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

Silicone breast implants in the Netherlands

A market surveillance study

RIVM Letter report 2015-0100
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Publiekssamenvatting

Siliconen borstimplantaten in Nederland
Een onderzoek in het kader van markttoezicht

Voor medische hulpmiddelen, zoals siliconen borstimplantaten, zijn fabrikanten verplicht om 'technische dossiers' aan te leggen op basis waarvan wordt bepaald of het product op de markt wordt toegelaten. Dossiers van 10 fabrikanten die in Nederland siliconen borstimplantaten op de markt brengen, blijken duidelijke tekortkomingen te hebben. Volledige en correcte dossiers zijn essentieel om de veiligheid van de patiënt te waarborgen. Bij laboratoriumonderzoek van de implantaten zelf zijn geen afwijkingen aangetroffen die de gezondheid zouden kunnen schaden.

Dit blijkt uit verkennend onderzoek van het RIVM dat in opdracht van de Inspectie voor de Gezondheidszorg is uitgevoerd (IGZ). Hiervoor zijn belangrijke onderdelen van de technische dossiers van 10 fabrikanten van siliconen borstimplantaten tegen het licht gehouden. Daarnaast is laboratoriumonderzoek verricht naar de chemische samenstelling en de mate waarin de implantaten schadelijke eigenschappen hebben.

Uit het laboratoriumonderzoek bleek dat de producten voldoen aan een internationaal erkende veiligheidstest die schadelijke effecten op cellen meet. Chemische analyse liet zien dat twee fabrikanten een andere grondstof hadden gebruikt dan vastgelegd in hun technisch dossier. In één implantaat werden relatief hoge concentraties van bepaalde onzuiverheden (cyclosiloxanen) aangetroffen. Deze afwijkingen hebben naar verwachting geen negatief effect op de patiëntveiligheid.

Kernwoorden: borstimplantaten, siliconen, biocompatibiliteit, productsamenstelling, productveiligheid.

Synopsis

Silicone breast implants in the Netherlands
A market surveillance study

For medical devices such as breast implants, manufacturers are obliged to compile a 'technical file' based on which market authorization of the product will be decided. Files of 10 manufacturers placing breast implants on the Dutch market show clear shortcomings. Complete as well as correct files are essential to warrant patient safety. Laboratory analyses of the actual implants showed no deviations that could cause health damage.

This was the result of an explorative RIVM investigation, commissioned by the Dutch Health Care Inspectorate. For this investigation, important parts of the technical files of 10 manufacturers of silicone breast implants have been evaluated. In parallel, laboratory analyses were performed on the chemical composition and potentially harmful properties of the implants.

The laboratory analyses showed that the products comply with an internationally accepted safety test used to determine harmful effects on cells. Chemical analysis showed that two manufacturers have used a starting material differing from the type declared in their technical files. In one implant relatively high concentrations of impurities (cyclosiloxanes) were found. These deviations are not expected to have any negative effect on patient safety.

Keywords: breast implants, silicones, biocompatibility, product composition, product safety

Contents

Summary

In this study, we have assessed the technical files and analysed product samples from 10 manufacturers marketing silicone breast implants (SBIs) in the Netherlands.
The following five questions were addressed:

1. Do the technical files provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD) [11]?
2. Are key physicochemical characteristics of the products in line with the information in the technical documentation?
3. Are these physicochemical characteristics in line with the state-of-the art?
4. Is the silicone material as present in the products biocompatible?
5. In case of shortcomings, do these lead to a concern for patient safety?

As a general conclusion files of 10 manufacturers show clear shortcomings. Complete as well as correct files are essential to warrant patient safety. The quality of the products with regard to several key physicochemical characteristics and biocompatibility as determined in the laboratory analysis was good.

1 Introduction

1.1 Background

Breast implants are medical devices that are used for reconstructive and cosmetic purposes. For example, they are applied in reconstructive surgery in patients who have undergone a mastectomy. However, most frequently they are used for breast augmentation for cosmetic reasons. Many different types of breast implants are available. In general, breast implants consist of a silicone shell (envelope) with a filling material inside. The implants with a silicone gel-based filling inside are the most commonly used. Silicone breast implants (SBIs) represent a large market. In 1999, it was estimated that 25.000 to 30.000 Dutch women carried SBI [1]. The current estimation is that annually 20.000 to 30.000 Dutch women receive SBIs [2].

SBIs have been suggested to be associated with adverse health effects, ranging from inflammatory reactions to cancer, but also with autoimmune syndromes induced by adjuvants (ASIA) [3-7]. Causal relations with the SBI were so far only demonstrated for local complications like inflammation or capsular contraction. Such local symptoms are usually considered acceptable when weighed against the benefit. On the other hand, women with SBIs have reported a variety of systemic complaints such as chronic fatigue, connective tissue disease and rheumatic problems, which are associated with auto-immune diseases. However, large epidemiological studies did not show a causal relation with SBIs. Researchers are currently investigating whether certain women might be more sensitive to SBIs.

In the prevention of complications, a constant high quality of SBIs is paramount. SBIs must be manufactured in controlled conditions, according to the specifications described in the approved product file. Failure to do so has been linked to local complications due to implant rupture or leakage of silicone gel filling. This is illustrated by the problems with SBIs marketed by Poly Implant Prothèse (PIP) [8, 9]. PIP had used non-medical grade silicones in some of their SBIs produced from 1991 to 2010. In addition, the shell was found to be of low quality, resulting in a high incidence of early ruptures. In 2010, PIP implants were removed from the market worldwide, including the Netherlands. In 2014 the European Commission and its non-food Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published the final opinion on the safety of PIP implants [10]. In this opinion, the PIP implants were described to be of poor quality due to the relatively high levels of impurities as well as a relatively high rupture rate. However, no increased health risk has been associated with exposure to silicone gel emanating from a ruptured PIP implant, as compared with an implant from another manufacturer.

Originating from previous thematic research topics like metal-on-metal hip implants and meshes, the policy of the Dutch Health Care Inspectorate (IGZ) is to periodically focus on product research. The ongoing discussion on SBIs has been the incentive for the current focus

on this product group. As the competent authority for medical devices in the Netherlands, the IGZ decided to perform a market surveillance study on SBIs on the Dutch market in 2014. The IGZ requested the ten relevant manufacturers (See Table 1.1) to submit a number of sample products as well as the technical documentation (from now on referred to as "technical file") required to show conformity with the Medical Devices Directive (MDD) [11]. Subsequently, the IGZ has requested the National Institute for Public Health and the Environment (RIVM) to assess the quality of both the products and their technical files as well as to study the biocompatibility of the silicone material the implants are manufactured from.

Table 1.1: SBI manufacturers participating in the market surveillance study in alphabetical order.

Allergan
Establishment Labs SA
Eurosilicone SAS
Groupe Sebbin SAS
Laboratoires Arion SAS
Mentor Medical Systems BV
Nagor Ltd
Pérouse Plastie SAS
Polytech Health & Aesthetics GmbH
Silimed

1.2 Aim

The aim of this report is to investigate the quality of SBIs available on the Dutch market. In order to do this, we have addressed the following questions:

1. Do the technical files provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD) [11]? For a manufacturer to legally place a medical device on the EU market, these requirements have to be met.
2. Are key physicochemical characteristics of the products, such as the silicone materials used, in line with the information in the technical documentation?
3. Are the physicochemical characteristics in line with the state-of-the art? SBI have been in use for more than fifty years and product design has evolved ever since.
4. Is the silicone material as present in the products biocompatible?
5. In case of shortcomings, do these lead to a concern for patient safety?

1.3 Guide to reading the report

In the following chapter the results of the assessment of the technical files are described. Subsequently, in Chapter 3 the results of the physicochemical analyses are presented. The biocompatibility studies are presented in Chapter 4. Finally, the general conclusions are presented and discussed.

2 Assessment of technical files

This chapter describes the assessment of the technical files of the ten SBI brands included in this study. The information received from manufacturers often dealt with several variants of SBIs. In these cases, one variant was chosen for the assessment. The method used is described in detail in Annex 2. In order to get access to the European market, a manufacturer of an SBI has to provide an extensive technical file to a notified body[1], showing compliance with the requirements in the MDD [11]. For this investigation, a relevant part of the technical file was requested, using a checklist detailing items and sub-items (see Annex 4). Following receipt of the documentation by RIVM, the file was checked for completeness and any missing documentation was requested once more. An assessment form was developed in order to enable a structured and uniform assessment of the files (see Annex 5). For every sub-item requested, presence of adequate information was scored with a yes, a no, or partial if applicable. For certain sub-items, a similar scoring was used, but using dedicated terminology for that sub-item, e.g. 'no', 'limited', 'clear' for summary of Post Market Surveillance (PMS) data. Using a scoring system that discerned sub-items of normal and major importance in relation to risk and safety aspects (see also Annexes 2 and 5), eventually an item was classified as 'good', 'moderate' or 'insufficient'. Failing for one major sub-item immediately led to an insufficient score for the item as a whole. For the PMS and vigilance procedures and summary and analysis of PMS-data all items were considered crucial.
The detailed anonymized results of the assessment are included in Annex 6. In the following paragraphs the results of the assessment are summarised. First, the findings per item are described, followed by a paragraph showing the overall quality per item and per file. At the end of the chapter, an evaluation is carried out of the impact on patient safety of the shortcomings found in the files, followed by a conclusion on the assessment of technical files.

2.1 Device description

The majority of SBI files contained all required information concerning the device description. Although patient's age is not a requirement in the MDD [11], several manufacturers indicated a minimal age of patient eligibility for breast augmentation or reconstruction, while others did not. Note that minimal patient age might be subject to national legislation. Overall, most files contained a good or moderate device description, while one file scored 'insufficient'.

Figure 2.1: Assessment scores for Device description (red=insufficient, yellow=moderate, green=good)

[1] A notified body is an independent, government-approved testing and certification organization which verifies whether medical devices meet all quality requirements and the specifications laid down by law. A manufacturer may choose which of the European notified bodies is to inspect and assess its products. [Source: http://www.igz.nl/english/medical_devices/]

2.2 IFU and label

The instructions for use (IFU) were clearly written and well-structured, in English and/or Dutch except for one IFU which had an atypical Dutch translation in some sections.
Many IFUs and labels did not fully comply with the relevant essential requirements in the MDD. Four IFUs lacked clear details to identify the device. General terms such as gel-filled mammary implants were used rather than brand names or more specific descriptions such as "cohesive gel-filled, round, textured breast implant". In some cases, a number of important warnings, precautions and contraindications were not included in the IFU.
In only one file, the labelling fulfilled all the relevant requirements in the MDD. Reasons for non-compliance of labels included missing symbols on storage/handling conditions and on the indication that warnings/precautions are included in the IFU.
The description of surgical techniques was scored partially adequate in five of the ten cases because important aspects like the anatomical position of the implant, the surgical approach, avoidance of applying excessive pressure during insertion, or correct orientation of anatomical implants using markers were not included in the IFU. Some IFUs only indicated that the surgeon has to be familiar with the latest techniques related to selecting and implanting SBIs.
Essential requirement 2 of the MDD prescribes that risks have to be eliminated or reduced as far as possible through inherently safe design, that adequate protection measures have to be taken in relation to risks that cannot be eliminated, and that users have to be informed about residual risks. Therefore, residual risks for which the risk analysis indicated that they were to be addressed in the IFU shall be mentioned there. In most IFUs, 80% or more of the residual risks were actually mentioned in the IFU. In two IFUs this coherence between the IFU and risk analysis was mediocre.
However, half of the IFUs did not adequately reflect the risks and contra-indications as identified by the assessors in the literature (Attachment II of assessment form). Also the chemical composition and the potential toxicity of the chemical ingredients were missing in half of the IFUs.
Although this was not requested, several manufacturers included a patient brochure in the submitted documentation. These brochures contained information on the surgical procedure and possible complications or questions that a patient could ask the surgeon. If the brochure is provided to the patient, this should help informed decision making.
Overall, most files scored insufficient on label and IFU.

Figure 2.2: Assessment scores for IFU & label (red=insufficient, yellow=moderate, green=good)

2.3 Risk analysis

More than half of the risk analyses addressed all required general risk categories based on hazards as derived from the standard for risk

management of medical devices (EN ISO 14971, 2012, [12]). Examples of categories missing in some cases are chemical hazards, incomplete design requirements, hazards related to the manufacturing process and failure modes (see also attachment 1 in Annex 5).
SBI-related risks, including contra-indications, as identified in the literature were adequately addressed in 80% of the risk analyses. One manufacturer did not analyse risks related to the chemical composition and the potential toxicity of chemical ingredients. Another did not address risks related to the design and geometry of the components.
All manufacturers had a system to decide whether or not a risk was acceptable, often based on assigning numerical values to the severity of the potential consequence of a risk and to the frequency of occurrence, which were then multiplied to give a score. Usually, three categories of scores were identified indicating negligible risk, intolerable risk and a category in between, where risks could be acceptable. In several files, adequate substantiation of the scoring system was missing. In many cases, no further action was considered necessary when the risk "could be acceptable" using the scoring system, although EN ISO 14971 and the MDD require the risk to be reduced as far as possible. Further analysis of this issue was beyond the scope of this investigation.
In the majority of cases, 20% to 80% of the warnings, precautions and contra-indications as mentioned in the IFU were analysed in the risk analysis. In two cases this was more than 80%.
Overall, half of the files scored insufficient on risk analysis, while only one was assessed as 'good'. The four 'moderate' scores were all due to partial analysis of risks related to warnings/precautions/contra-indications in the IFU.

