> - Inadequate packaging - Contamination or deterioration - Inappropriate environmental conditions 	

Environmental factors	
<ul style="list-style-type: none"> - Physical, e.g. heat, pressure, time - Chemical, e.g. corrosions, contamination 	
Cleaning, disinfection and sterilization	
<ul style="list-style-type: none"> - Lack / inadequate specification for, validated sterilization procedures, if applicable cleaning / disinfection - Inadequate conduct of cleaning, disinfection and sterilization 	
Disposal and scrapping	
<ul style="list-style-type: none"> - No or inadequate information provided 	
Formulation	
<ul style="list-style-type: none"> - (Bio)degradation - Inadequate warning of hazards associated with incorrect formulations 	
Potential for use errors triggered by design flaws, such as	
<ul style="list-style-type: none"> - Missing instructions for use - Ambiguous or unclear device state - Ambiguous or unclear presentation of settings, measurements or other information 	
Failure modes	
<ul style="list-style-type: none"> - Unexpected loss of mechanical integrity - Deterioration in function, as a result of ageing - Loss of sterility 	

Attachment III

Clinical evaluation of urogynaecological mesh implants for the treatment of pelvic organ prolapse

Note: these lists are not exhaustive (x = addressed)

1. Indications	
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- Indicated for tissue reinforcement and stabilization of fascial structures of the pelvic floor in vaginal wall prolapse, where surgical treatment is intended, either as mechanical support or bridging material for the fascial defects
- Indicated for use as a bridging material for sacrocolposuspension / sacrocolpopexy (i.e. abdominal placement via laparotomy, laparoscopy, or robotic approach) where surgical treatment for vaginal vault prolapse is warranted
- Intended for the surgical treatment of the anterior and posterior prolapse by means of tissue reinforcement and stabilization of the soft tissues of the female pelvic floor
- Intended for the surgical treatment of the posterior and apical prolapse by means of tissue reinforcement and stabilization of the soft tissues of the female pelvic floor
- Intended to provide surgical support, act as a bridging material and/or provide reinforcement for the body's natural structures
- Indicated for use as a bridging material for sacrocolposuspension / sacrocolpopexy (laparotomy or laparoscopic approach) where surgical treatment for vaginal vault prolapse is warranted
- Indicated for use as a bridging material for apical vaginal and uterine prolapse where surgical treatment (laparotomy or laparoscopic approach) is warranted

2. Contraindications	
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- Pregnant women, women that are considering/planning future pregnancy
- Potential of future / for further growth (e.g. infants, children, adolescents)
- Patients undergoing anticoagulant therapy
- Patients with known sensitivity or allergy to polypropylene products
- Presence of known or suspected cancer of the vagina, cervix, or uterus
- (Active / pre-existing / latent) Systemic or local infection, especially genital or related to the urinary tract
- Blood coagulation disorder
- Renal insufficiency and upper urinary tract obstruction
- Autoimmune connective tissue disease
- Any pathology that would limit blood supply and compromise healing (e.g. decreased blood supply to organs due to treatments such as radiation therapy, chemotherapy)
- Any pathology, including known or suspected uterine pathology, which would compromise implant placement
- Pathology of soft tissue into which the mesh is to be placed

- Patients with pre-existing conditions that pose an unacceptable surgical risk
- Planned intraoperative or accidental opening of the gastrointestinal tract
- Mesh should be used with precaution in diabetic women

3. Safety	
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- Abscess
- Adhesion formation
- Allergy, hypersensitivity or other immune reaction
- Bladder damage
- Bleeding, including haematoma, haemorrhage
- Bowel damage
- Contracture
- Discomfort
- Fistula formation
- Granulation tissue formation
- Infection / potentiation of existing infection
- Inflammation
- Mesh exposure, erosion or extrusion
- Mesh migration
- Necrosis
- Nerve damage
- Pain
- Pain during intercourse (dyspareunia)
- Painful urination (dysuria)
- Recurrent prolapse
- Reoperation / resurgery
- Scarring / vaginal scarring
- Seroma
- Ureteral obstruction
- Urethra damage
- Urinary incontinence (stress urinary incontinence, urge incontinence)
- Urinary retention / obstruction
- Vaginal wall damage
- Vessel damage
- Voiding dysfunction
- Wound dehiscence

4. Performance (anatomical success, efficacy outcome)	
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- Anatomical success, i.e. pelvic organ prolapse quantification (POP-Q)
- Subjective success, e.g. quality of life (QoL)
- Sexual function score, e.g. pelvic organ/urinary incontinence sexual questionnaire 12 (PISQ-12)