Figure 2.3: Assessment scores for Risk analysis (red=insufficient, yellow=moderate, green=good)

2.4 Biocompatibility

Evaluation of biocompatibility has to be carried out as part of the design and development process and be integrated in the risk management process. A systematic evaluation using Annex B of the harmonised standard in Europe for biological evaluation of medical devices (EN ISO 10993-1, [13]) or an equivalent alternative approach to determine the tests to be carried out was missing in two cases. Manufacturers should always take account of the generally acknowledged state of the art. Furthermore, animal welfare requirements demand that no unnecessary animal testing be performed. For these reasons, a literature review is considered to be essential as a first step to determine biocompatibility issues, evaluate any existing data on these issues, and subsequently decide on the need for further biocompatibility testing. In five files, such a literature review was not found. In all cases, however, a comprehensive set of biocompatibility tests were always conducted and the applicable standards for these tests were used. Overall, only two files were assessed as 'good' and one was moderate.

Figure 2.4: Assessment scores for Biocompatibility (red=insufficient, yellow=moderate, green=good)

2.5 Mechanical testing

All manufacturers performed mechanical testing for their SBIs. Appropriateness of the tests was, however, not or partially addressed in half of the files, e.g. testing the shell only for the smooth surface SBI, rather than for all available surface types. While mechanical tests were always conducted, mostly referring to standards, test protocols were either not or only partially provided. Additionally, analysis of the data, summary of results and conclusions were not always adequately covered. The analysis of data as well as substantiation of the appropriateness of testing was incomplete in half of the files.
Overall, technical files were of moderate or insufficient quality with regard to mechanical testing.

Figure 2.5: Assessment scores for Mechanical testing (red=insufficient, yellow=moderate, green=good)

2.6 Clinical evaluation

If the characteristics of two medical devices are similar to a large extent, it can be assumed that there would be no clinically significant difference in their safety and performance. Subsequently, the clinical data of one device can be used in the clinical evaluation of the other device without conducting a new clinical investigation. This equivalence principle can only be used if there is strong literature evidence. In addition, clinical, technical, and biological characteristics should be included in the demonstration of equivalence according to the MEDDEV guidance document on clinical evaluation [14].
Most manufacturers submitted a clinical evaluation report based on the equivalence principle. In the files, SBIs were compared with SBIs of competitors and/or with other SBI types of the same manufacturer. Similarities and differences of SBI characteristics were listed with varying levels of detail and completeness. Whether the available argumentation could indeed be used as a valid rationale for equivalence was not clear in all cases. For example, equivalence of smooth and textured types was claimed. Furthermore, intended use was often indicated as "for reconstruction and augmentation purposes" without separating the two, while other manufacturers did distinguish between the two in their evaluation of clinical data. Based on available texts of the future new medical device regulation, which is currently under negotiation, it can be assumed that the application of the equivalence principle will be subject to limitations and more stringent requirements in the future.
Clinical evaluation reports were often verified with input from PMS, as they should be. In addition, a systematic literature review was often

conducted. In some cases however, literature reviews included in the file were showing updates with recent publications only, while the original review and previous updates were not submitted. Safety and performance claims were usually only stated in general terms. Contra-indications, safety aspects, and survival rate of the implant were missing in some of the clinical reports. The quantity of the clinical data varied considerably.
Overall, clinical evaluation was assessed as moderate or insufficient in all files.

Figure 2.6: Assessment scores for Clinical Evaluation (red=insufficient, yellow=moderate, green=good)

2.7 PMS procedure

Most of the submitted PMS procedures contained a description for the collection and review of experiences concerning SBIs in an active manner, using at least two methods (e.g., literature review, customer surveys), however, three procedures did not. Complaints as a passive source for PMS data were almost always used. Risk management activities were briefly mentioned as stand-alone reference in two cases and one time not at all. Criteria for the necessity to take actions were well-defined in only three PMS procedures. Nearly all manufacturers indicated that a periodic review of PMS data will be conducted. Corrective and preventive actions (CAPA) were also often mentioned. The concept of the continuous cycle of improvement of medical devices requires the manufacturer to use results from PMS activities as feedback in the risk management process and to consider the need for CAPA, including changes in design and/or IFU [15].
Overall, two PMS procedures scored 'good', and eight procedures need to be improved. Based on available texts of the future new medical device regulation, which is currently under negotiation, it can be expected that post market surveillance activities will be subject to considerably more stringent requirements.

Figure 2.7: Assessment scores for PMS procedure (red=insufficient, yellow=moderate, green=good)

2.8 Summary and analysis of PMS data

All manufacturers submitted a summary and analysis of PMS data. Most of the required information was present. However, in three cases the decision on action to be taken based on the PMS findings was not described and in one case PMS sources were not identified. In one of the files, PMS sources were actually the only aspect that was well addressed. Overall, the summary and analysis of PMS data was assessed as good in six files and insufficient in four files.

Figure 2.8: Assessment scores for Summary and analysis of PMS data (red=insufficient, green=good)

2.9 Vigilance procedure

All vigilance procedures described incident reporting to competent authorities. Overall, four vigilance procedures scored 'good', and six need to be improved. In six files, the link to risk management activities should be improved and also links to field safety corrective actions (FSCA), e.g., device recall or exchange, or CAPA were not always included.

Figure 2.9: Assessment scores for Vigilance procedure (red=insufficient, yellow=moderate, green=good)

2.10 Overall quality of technical files

All file items had shortcomings in one or more files (see Figure 2.10). Items that never scored 'good' were IFU and label, mechanical testing, and clinical evaluation. The only item that mostly scored 'good' or 'moderate' was device description.

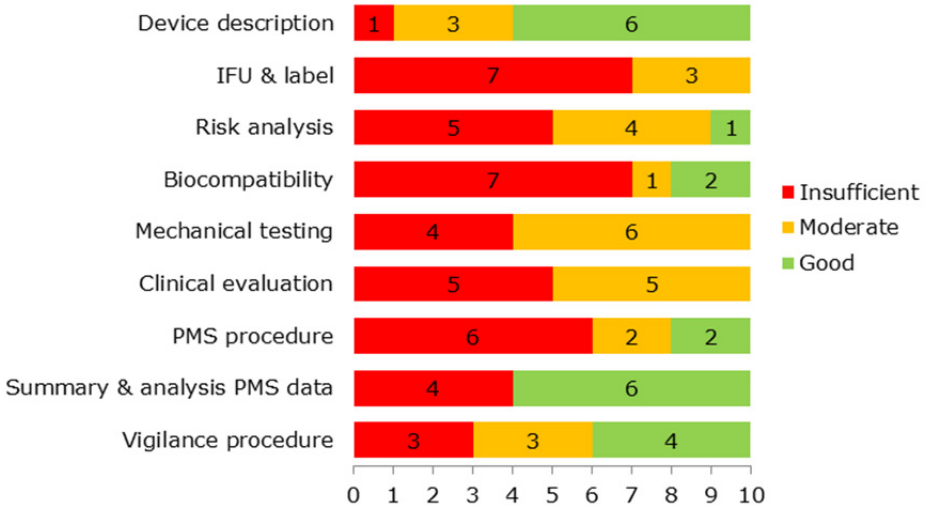

Figure 2.10: Assessment scores for all file items showing the number of files with a particular score per file item.

Overall, the assessment of the SBI files revealed that 47% of all items scored 'insufficient', 30% 'moderate', and 23% 'good'.

When looking at the results per SBI file, differences can be observed with regard to the scores (Figure 2.11). None of the files were completely 'good', 'moderate' or 'insufficient'. In four of the files, at least

50% of the items scored 'insufficient', while three files had only one or no items scoring 'good'.

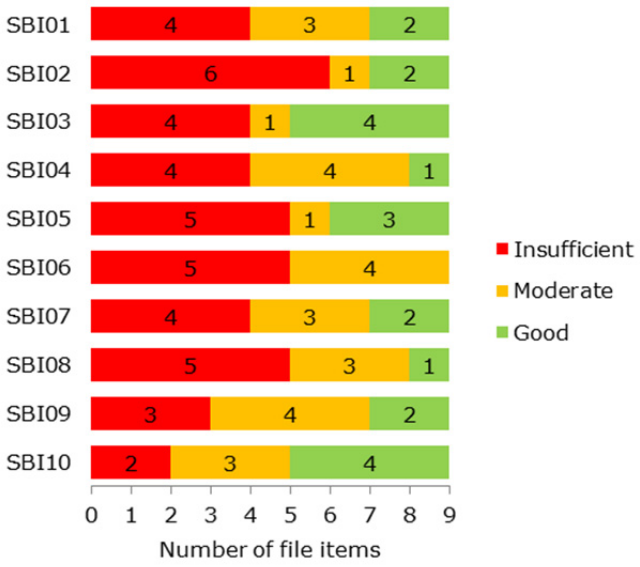

Figure 2.11: Assessment score of file items for each SBI file, showing the number of file items with a particular score.

It should be realised that a rather strict assessment system was used, in which missing one major sub-item or an equivalent number of points led to an 'insufficient' score for a file item. That was considered justified based on the principle that all essential elements (i.e. major sub-items) are needed to show a good control of the aspect(s) the particular file item is covering. This can be compared to a chain, for which all links are crucial for its strength and correct functioning.

2.11 Impact of findings on patient safety

Shortcomings in the technical documentation could imply that product safety and safe use of the device are insufficiently guaranteed, which could in turn have impact on patient safety. This paragraph describes to what extent the findings described above may impact patient safety. The shortcomings found for 'device description' and 'biocompatibility' cause little concern because they are of administrative nature, respectively are counterbalanced by the available information. The negative outcome for biocompatibility is primarily caused by not correctly following procedures to decide on which tests are needed. However, they did perform a standard set of tests according to applicable standards and the results did not indicate problems. Reason for concern are the shortcomings found for the items 'label and IFU', 'PMS and vigilance procedures' and 'summary and analysis of PMS data'. Depending on the knowledge and expertise of health care professionals involved, inadequate information on storage/handling conditions, surgical techniques and warnings/precautions/contra-indications could have an impact on patient safety. Furthermore, shortcomings in the PMS activities may lead to late or no discovery of aspects to be improved with regard to product safety and performance. In addition, when links to risk management activities and field safety

corrective actions (FSCA), e.g. device recall or exchange, or corrective and preventive action (CAPA) are missing in the vigilance procedure, structural elimination of problems and essential improvements to products may be omitted. This could clearly have impact on patient safety.
Finally, the observed shortcomings for the items 'risk analysis', 'mechanical testing' and 'clinical evaluation' could certainly have an impact on patient safety. When not all relevant risks are analysed or adequate risk control is shown, important measures to mitigate these risks may be missed. Mechanical testing is necessary to identify any weaknesses in the implant shell and thus reduce the likelihood of early rupture. Incomplete information on or substantiation of adequate testing is therefore a reason for concern. Furthermore, clinical evaluation is critical for the evaluation of safety and performance and information in the technical file should be upgraded to current standards. The negative assessments for this item might be partially explained by the fact that these products have often been on the market for many years, and data requirements may have been less stringent when they were originally placed on the market. In literature, while potential local effects of implants are acknowledged, so far no clear causal relationship has been established between SBIs and systemic health effects [7, 10, 16, 17]. Even so, manufacturers should still perform their own thorough clinical evaluation.
Complete as well as correct files are essential to warrant patient safety. In order to estimate the extent of the potential impact on patient safety of identified shortcomings in items like the risk analysis mechanical testing and clinical evaluation, more detailed assessments than those performed within the scope of the current study would be needed.

2.12 Conclusions assessment technical files

All SBI files showed shortcomings in one or more of the submitted file items. These shortcomings were most frequently found in the IFU and label, risk analysis, biocompatibility testing, mechanical testing, clinical evaluation and PMS activities. The only item that frequently scored 'good' or 'moderate' was the device description. This means that, in general, the technical files should be improved substantially.
Shortcomings in the submitted technical file do not necessarily mean that the quality and safety of the SBIs is insufficient. However, the regulatory system of medical devices depends to a large extent on the quality of the submitted technical file to demonstrate compliance to the applicable requirements. Shortcomings in that documentation could imply that product safety and safe use of the device are insufficiently guaranteed. If the concept of continuous cycle of improvement of medical devices, feeding back PMS results into the risk analysis and taking appropriate action where necessary, is not applied adequately, opportunities to improve product performance and safety might be missed.
Based on available texts of the future new medical device regulation, which is currently under negotiation, it can be expected that requirements for important elements of the regulatory system like clinical evaluation and post market surveillance activities will be considerably strengthened in the future.

Identified shortcomings in the technical files could impact patient safety. A more elaborate investigation per individual file is required to determine the extent of the potential impact. Complete as well as correct files are essential to warrant patient safety. Therefore, it is important that shortcomings are adequately addressed.

3 Physicochemical analysis

The compositions of the silicone gel and shell as well as the presence of impurities are SBI characteristics directly related to the quality of the breast implant. It has been shown that these three parameters can be monitored by physicochemical means [18]. In this study, a total of 77 SBIs from 10 manufacturers (SBI01-SBI10) were submitted to be analysed experimentally. The results of the chemical analyses on 69 of these implants are provided in the following paragraphs. Duplicate implants from the same batch were initially not tested and only used for control analyses if required. The analytical methods used are described in Annex 7. Detailed results are included in Annex 8.

3.1 The type of silicone gel

The silicone gel used in breast implants is commonly produced according to the method described in NEN-ISO 14949 [19]. Chains of methylated silicones are crosslinked with vinyl silicones, see Figure 3.1. After a correct use of this method, a surplus of non-toxic non-crosslinked vinyl silicones remains present in the gel. In some of the implants originating from the manufacturer PIP, no surplus of vinyl groups could be determined, indicating a production process that was not state of the art [20]. In this study, the presence of residual vinyl silicones has been analysed using nuclear magnetic resonance (NMR) spectroscopy.

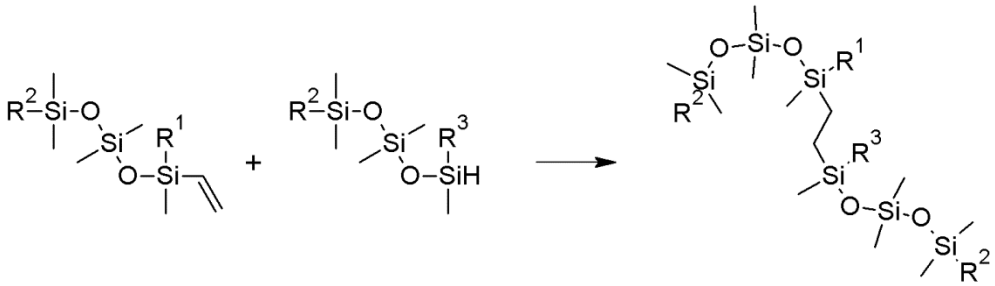

Figure 3.1: Schematic formation of a crosslink in a silicone gel. The vinyl reacts with the SiH forming an ethylene bridge. R_1=CH_3 or $(OSi(CH_3)_2)_n$, R_2 = $(OSi(CH_3)_2)_o$, R_3=CH_3 or $(OSi(CH_3)_2)_p$ where n, o and p can be any integer.

The vinyl group of the crosslinker can be either at the end of the polymeric chain (terminal, R_1=CH_3 in Figure 3.1), or not at the end of the chain (pendant, R_1= $(OSi(CH_3)_2)_n$). These two types of vinyl groups can easily be distinguished by NMR spectroscopy (Figure 3.2). Previous experiments have indicated that the vinyl group position was typical for the supplier of the starting material [18, 21]. During the period that the SBIs were submitted for this study, there were two suppliers of medical grade silicones: Applied Silicone and Nusil Silicones. It was previously found that the Applied Silicone samples tested all contained a crosslinker with a terminal vinyl group and all Nusil Silicones samples tested contained a crosslinker with a pendant vinyl group [18, 21]. Upon inquiry with the suppliers we learned that both of them offer both types of gel in their range of products.

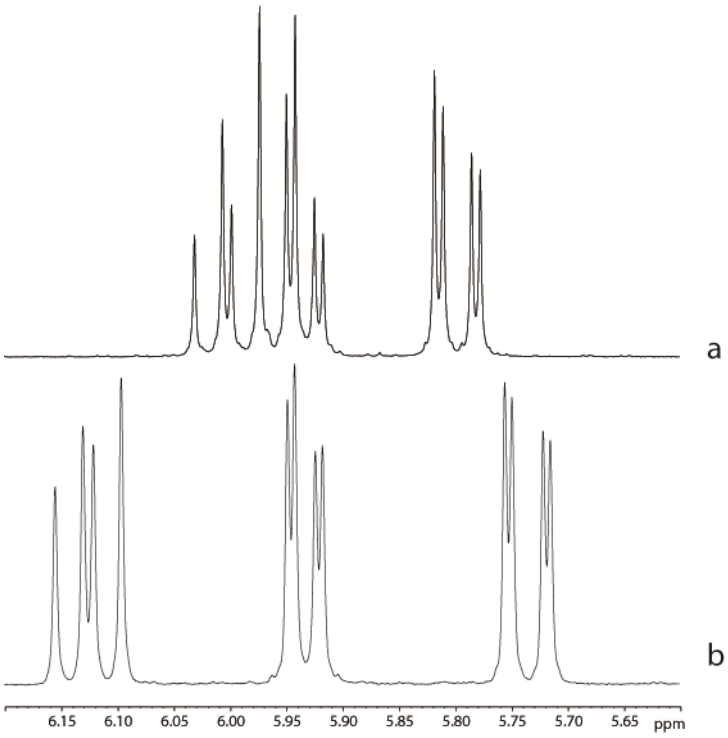

Figure 3.2: ^{1}H-NMR spectra of silicone gel extracts of an implant (order number A072229) made using a crosslinker with a pendant vinyl group (a) and an implant (order number A072401) made using a crosslinker with a terminal vinyl group (b). See Annex 7 for experimental details.

To confirm the NMR spectroscopic analysis, the gels have been subjected to near-infrared (NIR) spectroscopy. Previous research has indicated that specifically the signals from the vinyl groups contribute to the differences observed in the NIR spectra of silicone gels and that two clusters are formed; one containing the pendant vinyl groups and another containing the terminal vinyl groups [18].

The silicone gel of 69 breast implants was analysed for the presence of a surplus of vinyl groups. As a result it was found that all breast implants analysed contain a surplus of vinyl groups. Therefore, all these implants seem to contain a silicone gel that has been prepared according to the standard NEN-ISO 14949. In the principal component analysis of the NIR data, one cluster is formed by the SBI that according to the NMR spectroscopy contain a pendant vinyl group and the other cluster is formed by the SBI that contain a terminal vinyl group (Figure 3.3).

The experimentally determined type of vinyl signals have been compared with the data in the technical files (see Table 3.1 and Annex 8). The silicone gel manufacturers Applied Silicone and Nusil Silicones provided additional information on the vinyl position in the crosslinker in some of their products. It appeared that both suppliers provide crosslinkers containing both terminal as pendant vinyl groups.

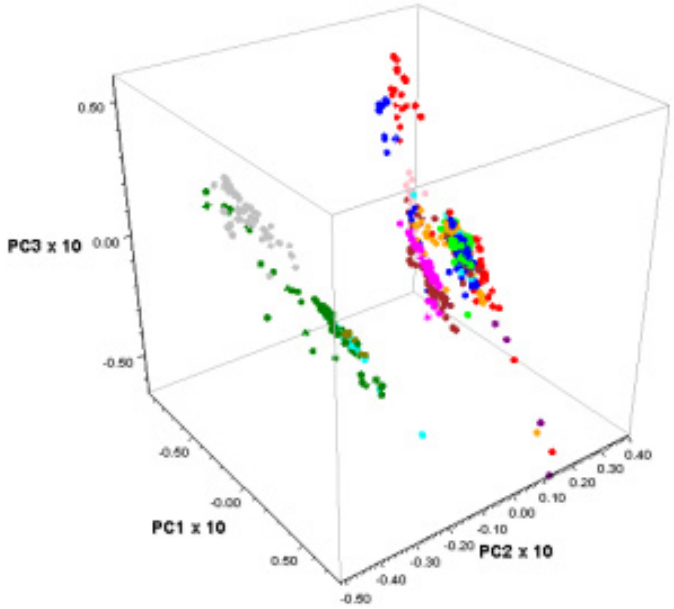

Figure 3.3: Principal component analysis of NIR spectra of the silicone gels of the examined breast implants, showing two separate clusters for gels made using a crosslinker with a terminal vinyl (cluster on left side), respectively not-terminal. The various suppliers are color coded: firebrick, SBI01; magenta, SBI02; cyan, SBI03; light green, SBI04; purple, SBI05; grey, SBI06; blue, SBI07; green, SBI08; red, SBI09; orange, SBI10; pink, Nusil MED3-6300; olive, Applied Silicone PN 40135.

Table 3.1: Comparison between the type of silicone gel as documented in the technical file and as determined experimentally.

Supplier	**Type of gel as documented[1]**	**Vinyl position according to gel manufacturer**	**experimentally determined vinyl position**
SBI01	40004 / MED3-6300	Pendant / pendant	Pendant
SBI02	PN 40004/ PN 40135	Pendant / not specified	Pendant
SBI03	MED9-6300 / ASC 40077 / ASC 40008	Not specified	Terminal
SBI04	Nusil, type not specified	Not specified	Pendant
SBI05	MED3-6300	Pendant	Pendant
SBI06	MED3-6300	Pendant	Terminal
SBI07	MED3-6300	Pendant	Pendant
SBI08	40004 /40000	Pendant / shell elastomer	Terminal
SBI09	MED3-6300	Pendant	Pendant
SBI10	MED3-6300	Pendant	Pendant

[1]The geltypes coded MED are obtained from Nusil Silicones, the type of gel with a 40* code are from Applied Silicone.

In two cases (manufacturers SBI06, SBI08 in Table 3.1), the experimentally determined type of gel does not match with the data submitted in the technical file. Upon confrontation with these findings, manufacturer SBI06 stated to only use Nusil Silicones material for the

production of their implants. However, it should have been MED3-6311 rather than MED3-6300 to explain the terminal vinyl position in the crosslinker.
If manufacturer SBI08 used Applied Silicone material for the production of their implants, it cannot have been part numbers 40004 or 40000, which according to Applied Silicone respectively contain a pendant vinyl group or is used to prepare the shell elastomer.

3.2 Impurities in the silicone gel

The starting material for silicone gel is produced from cyclosiloxanes [22]. Therefore, residues of these cyclosiloxanes are found in silicone gels. For a medical grade silicone gel, cyclosiloxanes are actively removed because of possible toxicity [23]. For technical grade silicone gels, cyclosiloxanes are not removed. For breast implants the use of medical grade silicone gel is required.
With the use of NMR spectroscopy, silicone gels can be analysed for the presence of residues of cyclosiloxanes [18]. The silicone gel of 70 SBIs have been analysed for the presence of cyclosiloxanes D4, D5 and D6. In 69 of the implants, no cyclosiloxanes were found. In one implant, order number A072238, from manufacturer SBI08, various cyclosiloxanes were detected (Figure 3.4).

The presence of the cyclosiloxanes in order number A072238 was verified by gas chromatography hyphened to a mass spectrometer (GC-MS). From this analysis, D4, D5 and D6 appeared to be present, as well as the larger cyclosiloxanes D7, D8 and D9 (Figure 3.5).
Quantitation of the signals in order number A072238 showed that it contains 8 ppm D4, 156 ppm D5 and 918 ppm D6 (based on extrapolation of the signal of the D5 reference standard). These values are comparable to those found in PIP2 SBI [20]. According to the recent SCENIHR opinion SBIs [10], this is well below levels of toxicological concern, so although it is a shortcoming, it does not raise a concern for patient safety. Another implant from the same manufacturer which tested negative in the NMR spectroscopy screening was quantitatively analysed as a negative control experiment. This implant, order number A072416, was found to contain no D4, D5 or D6. Both A072238 and A072416 were also evaluated in the cytotoxicity assay for biocompatibility to determine whether the presence of cyclosiloxanes affects the cytotoxic potential (see below).