Annex 6: Conclusions of the assessment of technical documentation

BSC Mesh (A.M.I.) - transvaginal mesh		
File item	Year ¹	Conclusion
Device description	2018	No shortcomings. The device is sufficiently described.
IFU	2018	Minor shortcomings. Specific (local) guidelines on the use of transvaginal meshes are not mentioned, the physician is encouraged to discuss the matter with the patient. The above mentioned guidelines should be taken into consideration during this discussion. Given the current insights into the risk / benefit of transvaginal meshes, it is recommended by the assessors that the manufacturer also considers modifying the indications for use based on these guidelines.
Risk analysis	2018	Major shortcomings. The risk management plan is not specific enough. The link to PMS should be improved. For warnings, no risk reduction could be estimated. The risk analysis does not adequately substantiate why no other risk control measures were possible, e.g. in the design.
Chemical composition	2018	Major shortcomings were observed. Limited information has been supplied, lacking insight into chemical specification of both the mesh and the accessories. More in-depth information is considered necessary.
Biocompatibility	2018	Major shortcomings. Only test reports for biocompatibility have been provided, where it is not always clear if the samples tested were related to the BSC Mesh. No rationale for the tests selected, no discussion of available information. A literature review on existing data should be performed 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.
Clinical evaluation	2018	Major shortcomings The CER, dated December 2014, is of poor quality, providing mainly high-level information on the use of mesh products in POP procedures and containing nearly no clinical data or analysis of such data. No clinical investigations with the BSC mesh product were performed, and substantiation of equivalence with other mesh products is lacking. However, it is stated that safety and performance are substantiated.
	2020	Major shortcomings. Clinical evidence is mainly based on clinical data of competitor meshes. Discussion on equivalence or comparison with other meshes to substantiate extrapolation of results to the BSC Mesh, or the other A.M.I. meshes, is not included or referred to in the main text. In the table of contents an Annex on equivalence was mentioned, which was not submitted. Clinical data of the BSC Mesh is limited, only three references are included with few patients and short-term follow-up.
Summary & analysis of PMS data	2018	No assessment. The summary and analysis of PMS data were dated after the deadline for this study.

¹ 2018 and 2020 – year of request

Calistar S (Promedon) - transvaginal mesh		
File item	Year ¹	Conclusion
Device description	2018	No shortcomings. The device is sufficiently described.
IFU	2018	Minor shortcomings. Specific (local) guidelines on the use of transvaginal meshes are not mentioned, the physician is encouraged to discuss the matter with the patient. The above mentioned guidelines should be taken into consideration during this discussion. Given the current insights into the risk/benefit of transvaginal meshes, it is recommended by the assessors that the manufacturer also considers modifying the indications for use based on these guidelines.
Risk analysis	2018	Major shortcomings. Risks analysed, risk reduction, acceptability of risks in relation to benefit, and conclusions are insufficiently addressed.
Chemical composition	2018	Major shortcomings were observed. The chemical specifications and information on preparation of the mesh need to be elaborated upon.
Biocompatibility	2018	Major shortcomings were observed. The applicability of existing data from other products for Calistar S is not sufficiently shown.
Clinical evaluation	2018	Major shortcomings. No clear safety and performance claims were made. Equivalence was used to show safety and performance. However, as Calistar S is composed of two types of mesh (low density and high density), which is not the case for the other meshes used for the comparison, equivalence is not adequately substantiated. There are some other differences as well.
	2020	Major shortcomings. Only preliminary data from Calistar S were available. Candidates for equivalence were selected, i.e. the Calistar A from Promedon and the Elevate Anterior from AMS/Astora. Although equivalence of the two other devices with Calistar S was not claimed, the data on these two devices were used as the basis for conclusions on safety and performance of the Calistar S. This is not in line with the MEDDEV guidance. The indications for the Calistar S were narrowed by the manufacturer to surgical treatment of recurrent prolapse and primary prolapse with high risk for recurrence. The manufacturer is sponsoring a PMCF study to address the gaps about gaining clinical evidence from Calistar S device itself and to gather long-term clinical follow-up. This study will use the narrowed indication.
Summary & analysis of PMS data	2018	Major shortcomings. PMS is only briefly mentioned in the CER. The assessors consider the extent of PMS too limited to allow sufficient insight into the experiences gained with the use of the mesh.