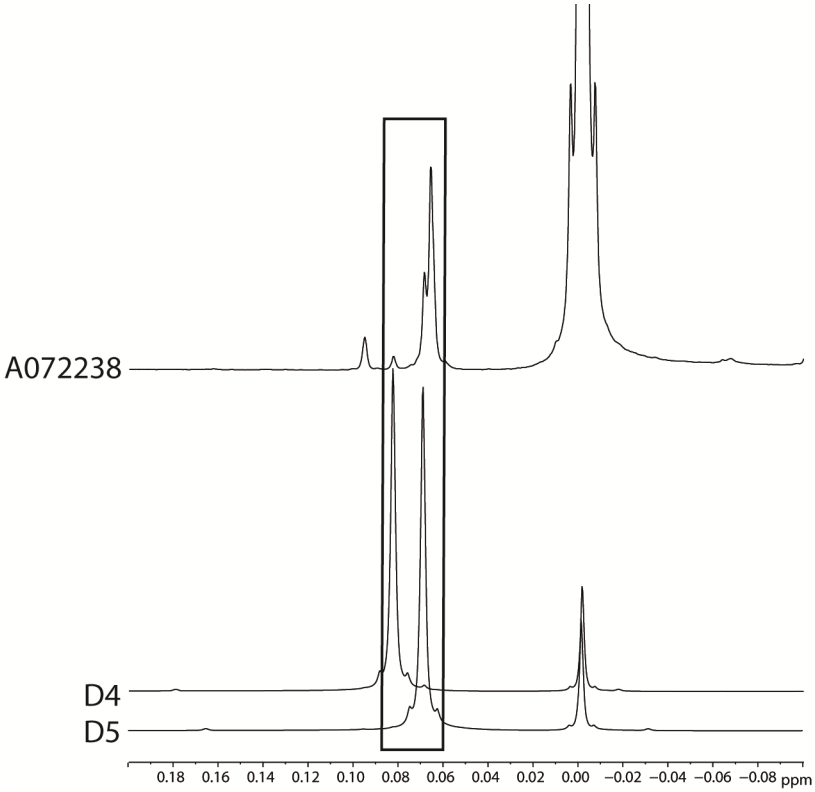

Figure 3.4: [1]H-NMR spectra of a silicone gel extract of implant ordernumber A072238 and of the reference standards cyclosiloxanes D4 en D5. See Annex 8 for technical details.

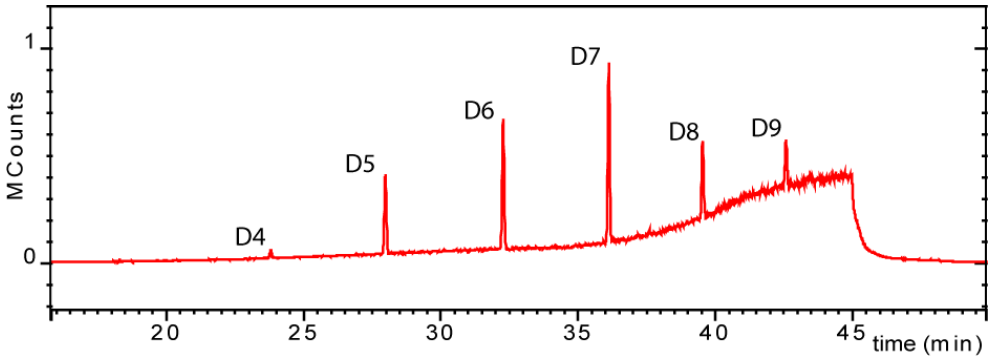

Figure 3.5: Chromatogram of a methanolic extract of order number A072238. The total ion current as determined by the mass spectrometer is plotted against the retention time on the gas chromatograph. The identities of the components are determined using the NIST database [24]. D4 and D5 are confirmed with a reference standard.The baseline is not corrected and reflects the temperature gradient.

3.3 Barrier layers in the shell

To prevent the leakage from low molecular silicones from the implant (bleeding), the shells of silicone based breast implants are often equipped with a barrier layer. This can be considered state-of-the-art [22]. Known barrier layers are diphenyl-silicone and fluoro-silicone. Shells consist of silicone material and are constructed in layers making use of a mold. For one or more of these layers, the fluoro- or phenyl-

functionalized silicones are used. It was previously found that PIP implants do not contain a barrier layer in their shell [18].
The presence of barrier layers has been determined using a Raman microscope. With the use of the microscope, the layering of the shell is readily observed in a cross-section. By taking Raman spectra of the surface of the cross-section, the molecular components can be determined and mapped (Figure 3.6). The identified components were subsequently compared with the spectra in a database.
All 67 implants analysed were equipped with a barrier layer in their shells. Of these implants, 13 contained a fluoro-silicone barrier layer and 54 contained a diphenyl-silicone barrier layer. In all cases this matches the information found in the technical file (see Annex 8).

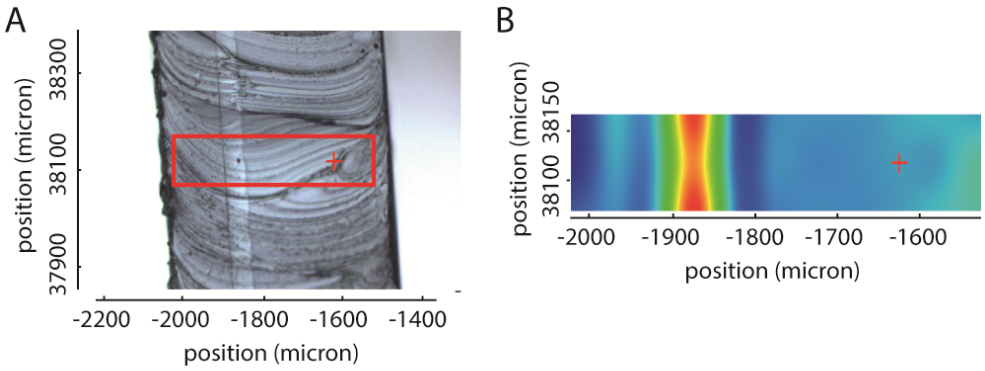

Figure 3.6: Analysis of the shell of order number A072237. A: microscopic photograph of a cross-section of the shell, displaying the area of the Raman spectroscopic analysis in a red square. B: Raman chemigram at 3050 cm^{-1}, a wavenumber at which there is an absorbance maximum of diphenyl-silicone. The intensity of the signal increases from blue to red. The red cross marks the identical position in A and B.

3.4 Polyurethane layer

To reduce excessive capsule formation in the breast tissue, an implant can be equipped with a layer of polyurethane [25]. For 21 implants (see Annex 8) it was visually determined that they contain a layer of foam. In all cases this matched the information in the technical file. The chemical identity of the foam could not be determined by use of Raman or IR spectroscopy. No other techniques were applied.

3.5 Conclusions physicochemical analysis

All investigated implants were found to contain silicone gel manufactured according to the protocol in the relevant international standard for silicone elastomers for surgical implants. In one case, however, the silicone gel was found to contain cyclosiloxanes contaminants which should not be present in medical grade material. Given the amount of contaminants found, this has no impact on patient safety.
With regard to the type of gel, discrepancies were found for two suppliers between the experimentally determined type and the information in the technical file. These shortcomings will not have an impact on patient safety, since these types of gels are of medical grade.

It is noted that the implant containing the impurities is also one of the implants of which the experimentally determined gel deviates from the type listed in the technical file. However, the number of implants investigated is too limited to state whether the over-all quality of products from SBI08 are less than those of the products of the other manufacturers.
All investigated implants contained a barrier layer in the implant shell, which is in line with the state-of-the-art and consistent with the descriptions in their technical files.
In summary, the physicochemical analyses show that the examined SBIs generally comply with the key characteristics tested. The small number of shortcomings found will not impact patient safety.

4 Biocompatibility studies

One of the most common assays for evaluation of biocompatibility is an *in vitro* cytotoxicity assay using an *in vitro* cell culture system. This assay provides a relatively quick screening to determine potential toxicity or leaching of toxic compounds from an implant. It is especially useful in comparing the relative toxicity between various products. The assay and the sample preparation applied in this study were performed according to the relevant European standards [26, 27]. The *in vitro* cytotoxicity assay is performed to identify the presence of toxic substances that are able to leach from a medical device. When toxic compounds are present in the extracts prepared from medical devices they can be detected in an *in vitro* cell culture system by their toxic activity inducing cell death or affecting cell functionality. The methods used are described in annex 11. A detailed overview of the results is included in annex 12. In total 11 SBI were evaluated of the 10 SBI manufacturers. For one manufacturer (SBI08) both an implant with a high (A072238) and a low (A072416) cyclosiloxane content was evaluated for possible effects of the presence of the cyclosiloxanes in the SBI on the cytotoxic activity of the extract of that SBI.

4.1 Results

For none of the evaluated SBI implants cytotoxic activity could be established when either L929 fibroblasts or RAW264.7 macrophages were incubated with extracts of either silicone gel or silicone shell material. An example of the results obtained in the cytotoxicity assays performed with the RAW 264.7 macrophage cell line is presented in Figures 4.1 and 4.2. Both macrophage cells and fibroblasts showed similar survival (approximately 100%) when compared to the control (non-treated cells). As no effects were noted for the first two investigated implants, it was decided to do only one test for the other evaluated SBIs.

In vitro cell growth does show variability both in growth of non-treated control cells and cells exposed to the test sample. In view of this variability in this kind of biological assay, cytotoxicity is considered to occur when cell survival is below 80% of the control cells. In the presence of a clear cytotoxic response the IC_{50} being the concentration inducing 50% cell survival (indicating 50% cell death) is used for comparing the relative toxicity of different test samples.
For two implants A072238 and A072416, the assay was performed three times. As the results showed consistently for all variations in the incubation (times of exposure, with and without serum addition) the absence of cytotoxicity, additional implants were only evaluated once. In some incubations the tissue cultures became contaminated. The contamination was only observed in those incubations in which the cells were exposed to extracts containing fetal bovine serum (FBS). In view of the general lack of cytotoxicity in all other assays these contaminated incubations were not repeated.

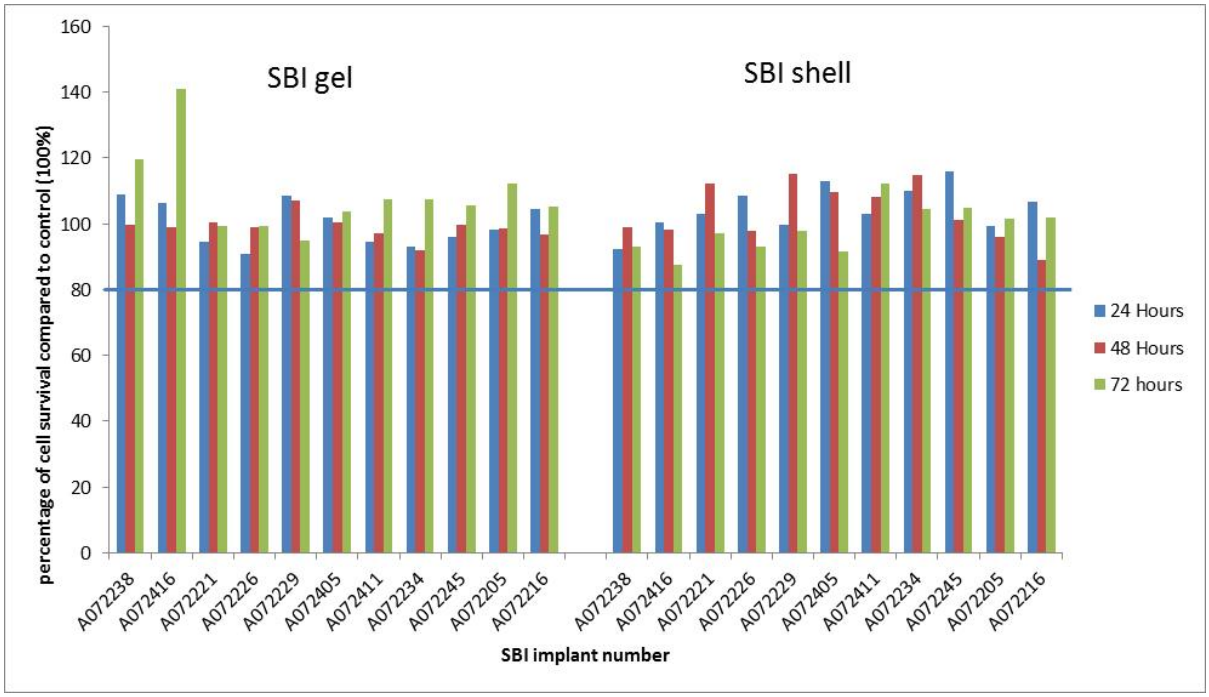

Figure 4.1: Survival of RAW 264.7 macrophage cells after incubation with SBI extracts in medium without serum. Cytotoxicity is considered to occur when cell survival is below 80% (blue horizontal line) of the control cells.

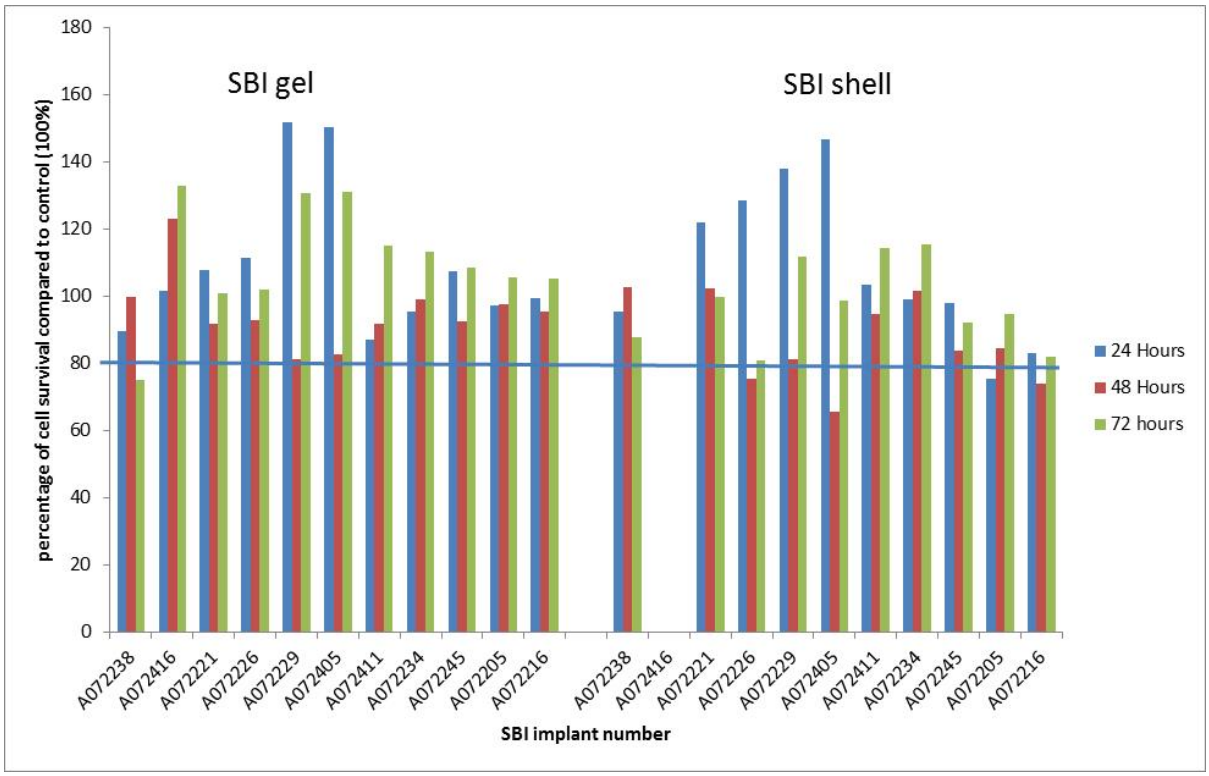

Figure 4.2 Survival of RAW 264.7 macrophage cells after incubation with SBI extracts in medium with serum. Cytotoxicity is considered to occur when cell survival is below 80% (blue horizontal line) of the control cells.

Only incidentally (for five different SBIs when cells were incubated with serum containing extracts) an indication for minimal cytotoxicity was observed, as indicated by a cell survival ranging from 66% to 75% (see data presented in Figure 4.2 and Annex 10). For each of these SBIs only in one out of twelve incubation conditions (i.e. 3 time points, 2 extract conditions, and 2 cell lines) a survival below the 80% level was observed. So, there was no consistent pattern in the cytotoxic responses. If a cytotoxic compound would have been present for all time points evaluated a cytotoxic activity should have been observed similar to the results with the positive Sn stabilized PVC control material (see Annex 10, Table 6.15). In addition, the cytotoxicity measured was limited with a cell survival ranging from 66% to 75%. Therefore, the observed cytotoxic responses are considered not relevant.

For the positive control tin stabilized polyvinylchloride, cytotoxicity was observed consistently in both cell lines (Annex 10, Table 6.15). Undiluted extract resulted in no cellular survival already after 24 hours of incubation with both tissue culture medium extracts with and without FBS. Also after fourfold and fivefold dilution approximately 50% cell death was observed for the medium extracts without serum whereas for the serum containing extracts still 100% cytotoxicity was present (Annex 10, Table 6.15). The tissue culture medium containing the FBS consistently showed a higher cytotoxicity compared to the extracts without FBS added, an effect that could not be explained.

4.2 Conclusions

In the experiments performed no indication was observed for either the silicone gel or the silicone elastomeric shell to induce significant cytotoxicity in two different cell lines, the macrophage cell line RAW264.7 and the fibroblast cell line L929. Therefore, it can be concluded that there was no leakage of toxic compounds from either the silicone gel or the silicone elastomeric shell in hydrophilic tissue culture medium extracts as indicated by a lack of cytotoxicity in two different cell lines.

In total, for eleven different SBIs of the 10 different SBI manufacturers no significant cytotoxicity could be observed, showing that the silicone materials used are non-toxic for cells over a broad range of SBI brands, which indicates good biocompatibility. Also for the product with a high content of cyclocyloxanes no cytotoxicity was observed. However, to determine biocompatibility for the product as a whole also other tests would need to be performed (e.g. irritation and sensitization, and implantation tests).

A remarkable difference was noted when the extraction medium used was with or without serum. The ISO 10993-5 standard prescribes the use of tissue culture medium as it is used for cell culture thus including serum. As shown in Annex 10 Table 6.15 almost 100% cytotoxicity was observed for the positive control biomaterial Sn stabilized PVC. In the serum containing extract also for the diluted extracts almost 100% cytotoxicity was observed. The serum effect can be attributed to the extraction phase of the experiment as the cytotoxicity assay itself is performed in serum containing medium. It might be speculated that the

serum in the extraction medium binds the leaking chemicals thus reducing the concentration in the extraction medium. As the extraction is a passive process this might result in a higher release from the material. Table 6.15 in Annex 10 also indicates that the L929 fibroblast cells were more sensitive for cytotoxic compounds in the extracts than the RAW 264.7 macrophage cells.

5 General conclusions and discussion

In this study, we have assessed the technical files and analysed product samples from 10 manufacturers marketing silicone breast implants (SBIs) in the Netherlands. As a general conclusion, the quality of the products with regard to several key physicochemical characteristics and biocompatibility as determined in the laboratory analysis was good. Small shortcomings are considered not to have impact on patient safety. However, the technical files did not provide adequate proof of conformity with the relevant regulatory requirements. Complete, correct files are essential to warrant patient safety. Therefore, it is important that shortcomings are adequately addressed.

To arrive at this over-all conclusion, five questions were addressed as described below.

Do the technical files provide adequate proof of conformity with the requirements of the Medical Devices Directive (MDD) [11]*?*
All technical files showed shortcomings in one or more items, and thus did not provide adequate proof of conformity with the requirements of the MDD. This included both minor and major shortcomings. Shortcomings were most frequently found in the IFU and label, risk analysis, biocompatibility testing, mechanical testing, clinical evaluation and PMS activities. The only items that mostly scored 'good' or 'moderate' was the device description.

Are key physicochemical characteristics of the products in line with the information in the technical documentation?
In general, the experimentally determined parameters of the implants were found to be in accordance with what was described in the technical documentation. In two cases, the type of silicone gel used appeared to be different from the specification in the file. In one case, the level of cyclosiloxanes contaminants was higher than the specification.

Are these physicochemical characteristics in line with the state-of-the art?
In all cases free vinyl groups were found to be present in the silicone gel and a barrier layer was present in the elastomeric shell. These physicochemical characteristics can be considered state-of-the art. The elevated levels of contaminants found in one case should not be present in medical grade starting material.
It is noted that that the higher levels of contaminants were encountered in an SBI from a manufacturer of which also the experimentally determined type of silicone gel did not match the technical file. The amount of SBI studied however, is too small to grade this manufacturer below the others.

Is the silicone material as present in the products biocompatible?
The biocompatibility of both the silicone gel and the silicone elastomeric shell has been evaluated *in vitro* in two different cell lines. In total for eleven different SBIs no cytotoxicity could be observed, showing that the silicone materials used for a broad range of SBI brands are non-toxic

for cells, which indicates good biocompatibility. This is in line with conclusions based on the assessment of the technical file.

In case of shortcomings, do these lead to a concern for patient safety?
Shortcomings in the technical files do not necessarily mean that the quality and safety of the SBIs is insufficient. However, the regulatory system of medical devices depends to a large extent on the quality of the submitted technical documentation. Therefore, any shortcomings in that documentation could imply that product safety and safe use of the device are insufficiently guaranteed. Given the type of shortcomings found, it can be concluded that some of them in label and IFU, as well as in PMS and vigilance activities potentially have an impact on patient safety. The same is also true for shortcomings in the risk analysis, the mechanical testing and the clinical evaluation, however, a more extensive and detailed analysis per individual file is required to determine the extent of the potential impact.
In the two cases where a different type of silicone gel compared with specifications seemed to be used, no impact on patient safety is expected, since also the aberrant gels are medical grade. In the case where the silicone gel was found to contain contaminants at levels which should not be present in medical grade starting material, the presence of these contaminants at the measured levels does not lead to an increased health risk for the user.

6 Annexes

6.1 Annex 1: References

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6.2 Annex 2: Methods of assessment technical files

Information requested
A set of documentation was requested from manufacturers marketing SBIs in the Netherlands. Identification of the manufacturers and sending out the request was performed by the IGZ (a copy of the letter is enclosed in Annex 3. The checklist enclosed with the letter requesting the technical file (see Annex 4) described details of the items to be submitted. The checklist was developed by RIVM and was largely based on the Summary Technical Documentation (STED) from the Global Harmonisation Task Force [28].[2] The following information was requested from the manufacturers:

- Device description;
- IFU and label;
- Risk analysis;
- Product verification and validation, in particular:
  - Biocompatibility;
  - Mechanical testing;
  - Clinical evaluation;
- Procedures and reports, in particular:
  - PMS procedure;
  - Summary and analysis of PMS data;
  - Vigilance procedure.

Technical files were received from ten manufacturers. The files were checked for completeness, without checking the contents of the documentation submitted. Since no items were missing, no additional requests needed to be sent out.
The information received from manufacturers often dealt with several variants of SBIs. In these cases, one variant was chosen for the assessment.

Assessment form
A form was developed for the assessment of the file (Annex 5), including an item for each section of the checklist in Annex 4. This method was also used for a previous investigation of metal-on-metal hip implants [29]. For each item, a set of sub-items was listed, largely based on the additional information listed in the STED. The first section of the checklist in Annex 4 on chemical composition / product specification was used for the physicochemical analyses and not for the assessment. In general, the assessment was based on the presence / description of that particular sub-item in the documentation. Sub-items were assigned N (no), P (partial), or Y (yes). For the assessment of the risk analysis, it was checked whether general risk categories, as derived from the harmonised standard for risk management of medical devices were covered [12]. In addition, a list of specific SBI-related risks was developed (see 2.3). Similarly, a list of SBI-related topics to be covered in the clinical evaluation was drawn up (see 2.6). For the assessment of addressing specific SBI-related risks, SBI-related topics for clinical evaluation and coherence between IFU and risk analysis, cut-off values

[2] The 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.

of <20% (low), 20-80% (medium) and >80% (high) were used. Coherence between the IFU and risk analysis implies that residual risks identified in the risk analysis are mentioned in the IFU and vice versa warnings, precautions and contra-indications mentioned in the IFU are addressed in the risk analysis. Using expert judgement of the RIVM, a higher weight and a higher score were given to important sub-items, related to risk and safety aspects, compared to the other items, often more of an 'administrative' nature. For the PMS and vigilance procedures and the PMS data, no distinction was made for the weight of the sub-items, as they were considered to be of equal importance. As all sub-items were considered crucial, missing one sub-item leads to an insufficient score. In Annex 5, the details on the score and weight of each sub-item are given.
To provide the possibility to comment on assigned scores and to include additional findings in the assessment form, an option was created to give qualifying remarks for every item. These remarks were used in the discussion of the results.

SBI-related risks and topics for clinical evaluation
Largely based on the SCENIHR opinions on SBIs [10, 17], risks associated with SBIs were identified. Based on the identified risks, lists of identified risks and clinical evaluation-related points of interest (Attachments II and III in the assessment form) were created. The lists were not intended to be exhaustive lists of all SBI-related risks or SBI-related topics for clinical evaluation.

Quality of technical file items
The overall score for technical file items was obtained as the sum of the sub-item scores. The sum translated into a 'good', 'moderate' or 'insufficient' score. Items scored 'good' if the sum was maximal, i.e. every sub-item was adequately addressed and received four points for a major sub-item or otherwise two points. A file item scored 'insufficient' if one major sub-item (or more) was missing or if any other combination of missing or partially addressed sub-items resulted in an equivalent number of missing points (i.e., ≥4). For the summary and analysis of PMS data and the vigilance procedure, an 'insufficient' score was obtained if ≥3 points were missing.

Assessment
All technical files were independently assessed by two assessors. The two assessments were compared during a meeting between the two assessors. The differences between the assessments were discussed and a decision on the assessment was made on a final assessment.