¹ 2018 and 2020 – year of request

Nuvia™ SI Single Incision Prolapse Repair System (BD) - transvaginal mesh		
File item	Year ¹	Conclusion
Device description	2018	Minor shortcomings. Information expected in the general description was scattered over multiple file items. The information needs to be included in a separate section, especially for a complex system as the Nuvia SI. Description of the functional elements "needle tip" or "ferrule" should be clarified and description plus pictorial representation of the knitting pattern should be included.
IFU	2018	Minor shortcomings. Specific (local) guidelines on the use of transvaginal meshes are not mentioned, nor the recommendation to use transvaginal meshes only when other surgical options are not feasible. Given the current insights into the risk/benefit of transvaginal meshes, it is recommended by the assessors that the manufacturer also considers modifying the indications for use based on these guidelines.
Risk analysis	2018	Major shortcomings. It is not clear how risk reduction in line with essential requirement 2 was achieved in practice. No risk management plan was submitted. Due to the uncertainty on the risk control and the substantiation of the benefit in the CER, it is uncertain if the conclusions on the benefit-risk acceptability are valid.
Chemical composition	2018	Major shortcomings. The specific information on the chemical specification of the various polypropylene materials, e.g. molecular weight, is lacking. The preparation protocol and the chemical specification of the mesh are lacking.
Biocompatibility	2018	Major shortcomings. The biological evaluation is based on tests performed on other Bard products with insufficient substantiation that this is a valid approach. Especially the relevance of an implantation test on a product with a different shape or mesh knit pattern should be discussed. Tests performed on the other Bard products are listed and it was stated that they had been passed, but protocols and results were not provided. No other endpoints specific for the product were considered besides standard endpoints. The duration of the implantation test was very short for a permanent implant. A literature review on existing data should be performed 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.
Clinical evaluation	2018	Major shortcomings. This update of the CER is discussing only data from the period covered by the update. Summarised description of the data as discussed in previous versions of the CER and conclusions on the complete data set are lacking. The use of equivalence is not adequately substantiated. Specific safety and performance claims are lacking, hampering the assessment of the safety and performance analysis. Safety and performance analysis, and discussion on clinical benefit need to be improved. Data for the different devices covered by the CER should be stratified per device consistently.
Summary & analysis of PMS data	2018	Minor shortcoming. PMCF is planned. The plan contains limited PMCF activities.

¹ 2018 – year of request

Restorelle® DirectFix™ Anterior, Restorelle® DirectFix™ Posterior (Coloplast)- transvaginal mesh		
File item	Year ¹	Conclusion
Device description	2018	Minor shortcoming. CE certificate submitted is not covering the Restorelle DirectFix Anterior and Restorelle DirectFix Posterior mesh. Moreover, the certificate was dated August 2019, while the certificate at the time of the original file submission was requested.
IFU	2018	Minor shortcomings. The recommendation to use a transvaginal mesh only when there is no viable alternative should be addressed more explicitly, preferably by including this in the indications for use. Furthermore, more specific information on the indications for use of the anterior, respectively the posterior variant, or both concurrently, should be included. A description of the shape of each variant could also be useful.
Risk analysis	2018	Major shortcomings. A specific risk management plan dated before the deadline for this study is missing. Risk estimation before mitigation is missing. Risk reduction as far as possible and the acceptability of the benefit-risk ratio are insufficiently substantiated.
Chemical composition	2018	Minor shortcomings. The specific information on the chemical specification of polypropylene, e.g. molecular weight, is lacking.
Biocompatibility	2018	Major shortcomings. The selection and specific methodology of appropriate tests, as well as the choice to use the data obtained with tests on Restorelle DirectFix Posterior for the Restorelle DirectFix Anterior were not adequately substantiated. History of clinical use or human exposure data were not included in the biological safety evaluation.
Clinical evaluation	2018	Major shortcomings. The submitted CER provides an update covering new information from 2017-2018. As no previous versions are available, it is not clear on which data the benefit-risk is based. No safety and performance claims are included. Data from PMCF studies are not provided. Safety and performance analysis, appraisal and discussion on clinical benefit need to be improved.
Summary & analysis of PMS data	2018	Major shortcomings. Decisions on acceptability of PMS results and actions taken are not included in the documentation. The results of the monthly PMS review process and meetings including the actions should be incorporated in an overall PMS report.

¹ 2018 – year of request

Alyte® Y-Mesh Graft (BD) - transabdominal mesh		
File item	Year ¹	Conclusion
Device description	2018	Minor shortcomings. Information expected in the general description was scattered over multiple file items. Limited information on construction / knitting pattern of the mesh.
IFU	2018	Minor shortcoming. Instructions should be included on training specific for the Alyte Y-Mesh Graft.
Risk analysis	2018	Major shortcomings. It is not clear how risk reduction in line with essential requirement 2 was achieved in practice. No risk management plan was submitted. Due to the uncertainty on the risk control and the substantiation of the benefit in the CER, it is uncertain if the conclusions on the benefit-risk acceptability are valid.
Chemical composition	2018	Major shortcomings. The specific information on the chemical specification of monofilament polypropylene, e.g. molecular weight, is lacking. The preparation protocol and the chemical specification of the mesh are lacking.
Biocompatibility	2018	Major shortcomings. The biological evaluation is based on tests performed on 3D MAX Mesh with insufficient substantiation that this is a valid approach. Especially the relevance of an implantation test on a product with a different shape should be discussed. Tests performed on the Bard 3D MAX Mesh are listed and it was stated that they had been passed, but protocols and results were not provided. No other endpoints specific for the product were considered besides standard endpoints. The duration of the implantation test was very short for a permanent implant. A literature review on existing data should be performed 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.
Clinical evaluation	2018	Major shortcomings. This update of the CER is discussing only data from the period covered by the update. Summarised description of the data as discussed in previous versions of the CER and conclusions on the complete data set are lacking. The use of equivalence is not adequately substantiated. Based on these two findings, it is uncertain that no PMCF is needed, as claimed by the manufacturer. Specific safety and performance claims are lacking, hampering the assessment of the safety and performance analysis. Safety and performance analysis, and discussion on clinical benefit need to be improved.
Summary & analysis of PMS data	2018	Major shortcoming. PMCF is not needed according to the manufacturer. It is uncertain whether this statement is correct because the complete data set needed to substantiate this is not used in the analysis, and because it is partly based on inadequately substantiated equivalence with a competitor product.

¹ 2018 – year of request

ARTISYN™ Y-Shaped Mesh (Johnson & Johnson International) - transabdominal mesh		
File item	Year ¹	Conclusion
Device description	2018	No shortcomings. The medical device is sufficiently described.
IFU ²	2018 2020	Minor shortcomings. More specific instructions for the surgical procedure should be included. According to the CER a more recent version of the IFU exists.
Risk analysis	2018	Major shortcomings. The reduction of risks as far as possible, as required in the MDD, is not adequately substantiated. No specific risk management plan was submitted, although this should have been drawn up according to the harmonised European standard and the manufacturer's risk management procedure. Improvement is considered necessary.
	2020	Major shortcomings. The reduction of risks as far as possible, as required in the MDD, is not sufficiently substantiated. This needs improvement. No specific risk management plan was submitted; the manufacturer indicated this was under development with a target date of 20 March 2020. A shortcoming in the risk estimation is also indicated as being resolved with a target date of 20 March 2020.
Chemical composition	2018	No shortcomings. Chemical composition is sufficiently described.
Biocompatibility	2018	Major shortcomings. Comparability of devices used in the actual testing and the selection of appropriate tests were insufficiently substantiated. Overall analysis should be more elaborate, discussing whether results from one endpoint might be outweighed by results for another endpoint.
Clinical evaluation	2018	Major shortcomings. In the current CER equivalence is claimed to ULTRAPRO Mesh (flat mesh) cut and sewn into a Y shape. This claim of equivalence is not considered sufficiently substantiated. No specific safety and performance claims have been made, leading also to shortcomings in the safety and performance analysis. Limited data of ARTISYN Y-Shaped Mesh are available. Safety and performance are insufficiently substantiated. A more in-depth technical assessment of the adequacy of the available clinical data set is beyond the scope of this assessment. The manufacturer indicated that he is working on setting up PMCF.
	2020	Major shortcomings. In the current CER equivalence is claimed to ULTRAPRO Mesh (flat mesh) cut and sewn into a Y shape. This claim of equivalence is not considered adequately substantiated. No specific safety and performance claims have been made, leading also to shortcomings in the safety and performance analysis. Limited data of ARTISYN Y-Shaped Mesh are available. Safety and performance are insufficiently substantiated. PMCF data from a clinical database have been analysed; additional necessary PMCF activities have been planned to verify the long-term safety and performance. Data resulting from these activities are not yet available.
Summary & analysis of PMS data	2018	Major shortcomings. Information from another product, for which the claim of equivalence is not acceptable, is used to state that PMCF is not needed. The number of sources is limited.
	2020	Minor shortcomings. No trend report was included. PMCF activities are described, results not yet available.