6.3 Annex 3: Letter to request information

Health Care Inspectorate
Ministry of Health, Welfare and Sport

> Postal address P. O. Box 2680 3500 GR Utrecht The Netherlands

REGISTERED LETTER

Pharmaceutical Affairs And Medical Technology

St. Jacobsstraat 16
Utrecht
P. O. Box 2680
3500 GR Utrecht
The Netherlands
T +31 30 233 87 87
F +31 30 232 19 12
www.igz.nl

Information with

Our reference

Enclosure(s)
1

Date August 25, 2014
Subject Request for silicone breast implants and additional documentation

Dear Sir/Madam,
The Dutch Health 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 silicone breast implants in the Netherlands. By request of the Inspectorate, the National Institute for Public Health and Environment (RIVM) will perform a study and laboratory analysis on breast implants. Therefore we request you to provide the following information to the Inspectorate:

- Within 1 week after receipt of this letter: 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. Additionally, please include the product names / types of the marketed silicone breast implants and distributors in/for the Netherlands. These data can be sent by e-mail to DienstpostbusIGZMedischetechnologie@igz.nl;
- The requested documentation as specified in the attached list. Please, provide the documentation in such a format that it clearly refers to the items as listed in the attachment, in order to prevent misinterpretation during assessment;

- Samples of 3 different batch numbers of smooth silicone breast implants;
- Samples of 3 different batch numbers of textured silicone breast implants

Our reference

Date
August 25, 2014

You are requested to send the implants and documentation, marked as confidential to:

The Dutch Healthcare Inspectorate
Secretariat Medical Technology
PO Box 2680
3500 GR Utrecht
The Netherlands

If you prefer to submit the documentation electronically, you can send it to:
_DienstpostbusIGZMedischetechnologie@igz.nl

It would be very much appreciated it if you could forward your information before:
October 6, 2014

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 finalizing the investigation, I will inform you regarding the findings concerning your medical device. If you have any questions regarding this letter or study, please do not hesitate to contact me at the letter head address or at: _DienstpostbusIGZMedischetechnologie@igz.nl

Yours sincerely,

Senior Inspector Medical Technology

Enclosure(s): Documentation required

6.4 Annex 4: Checklist for Dutch request SBI

Chemical composition/product specifications

- identity of raw materials (including chemical name);
- chemical specification of raw materials;
- list of suppliers of raw materials;
- preparation protocol of the gel;
- chemical specifications of the cross-linked gel[3];
- preparation protocol of the shell;
- chemical specifications of the cross-linked shell[4].

Device description

- a general description including its intended use/purpose;
- the intended patient population and medical condition to be diagnosed and/or treated and other considerations such as patient selection criteria;
- principles of operation;
- risk class and the applicable classification rule according to Annex IX of the European MDD;
- an explanation of any novel features;
- a description of the accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it;
- a description or complete list of the various configurations/variants of the device that will be made available;
- a general description of the key functional elements:
  - its parts/components (including software if appropriate),
  - its formulation,
  - its composition,
  - its functionality;

  where appropriate, this will include:
  - labelled pictorial representations (e.g. diagrams, photographs, and drawings), clearly indicating key parts/components, including sufficient explanation to understand the drawings and diagrams;
  - a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body, e.g. during extracorporeal circulation of body fluids.

Instructions for use and label[5]

The instructions for use and label(s) of the device as described in essential requirement 13, including requirements 7.5, 8.7 and 9.1 of the European Medical Devices Directive (MDD 93/42/EEC).

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

[3] Including underlying documentation on requirements of the gel and methods of analysis.
[4] Including underlying documentation on requirements of the shell and methods of analysis.
[5] For the purpose of the investigation, the instructions for use and labels of the device and its packaging should be the ones associated with the medical device as marketed in the Netherlands.

should be based on recognised standards, be consistent with the manufacturer's risk management plan, and be in English. It available, the risk management plan should be included.

- date/version number of risk analysis;
- 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.

Product verification and validation
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 only the following items:

- an evaluation of any published literature regarding the device or substantially similar devices;
- biocompatibility;
- mechanical testing;
- clinical evaluation;
- where no new testing has been undertaken, the documentation should incorporate a rationale for that decision.

Biocompatibility
Where biocompatibility testing has been undertaken to characterize the physical, chemical, toxicological and biological response of a material, detailed information should be included on:

- the tests conducted;
- standards applied;
- protocols of the in vitro and in vivo studies conducted;
- analysis of data;
- summary of results;
- a systematic evaluation using Annex B of ISO 10993-1, including assessment and summary/conclusion.

Mechanical testing
Where mechanical testing has been undertaken, detailed information should be included on:

- the tests conducted;
- standards applied;
- protocols of the tests conducted;
- analysis of data;
- summary of results;
- conclusion.

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 contains the following elements:

- the proprietary name of the medical device and any code names assigned during device development;
- identification of the manufacturer of the medical device;
- description of the medical device and its intended application;
- intended therapeutic and/or diagnostic indications;
- safety and performance claims made for the medical device;
- context of the evaluation;
- choice of clinical data types;
- description of clinical follow-up;
- summary of the clinical data and appraisal;
- performance analysis of the medical device;
- safety analysis of the medical device, including serious adverse events that occurred;
- consistency of medical device literature and instructions for use with clinical data;
- conclusions.

More information on the contents of the clinical evaluation report can be found on the website of the Global Harmonization Task Force (http://www.ghtf.org/).

Post-market surveillance (PMS) procedure

The submitted documentation should contain the post-market surveillance procedure, as laid down in the European Medical Devices Directive, plus any directly related procedures, preferably in English. This should include:

- customer or user complaints procedure;
- a principle or procedure for the active collection and review of experiences (e.g., customer satisfaction questionnaire / surveys), to collect experiences other than (customer / user) complaints[6];
- corrective and preventive actions will be taken: a principle or procedure for corrective and preventive actions is mentioned, i.e., procedure is referenced in post-market surveillance procedure;
- criteria for the necessity to take actions;
- risk management activities will be taken, e.g., update of the results of risk analysis is mentioned (post-market surveillance should be part of the risk management plan).

Summary and analysis of PMS data

The submitted documentation should contain a PMS report of the last two years containing the following elements:

- summary of the PMS data, including the sources used;
- analysis of PMS data;
- actions taken based on the analysis of the PMS data.

[6] Sources of information for post market surveillance are (active / reactive) are for instance expert users groups, customer complaints and warranty claims, post CE market clinical studies, literature reviews, user feedback other than complaints: surveys, customer satisfaction, device tracking / implant registries, user reactions during training programs, competent authorities, the media (including internet and email), experience with similar devices made by the same or different manufacturer, maintenance / service reports, retrieval studies on explants, in-house testing, failure analysis (analysis of complaints), fieldworkers, retailers, buyers satisfaction forms, panel sessions, meeting with users, feedback from marketing data.

Vigilance procedure

The submitted documentation should contain the vigilance procedure, as laid down in the European Medical Devices Directive, plus any directly related procedures, preferably in English. This should include:

- principle or procedure for incident reporting and the notification duty to competent authorities of any malfunction or shortcoming of the medical device;
- principle or procedure for field safety corrective action (formerly known as recall) is mentioned or described;
- (internal) corrective actions will be taken: a principle or procedure for corrective (and preventive) actions (field safety corrective action) is mentioned, i.e., procedure is referenced in the vigilance procedure;
- risk management activities will be taken, e.g., update of the risk analysis is mentioned.

6.5 Annex 5: Assessment form

		Manufacturer:			
		Medical device:			
Major (M)			**Options**	**Score options**	**Score**
		Device description			
	1	General description, including intended use/purpose	No, partially, yes	0, 1, 2	
	2	Intended patient population	No, partially, yes	0, 1, 2	
	3	(Medical) condition to be treated	No, partially, yes	0, 1, 2	
	4	Other considerations, such as patient selection criteria	No, partially, yes	0, 1, 2	
	5	Principles of operation i.e. mechanism of action (e.g. reconstruction)	No, partially, yes	0, 1, 2	
	6	Risk classification	No, yes	0, 2	
	7	Substantiation classification (2003/12/EC)	No, yes	0, 2	
	8	Explanation of novel features	No, partially, yes (NA)	0, 1, 2	
	9	Description of accessories, other medical devices and other products which are intended to be used in combination with it	No, partially, yes (NA)	0, 1, 2	
	10	Description or complete list of the various configurations/ variants of the SBI	No, partially, yes	0, 1, 2	
	11	Description of key functional elements (parts, formulation, composition, functionality)	No, partially, yes	0, 1, 2	
	12	Labelled pictorial representations (diagrams, photographs, drawings)	No, yes	0, 2	
	13	Description of materials incorporated into key functional elements and those making either direct or indirect contact with the human body	No, partially, yes	0, 1, 2	
		Total		*26*	
			Good	*26*	
			Moderate	*23-25*	
			Insufficient	*<23*	
		Qualifying remarks			

		IFU and label			
	1	IFU comply with the ERs 13.6.a – 13.6.q (see attachment IV)	No, partially, fully	0, 1, 2	
	2	Label complies with the ERs 13.3.a – 13.3.m (see attachment IV)	No, partially, fully	0, 1, 2	
M	3	IFU contain or refer to a document describing the surgical techniques (position of implant (e.g. sub-muscular placement), surgical approach (e.g. via inframammary fold), avoidance of applying (excessive) pressure during insertion, correct orientation of (anatomical) implants with markers, etc.). Where necessary the special surgical instruments needed are mentioned.	No, partially, yes	0, 2, 4	
	4	IFU are in English or Dutch	No, yes	0, 2	

M	5	Coherence RA-IFU: residual risks from the risk analysis, for which the risk analysis indicated that they are to be addressed in the IFU, are present in the IFU	<20% 20-80% >80%	0, 2, 4	
	6	Indications for use are mentioned	No, yes	0, 2	
M	7	Risks and contra-indications of SBIs, as identified based on literature, are clearly mentioned in the IFU (see attachment II)	No, partially, yes	0, 2, 4	
	8	IFU are clearly written	No, partially, yes	0, 1, 2	
	9	IFU are well structured	No, partially, yes	0, 1, 2	
		Total		*24*	
			Good	*24*	
			Moderate	*21-23*	
			Insufficient	*<21*	
		Qualifying remarks			

		Risk analysis			
	1	Dated / version number	No, yes	0, 2	
M	2	All risk categories (see attachment I) addressed	No, partially, yes	0, 2, 4	
M	3	SBI-related risks (see attachment II) addressed	No, partially, yes	0, 2, 4	
	4	Risks estimated	No, yes	0, 2	
M	5	Risk control/mitigation adequately described	No, partially, yes	0, 2, 4	
	6	Acceptability of residual risks addressed	No, yes	0, 2	
M	7	Coherence IFU-RA: WPCs mentioned in the IFU, are addressed in the risk analysis	<20% 20-80% >80%	0, 2, 4	
		Total		*22*	
			Good	*22*	
			Moderate	*19-21*	
			Insufficient	*<19*	
		Qualifying remarks			

		Biocompatibility			
	1	Literature review for the biocompatibility investigations	No, partially, yes	0, 1, 2	
M	2	Systematic evaluation using ISO 10993-1 to identify the tests to be carried out	No, partially, yes	0, 2, 4	
	3	Tests conducted	No, yes	0, 2	
	4	Appropriateness of the tests conducted for SBIs	No, partially, yes	0, 1, 2	
	5	Standards applied	No, yes	0, 2	
	6	Test protocols	No, partially, yes	0, 1, 2	
	7	Analysis of data	No, partially, yes	0, 1, 2	
	8	Summary of results	No, yes	0, 2	
	9	Conclusions	No, yes	0, 2	
		Total		*20*	
			Good	*20*	
			Moderate	*17-19*	
			Insufficient	*<17*	
		Qualifying remarks			

		Mechanical testing			
	1	Tests conducted	No, yes	0, 2	
	2	Appropriateness of the tests conducted for SBIs	No, partially, yes	0, 1, 2	
	3	Standards applied	No, yes	0, 2	
	4	Test protocols	No, partially, yes	0, 1, 2	
	5	Analysis of data	No, partially, yes	0, 1, 2	
	6	Summary of results	No, yes	0, 2	
	7	Conclusions	No, yes	0, 2	
		Total		*14*	
			Good	*14*	
			Moderate	*11-13*	
			Insufficient	*<11*	
		Qualifying remarks			

		Clinical evaluation			
	1	If clinical evaluation report is based on equivalency, is a valid rationale given to rationalise the equivalency	No, partially, yes (NA)	0, 1, 2	
	2	Proprietary name of the medical device or any code names assigned during device development	No, yes If no, the assessment can be stopped, as this is not correct devices	0, 2	
	3	Identification of the manufacturer of the medical device	No, yes	0, 2	
	4	Description of the medical device	No, yes	0, 2	
	5	Intended therapeutic indications	No, partially, yes	0, 1, 2	
	6	Safety and performance claims made for the medical device	No, partially, yes	0, 1, 2	
	7	Objective of the evaluation	No, yes	0, 2	
	8	Choice of clinical data types (literature, CI or combination) substantiated	No, yes	0, 2	
M	9	Summary of the clinical data and appraisal (considerations leading to conclusions)	No, only summary, summary and appraisal	0, 2, 4	
M	10	Performance and safety analysis of the medical device (incl. equivalency)	No, partially, yes	0, 2, 4	
M	11	Relevant topics adequately addressed (see attachment III)	<20% 20-80% >80%	0, 2, 4	
	12	Serious adverse events (SAEs) mentioned and evaluated (if applicable; if CI is performed for the specific breast implant)	No, mentioned but not evaluated, yes	0, 1, 2	
	13	Conclusions	No, yes	0, 2	
	14	Systematic, documented and appropriate literature search strategy (if applicable)	No, partially, yes (NA)	0, 1, 2	
		Total		*34*	
			Good	*34*	

			Moderate	*31-33*	
			Insufficient	*<31*	
		Qualifying remarks			

		PMS procedure			
	1	Customer or user complaints procedure (passive collection procedure)	No, yes	0, 2	
	2	Principle or procedure for the active collection and review of experiences (explicitly mentioned, not just a reference to another procedure)	No, yes	0, 2	
	3	Sources to actively collect experiences other than (customer / user) complaints ≥ 2	No, partially, yes	0, 1, 2	
	4	Corrective and preventive actions will be taken	No, only stand-alone reference, yes	0, 1, 2	
	5	Criteria for the necessity to take actions	No, not clearly defined (will be decided ad-hoc), yes (clear criteria)	0, 1, 2	
	6	Risk management activities will be taken	No, only stand-alone reference, yes	0, 1, 2	
	7	Periodic review of PMS data	No, yes	0, 2	
		Total		*14*	
			Good	*14*	
			Moderate	*13*	
			Insufficient	*<13*	
		Qualifying remarks			

		Summary and analysis of PMS data			
	1	PMS sources identified	No, yes	0, 2	
	2	Summary of PMS data	No, limited, clear (numbers, consequences etc.)	0, 1, 2	
	3	Analysis of PMS data	No, yes	0, 2	
	4	Decision on action to be taken	No, yes	0, 2	
		Total		*8*	
			Good	*8*	
			Moderate	*7*	
			Insufficient	*<7*	
		Qualifying remarks			

		Vigilance procedure			
	1	Principle or procedure for incident reporting and the notification duty to competent authorities	No, yes	0, 2	
	2	Principle or procedure for field safety corrective action (formerly known as recall)	No, only stand-alone reference,	0, 1, 2	

			yes		
	3	(Internal) Corrective actions will be taken	No, only stand-alone reference, yes	0, 1, 2	
	4	Risk management activities will be taken	No, only stand-alone reference, yes	0, 1, 2	
		Total		*8*	
			Good	*8*	
			Moderate	*7*	
			Insufficient	*<7*	
		Qualifying remarks			

Attachment I: Hazards and contributing factors

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

☐ **Biological**
- Contamination with bacteria
- Contamination with viruses

☐ **Chemical**
- Exposure of airway, tissues, environment or property, e.g. to foreign materials:
  - residues
  - contaminates
  - additives or processing aids
  - cleaning, disinfecting or testing agents
  - degradation products

☐ **Biocompatibility**
- Toxicity of chemical constituents, e.g.:
  - allergenicity/irritancy
  - pyrogenicity

☐ **Functional hazards**
- Loss or deterioration of function

☐ **Use error**
- Routine violation

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

☐ **Operating instructions**
- Inadequate specification of accessories to be used with the medical device
- Inadequate specification of pre-use checks
- Over-complicated operating instructions

☐ **Warnings**
- Of side effects
- Of hazards likely with re-use
- Of single-use medical devices

☐ **Incomplete requirements**
- Inadequate specification of:
  - design parameters
  - operating parameters
  - performance requirements
  - in-service requirements (e.g. maintenance, reprocessing)
  - end of life

☐ **Manufacturing processes**
- Insufficient control of changes to manufacturing processes
- Insufficient control of materials / materials compatibility information
- Insufficient control of manufacturing processes
- Insufficient control of subcontractors

☐ **Transport and storage**
- Inadequate packaging
- Contamination or deterioration
- Inappropriate environmental conditions

☐ **Environmental factors**
- Physical (e.g. heat, pressure, time)
- Chemical (e.g. corrosions, degradation, contamination)
- Electromagnetic fields (e.g. susceptibility to electromagnetic disturbance)
- Inadequate supply of power
- Inadequate supply of coolant

☐ **Cleaning, disinfection and sterilization**
- Lack of, or inadequate specification for, validated procedures for cleaning, disinfection and sterilization
- Inadequate conduct of cleaning, disinfection and sterilization

☐ **Disposal and scrapping**
- No or inadequate information provided

☐ **Formulation**
- Biodegration
- Biocompatibility
- Inadequate warning of hazards associated with incorrect formulations
- Use error

☐ **Potential for use errors triggered by design flaws, such as**
- Confusing or missing instructions for use
- Ambiguous or unclear device state
- Ambiguous or unclear presentation of settings, measurements or other information
- Misrepresentation of results
- Poor mapping of controls to actions, or of displayed information to actual state
- Use by unskilled / untrained personnel
- Insufficient warning of side effects
- Inadequate warning of hazards associated with re-use of single-use medical devices
- Incompatibility with consumables / accessories / other medical devices

☐ **Failure modes**
- Unexpected loss of mechanical integrity
- Deterioration in function (e.g. gradual occlusion of fluid / gas path, or change in resistance to flow, electrical conductivity) as a result of ageing, wear and repeated use

Attachment II: Risks and contra-indications based on literature for SBI

It should be checked whether the headings given are addressed, not whether all items are addressed.
(tick boxes: first column for instructions for use, second column for risk analysis)

IFU RA
☐ ☐ **1. Design and geometry of components**
☐ ☐ Surface finish
☐ ☐ Volume
☐ ☐ Composition shell / shell / membrane
Remark:

IFU RA
☐ ☐ **2. Contra-indications**
☐ ☐ Infection of body or blood
☐ ☐ Local inflammation
☐ ☐ Suppressed immune system [due to AIDS, high doses of corticosteroids and/or immune suppressants]
☐ ☐ Atopy (in relation to link with ASIA, depending date of risk analysis)
Remark:

IFU RA
☐ ☐ **3. Local complications**
☐ ☐ Implant failure / rupture
☐ ☐ Severe gel bleeding / leakage
☐ ☐ Local inflammation / swelling
☐ ☐ Regional swelling (axillary lymph nodes)
☐ ☐ Silicone migration
☐ ☐ Severe capsule formation and contracture
☐ ☐ Dislocation
☐ ☐ Hematoma
☐ ☐ Infection / inflammation
☐ ☐ Superficial wound
☐ ☐ (Ongoing severe) Pain
Remark:

IFU RA
☐ ☐ **4. Chemical composition and potential toxicity of chemical ingredients** (including used catalysts)
☐ ☐ Dimethylsiloxane (silicone) itself
☐ ☐ D4, D5, D6 siloxanes
☐ ☐ Presence of catalyst and/or other chemical residues
Remark:

IFU RA
☐ ☐ **5. Other hazards**
☐ ☐ Carcinogenicity, ALCL
☐ ☐ Limitation in breast cancer diagnosis
☐ ☐ Offspring effects
Remark:

IFU RA
☐ ☐ **6. Surgical technique**
☐ ☐ Surgeon’s experience
☐ ☐ Surgical approach
Remark:

IFU RA
☐ ☐ **7. General risk factors**
☐ ☐ Physical and chemical features of the implant
☐ ☐ Implantation procedure
☐ ☐ Time since implantation (chance of rupture)
☐ ☐ Patient specific factors (e.g. accidents)
Remark:

Attachment III: Clinical evaluation SBI
It should be checked whether the heading given are addressed, not whether all items are addressed.

See also:
- SCENIHR Opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants (2012).
- SCENIHR Opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants update of the opinion of February 2012 (2014).

☐ **1. General**
- Data obtained from literature [this could include device concerned and/or similar devices]
- Data obtained from a combination of clinical investigation and literature

☐ **2. Indications**
Common indications are:
- Cosmetic for breast enlargement
- Breast reconstruction after surgical treatment of breast cancer

☐ **3. Contra-indications**
- Age
- Infection of body or blood
- Suppressed immune system due to diseases such as AIDS or high doses of corticosteroids and/or immune suppressants
- Known sensitivity to chemical present in implant
- Atopy

☐ **4. Safety**
- Reconstructive surgery
- Other (secondary) operations
- Complications, implant rupture
- Implant severe leakage of filler component
- Anaplastic large cell lymphoma (incidental, low incidence)
- Systemic effects, e.g. chronic fatigue, connective tissue diseases general, multiple sclerosis/fibromyalgia/rheumatoid arthritis, ASIA (depending date of risk analysis)

☐ **5. Performance [efficacy / effectiveness]**
- Patient-oriented outcomes, e.g.
  - Pain
  - Quality of life
  - Ability to perform activities of daily living
  - Implantation success rate [survival]
- Other (surrogate) outcomes [surrogate outcomes substitute for a clinical event of true importance and the use of surrogate outcomes can be misleading], e.g.
  - Laboratory tests

☐ **6. Survival rates**
- Survival rate of implant device comparable to state of the art

- Follow-up period acceptable, i.e. longer than period on the market (survival rates with mean follow-up of 10-11 years have been published)

Attachment IV: Essential requirements

IFU

☐ ER 13.3.a Name of manufacturer
☐ ER 13.3.a Address of manufacturer
☐ ER 13.3.a Or name of EC-authorized representative, if applicable
☐ ER 13.3.a Or address of EC-authorized representative, if applicable
☐ ER 13.3.b Details to identify the device and contents of the packaging
☐ ER 13.3.c The word STERILE (can be a symbol)
☐ ER 13.3.f Single use indication
☐ ER 13.3.i Any special storage / handling conditions
☐ ER 13.3.j Any special operating instructions
☐ ER 13.3.k Any warnings / precautions
☐ ER 13.3.m Method of sterilization (can be a symbol)
☐ ER 13.6.b Performances
☐ ER 13.6.b Undesirable side-effects
☐ ER 13.6.e Risks in connection with implantation
☐ ER 13.6.f Risks of reciprocal interference posed by the presence of the device during specific investigations or treatment
☐ ER 13.6.g Instructions if sterile package is damaged
☐ ER 13.6.h Risks related to re-use
☐ ER 13.6.i Details treatment / handling prior to use

IFU include details allowing medical staff to brief patient on any contra-indications and any precautions to be taken

☐ ER 13.6.k Precautions if performance changes
☐ ER 13.6.l Precautions with regard to exposure in reasonably foreseeable environmental conditions (pressure, variations in pressure, acceleration, electrostatic discharge, external electrical influences, magnetic fields, etc.)
☐ ER 13.6.n Precautions to be taken against any special, unusual risks related to the disposal of the device

☐ ER 13.6.q Date of issue or latest revision of the IFU

Label

☐ ER 13.3.a Name of manufacturer
☐ ER 13.3.a Address of manufacturer
☐ ER 13.3.a Or name of EC-authorized representative, if applicable
☐ ER 13.3.a Or address of EC-authorized representative, if applicable
☐ ER 13.3.b Details to identify the device and contents of the packaging
☐ ER 13.3.c The word STERILE (can be a symbol)
☐ ER 13.3.d Where appropriate, the batch code, preceded by the word 'LOT',or the serial number
☐ ER 13.3.e Where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month
☐ ER 13.3.f Single use indication
☐ ER 13.3.i Any special storage / handling conditions
☐ ER 13.3.j Any special operating instructions
☐ ER 13.3.k Any warnings / precautions
☐ ER 13.3.m Method of sterilization (can be a symbol)

6.6 Annex 6: Results of the assessment of the technical files

Table 6.1: Assessment of the device description

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
General description	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Intended patient population	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
(Medical) condition to be treated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other considerations	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Principles of operation	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Risk classification	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Substantiation classification	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Description novel features	NA	NA	NA	Y	NA	Y	NA	N	NA	NA
Description accessories	NA	NA	Y	Y	NA	N	NA	Y	NA	NA
List of variants	Y	Y	Y	Y	Y	Y	P	Y	Y	Y
Key functional elements	Y	Y	Y	Y	Y	P	Y	Y	Y	Y
Pictorial representations	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Description materials	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment score	G	G	G	G	G	M	M	M	I	G

Sub-items scores: N – no, P – partial, Y – yes, NA – not applicable.
Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.2: Assessment of the IFU and label

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Compliance with ERs IFU	Y	P	P	Y	P	P	Y	Y	P	P
Compliance with ERs label	P	P	P	P	P	Y	P	P	P	P
Surgical techniques	P	Y	P	P	Y	Y	P	P	Y	Y
IFU in English or Dutch	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Coherence: residual risks in IFU	Hi	Hi	Hi	Hi	Hi	Hi	Me	NA	Hi	Me
Indications for use	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Risks and contra-indications	P	P	P	Y	P	Y	Y	P	Y	Y
IFU clearly written	Y	Y	Y	Y	Y	Y	P	N	Y	Y
IFU well-structured	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment score	I	I	I	M	I	M	I	I	M	I

Gray-shaded row is major sub-item.
ERs – essential requirements, IFU – instructions for use.
Sub-items scores: N – no, P – partial, Y – yes, Lo – low (<20%), Me – medium (20-80%), Hi – high (>80%), NA – not applicable (in risk analysis no residual risks were indicated to be addressed in the IFU).
Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.3: Assessment of the risk analysis

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Dated / version number	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All risk categories	P	Y	Y	Y	P	Y	Y	P	P	Y
SBI-related risks	Y	Y	Y	Y	Y	Y	Y	P	P	Y
Risks estimated	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Risk control / mitigation	Y	P	Y	Y	P	Y	Y	P	Y	Y
Acceptability of residual risks	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Coherence: WPC in risk analysis	Me	Me	Hi	Me	Me	Me	Me	Hi	Me	Me
Assessment score	I	I	G	M	I	M	M	I	I	M

Gray-shaded row is major sub-item.