¹ 2018 and 2020 – year of request

² IFUs requested in 2018 and 2020 were identical

GYNECARE GYNEMESH™ PS Nonabsorbable PROLENE™ Soft Mesh (Ethicon) - transabdominal mesh		
File item	Year ¹	Conclusion
Device description	2018	No shortcomings. The device description was adequate.
IFU ²	2018	Minor shortcomings. More specific instructions for the surgical procedure should be included. According to the CER, a more recent version of the IFU exists.
	2020	Minor shortcomings. More specific instructions for the surgical procedure should be included. According to the CER and two HLMR forms, a more recent version of the IFU / other IFU documents exists.
Risk analysis	2018	Major shortcomings. The reduction of risks as far as possible, as required in the MDD, is not adequately substantiated. Two hazard categories are not addressed in the risk analyses submitted. No specific risk management plan was submitted, although this should have been drawn up according to the harmonised European standard and the manufacturer's risk management procedure. Improvement is considered necessary.
	2020	Major shortcomings. The reduction of risks as far as possible, as required in the MDD, is not sufficiently substantiated. This needs improvement.
Chemical composition	2018	No shortcomings. The chemical composition is sufficiently addressed.
Biocompatibility	2018	Major shortcomings. Biocompatibility risk assessment indicates that data from other devices are used. Comparability of devices used in the actual testing and the selection of appropriate tests were insufficiently substantiated, especially Proceed is sterilized using another method and contains other additional materials. Overall analysis should be more elaborate.
Clinical evaluation ³	2018 2020	Major shortcomings. In the current CER, no clear safety and performance claims have been used to substantiate adequate safety and performance. Improvement is needed, as clear safety and performance claims should be included in the assessment of safety and performance. Moreover, the analysis of the available data should be improved to allow a conclusion on the safety and performance of GYNEMESH PS in relation to other treatments and other devices used for the same indication. It could be debated whether data on off-label use and lowest quality data on on-label use should be included in the analysis. In-depth technical assessment of the adequacy of the data set formed by the seven Level III studies plus the additional non-graded studies is beyond the scope of this assessment.
Summary & analysis of PMS data	2018	Minor shortcomings. The need for PMCF should be re-evaluated.
	2020	Minor shortcomings. No trend report was included. PMCF is mentioned, but not yet executed and therefore results are not available.

¹ 2018 and 2020 – year of request

² IFUs requested in 2018 and 2020 were identical

³ Clinical evaluation reports requested in 2018 and 2020 were identical

Restorelle M L XL (Coloplast) - transabdominal mesh		
File item	Year ¹	Conclusion
Device description	2018	Minor shortcomings. Additional information is needed on when to apply which of the various designs. In their response document the manufacturer provides more information on the use of the two designs. This information is not provided in the general description or elsewhere in the submitted technical documentation. This kind of information shall be made available in an unambiguous manner.
IFU ²	2018 2020	Minor shortcomings. The IFUs of Restorelle M, L, XL and Restorelle Y are identical with regard to the indications for use and the surgical procedure. For two types of products with different designs, some difference would be expected in the surgical procedure. More information is needed to allow an understanding when to use which design. In their response document the manufacturer does provide more information. This kind of information shall be made available in the IFU.
Risk analysis	2018	Major shortcomings. A risk management plan dated before the deadline for this study was missing. Risk estimation before mitigation is missing. Contraindications are not included. Risk reduction as far as possible and the acceptability of the benefit-risk ratio are insufficiently substantiated.
	2020	Minor shortcomings. Risk management plan does not differentiate between Restorelle M, L, XL and Restorelle Y. In the risk analysis it is, however, indicated whether risks are applicable to Y, flat or both. A more detailed benefit risk analysis is needed.
Chemical composition	2018	Minor shortcomings. The specific information on the chemical specification of polypropylene, e.g. molecular weight, is lacking.
Biocompatibility	2018	Major shortcomings. The selection and specific methodology of appropriate tests, as well as the choice to use the data obtained with tests on Restorelle DirectFix P for the Restorelle M, L, XL were not adequately substantiated. History of clinical use or human exposure data were not included in the biological safety evaluation.
Clinical evaluation	2018 2020	Major shortcomings. No description is included on differences in indications and surgical procedures between the two different designs of Restorelle M, L, XL and Restorelle Y and no stratification is made in the data analysis. Safety and performance claims were not adequate. Part of the literature data concerned applications that were not in line with the indications for use or concerned concomitant procedures, which hampers the assessment of the safety and performance. Safety and performance analysis, and discussion on clinical benefit need to be improved.
Summary & analysis of PMS data	2018	Major shortcomings. Decisions on acceptability of PMS results and actions taken are not included in the documentation. The results of the monthly PMS review process and meetings including the actions should be incorporated in an overall PMS report.
	2020	Major shortcomings. Decisions on acceptability of PMS results and actions taken are not included in the documentation. The results of the monthly PMS review process and meetings including the actions should be incorporated in an overall PMS report. The numbers of complaints and units sold differ markedly between version 3 and 5 of the CER. This should be elaborated upon.

¹ 2018 and 2020 – year of request² IFUs requested in 2018 and 2020 were identical

Restorelle Y (Coloplast) - transabdominal mesh		
File item	Year ¹	Conclusion
Device description	2018	Minor shortcomings. Additional information is needed on when to apply which of the various designs and on the geometry of Restorelle Y. In their response document the manufacturer provides more information on the use of the two designs. This information is not provided in the general description or elsewhere in the submitted technical documentation. This kind of information shall be made available in an unambiguous manner.
IFU ²	2018 2020	Minor shortcomings. The IFUs of Restorelle Y and Restorelle M, L, XL are identical with regard to the indications for use and the surgical procedure. For two types of products with different designs, some difference would be expected in the surgical procedure. More information is needed to allow an understanding when to use which design. In their response document the manufacturer does provide more information. This kind of information shall be made available in the IFU.
Risk analysis	2018	Major shortcomings. A risk management plan dated before the deadline for this study was missing. Risk estimation before mitigation is missing. Contraindications are not included. Risk reduction as far as possible and the acceptability of the benefit-risk ratio are insufficiently substantiated.
	2020	Minor shortcomings. Risk management plan does not differentiate between Restorelle Y and Restorelle M, L, XL. In the risk analysis it is, however, indicated whether risks are applicable to Y, flat or both. A more detailed benefit risk analysis is needed.
Chemical composition	2018	Minor shortcomings. The specific information on the chemical specification of polypropylene, e.g. molecular weight, is lacking.
Biocompatibility	2018	Major shortcomings. Only the standard tests to be included in the risk assessment for long-term implants according to ISO 10993-1 were discussed. No additional testing related to specific aspects of the mesh was considered, e.g. tissue in-growth which has been advocated as an advantage of ultralight weight meshes. Also, all tests were performed on Restorelle DirectFix P, which is a flat mesh for transvaginal use with different shape compared with the transabdominal flat and Y meshes and also some differences in thickness, surface area and mass. The potential effect of the different geometry of Restorelle Y versus the Restorelle DirectFix P mesh and of differences in other properties was not discussed; they were just declared equivalent. For tests using extracts this could be considered less relevant, however, for tests using the actual mesh material, e.g. implantation testing, this should be considered. As also indicated in ISO 10993-6, physical characteristics such as shape can influence the character of tissue response. Furthermore, insufficient justification was presented on the selection of the control sample, implantation site (type of tissue), type of experimental animal and duration of the implantation period (13 weeks is the shortest duration of generally accepted periods for long-term studies).
Clinical evaluation	2018 2020	Major shortcomings. No description is included on differences in indications and surgical procedures between the two different designs of Restorelle Y and Restorelle M, L, XL and no stratification is made in the data analysis. Safety and performance claims were not adequate. Part of the literature data concerned applications that were not in line with the indications for use or concerned concomitant procedures, which hampers the assessment of the safety and performance. Safety and performance analysis, and discussion on clinical benefit need to be improved.

Restorelle Y (Coloplast) - transabdominal mesh		
File item	Year ¹	Conclusion
Summary & analysis of PMS data	2018	Major shortcomings. Decisions on acceptability of PMS results and actions taken are not included in the documentation. The results of the monthly PMS review process and meetings including the actions should be incorporated in an overall PMS report.
	2020	Major shortcomings. Decisions on acceptability of PMS results and actions taken are not included in the documentation. The results of the monthly PMS review process and meetings including the actions should be incorporated in an overall PMS report. The numbers of complaints and units sold differ markedly between version 3 and 5 of the CER. This should be elaborated upon.

¹ 2018 and 2020 – year of request

² IFUs requested in 2018 and 2020 were identical