WPC – warnings, precautions and contra-indications.

Sub-items scores: N – no, P – partial, Y – yes, Lo – low (<20%), Me – medium (20-80%), Hi – high (>80%).

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.4: Assessment of the biocompatibility evaluation

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Literature review	N	Y	P	P	N	N	N	Y	P	N
Systematic evaluation (ISO 10993-1)	N	Y	P	P	Y	Y	N	Y	Y	P
Tests conducted	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Appropriateness of tests	Y	Y	Y	Y	Y	P	Y	Y	Y	Y
Standards applied	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Test protocols	N	Y	N	P	N	Y	Y	Y	P	N
Analysis of data	P	Y	P	P	N	Y	Y	Y	Y	N
Summary of results	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Conclusions	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Assessment score	I	G	I	I	I	I	I	G	M	I

Gray-shaded row is major sub-item.

Sub-items scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.5: Assessment of the mechanical testing

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Tests conducted	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Appropriateness of tests	Y	N	P	P	Y	Y	Y	Y	P	P
Standards applied	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Test protocols	P	N	N	P	P	N	P	P	N	P
Analysis of data	N	N	P	Y	Y	Y	P	Y	P	Y
Summary of results	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Conclusions	Y	N	N	N	Y	Y	Y	Y	Y	Y
Assessment score	M	I	I	I	M	M	M	M	I	M

Sub-items scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.6: Assessment of the clinical evaluation

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Rationale for equivalence	P	N	P	P	P	Y	NA	P	Y	NA
Proprietary name of medical device	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Identification of manufacturer	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Description of medical device	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Intended therapeutic indications	Y	Y	P	Y	Y	P	Y	Y	Y	Y
Safety and performance claims	P	P	P	Y	P	P	P	P	P	P
Objective of clinical evaluation	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Choice of clinical data substantiated	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Summary of clinical data & appraisal	Y	P	Y	Y	Y	Y	Y	Y	Y	Y
Performance and safety analysis	Y	P	Y	Y	P	Y	Y	Y	Y	Y
Relevant topics	Hi	Hi	Hi	Hi	Hi	Me	Me	Hi	Hi	Hi
Serious adverse events evaluated	Y	Y	Y	P	Y	Y	Y	NA	Y	Y
Conclusions	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Systematic literature search strategy	P	Y	P	Y	P	Y	N	P	Y	P
Assessment score	M	I	I	M	I	I	I	M	M	M

Gray-shaded row is major sub-item.

Sub-items scores: N – no, P – partial, Y – yes, NA – not applicable, Lo – low (<20%), Me – medium (20-80%), Hi – high (>80%).

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.7: Assessment of the PMS procedure

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Passive procedure (complaints)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Active procedure	N	Y	Y	Y	Y	N	Y	N	Y	Y
Sources ≥2, other than complaints	N	Y	Y	Y	Y	N	Y	N	Y	Y
Corrective and preventive action	Y	Y	Y	Y	Y	N	Y	P	Y	Y
Criteria for action	Y	N	P	P	Y	N	P	N	P	Y
Risk management activities	P	Y	Y	P	Y	N	Y	Y	Y	Y
Periodic review PMS data	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Assessment score	I	I	M	I	G	I	I	I	M	G

PMS – post market surveillance.

Sub-items scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.8: Assessment of the summary and analysis of PMS data

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
PMS sources identified	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Summary of PMS data	Y	Y	Y	P	Y	Y	Y	Y	Y	Y
Analysis of PMS data	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Decision on action	Y	N	Y	N	Y	N	Y	Y	Y	Y
Assessment score	G	I	G	I	G	I	G	I	G	G

PMS – post market surveillance.

Sub-items scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

Table 6.9: Assessment of the vigilance procedure

	Silicone breast implant									
Sub-item	01	02	03	04	05	06	07	08	09	10
Incident reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Field safety corrective action	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Corrective action	Y	Y	Y	Y	N	P	Y	P	Y	Y
Risk management activities	P	P	Y	P	N	N	Y	N	Y	Y
Assessment score	M	M	G	M	I	I	G	I	G	G

Sub-items scores: N – no, P – partial, Y – yes.

Assessment scores: I – insufficient, M – moderate, G – good.

6.7 Annex 7: Analytical methods

Materials
A total of 77 SBIs from 10 manufacturers (SBI01-SBI10) were submitted to the study. All implants received a unique ordernumber upon receipt. Some implants were from the same batch and therefore not subjected to all analyses. D4 and D5 cyclosiloxanes reference standards were obtained from Sigma Aldrich (Zwijndrecht, the Netherlands). Technical grade dimethyl-, diphenyl- and fluoro-silicones were obtained from Applied Silicone (Santa Paula, CA, USA) and were subsequently prepared according to the manufacturers protocols.

NMR spectroscopy
Silicone gels were extracted with d_6DMSO (0.3-0.5 g in 1.0 mL) and $CDCl_3$ (0.03-0.06 g in 1.0 mL) in glass tubes for 5 minutes, shaking at room temperature. The DMSO extracts were transferred to NMR tubes, $CDCL_3$ dissolved the gels yielding slurries that were transferred as a whole into NMR tubes. ^{1}H spectra were acquired at 14.1 T on a Bruker DMX 600 MHz spectrometer (Bruker, Wormer, the Netherlands) equipped with a TCI-Z-GRAD cryoprobe operating at 298 K. All samples were automatically tuned, matched and shimmed. Spectra were calibrated to the solvent peaks of $CHCL_3$ (7.2600 ppm) and DMSO (2.5000 ppm). Spectra were processed and analysed using Topspin 3.0 software (Bruker, Wormer, the Netherlands).

NIR spectroscopy
NIR measurements were performed using an Antaris II FT-NIR spectrometer and TQ-Analyst software vs 8.4 (Thermo Scientific, Madison USA). An auxiliary transflection piece with 1.2 mm spacer was used to create films of equal size of the gels. Spectra were collected in the transflection mode, resolution 8 cm^{-1}, spectral range 12000 – 3000 cm^{-1}. Principle Component Analysis (PCA) was carried out on the first derivative of the spectra in the range of 8000 - 4000 cm^{-1} without additional spectral pre-treatments.

Raman microscopy
A DXR Raman microscope (Thermo Scientific, Madison USA) was employed to record Raman spectra in area maps of a cross section of the shell of an implant. Measurements were carried out using a 10x objective, a 780 nm laser with a laser power of 14 mW, a collection time of 10 seconds and a slit width of 50 µm.

GC-MS
Silicone gel methanol extracts were prepared (0.03-0.06 g in 1.0 mL) in glass tubes, shaking for 5 minutes at room temperature. A Varian CP-3800 was coupled to an Agilent Technologies 240 ion trap MS equipped with a GL Sciences InertCap Aquatic-2 60 m x 0.25 mm column. A temperature gradient from 40 to 250º C was used, with an injector temperature of 180º C and helium as carrier gas. Varian Workstation software was used for operation and data analysis.

6.8 Annex 8: Results of the chemical analysis

Table 6.10: The supplier of the used silicone gel according to the NMR spectroscopy, the NIR spectroscopy and the technical file per analysed implant.

Order	Expiry date	NMR	NIR	Technical file
A072201	mei-19	Pendant	Pendant	Nusil
A072202	jun-19	Pendant	Pendant	Nusil
A072203	mei-19	Pendant	Pendant	Nusil
A072204	mrt-19	Pendant	Pendant	Nusil
A072205	jun-19	Pendant	Pendant	Nusil
A072206	mei-18	Pendant	Pendant	Nusil
A072207	okt-19	Pendant	Pendant	Nusil
A072208	okt-19	Pendant	Pendant	Nusil
A072209	okt-19	Pendant	Pendant	Nusil
A072210	okt-19	Pendant	Pendant	Nusil
A072211	feb-18	Pendant	Pendant	Nusil
A072212	dec-18	Pendant	Pendant	Nusil
A072213	jul-18	Pendant	Pendant	Nusil
A072214	sep-18	Pendant	Pendant	Nusil
A072215	sep-17	Pendant	Pendant	Nusil
A072216	jun-16	Pendant	Pendant	Nusil
A072217	okt-19	Pendant	Pendant	Nusil
A072218	okt-19	Pendant	Pendant	Nusil
A072219	okt-19	Pendant	Pendant	Nusil
A072220	okt-19	Pendant	Pendant	Nusil
A072221	okt-19	Pendant	Pendant	Nusil
A072222	mrt-19	Pendant	Pendant	Applied
A072223	apr-09	Pendant	Pendant	Applied
A072224	apr-19	Pendant	Pendant	Applied
A072225	jun-19	Pendant	Pendant	Applied
A072226	feb-19	Pendant	Pendant	Applied
A072227	mrt-19	Pendant	Pendant	Applied
A072228	mei-14	Pendant	Pendant	Nusil
A072229	mrt-14	Pendant	Pendant	Nusil
A072230	jun-19	Pendant	Pendant	-*
A072231	jun-19	Pendant	Pendant	-*
A072232	mrt-19	Terminal	Terminal	Nusil
A072233	jun-19	Terminal	Terminal	Nusil
A072234	okt-17	Terminal	Terminal	Nusil
A072235	mei-19	Terminal	Terminal	Nusil
A072236	feb-18	Terminal	Terminal	Nusil
A072237	feb-18	Terminal	Terminal	Nusil
A072238	jun-14	Terminal	Terminal	Applied
A072239	jul-14	Terminal	Terminal	Applied
A072240	jun-19	Pendant	Pendant	Nusil
A072241	jun-19	Pendant	Pendant	Nusil
A072242	aug-19	Pendant	Pendant	Nusil
A072243	apr-19	Pendant	Pendant	Nusil
A072244	-*	Pendant	Pendant	Nusil

A072245	-*	Pendant	Pendant	Nusil
A072401	jun-19	Terminal	Terminal	Applied
A072402	jun-19	Terminal	Terminal	Applied
A072403	jul-18	Pendant	Pendant	Nusil
A072404	nov-18	Pendant	Pendant	Applied
A072405	apr-19	Pendant	Pendant	Applied
A072406	mrt-19	Pendant	Pendant	Nusil
A072407	jun-19	Pendant	Pendant	Nusil
A072408	jan-18	Pendant	Pendant	Applied
A072409	jul-17	Pendant	Pendant	Nusil
A072410	sep-17	Pendant	Pendant	Nusil
A072411	okt-17	Pendant	Pendant	Nusil
A072412	sep-17	Terminal	Terminal	Applied
A072413	sep-17	Terminal	Terminal	Applied
A072414	sep-17	Terminal	Terminal	Applied
A072415	sep-16	Terminal	Terminal	Applied
A072416	sep-16	nd*	nd*	Applied
A072417	sep-16	nd*	nd*	Applied
A072418	sep-17	Terminal	Terminal	Applied
A072419	sep-17	nd*	nd*	Applied
A072420	sep-17	nd*	nd*	Applied
A072421	apr-16	Terminal	Terminal	Applied
A072422	apr-16	nd*	nd*	Applied
A072423	apr-16	nd*	nd*	Applied
A072424	sep-17	Terminal	Terminal	Applied
A072425	sep-17	nd*	nd*	Applied
A072426	sep-17	nd*	nd*	Applied
A072427	mei-19	Pendant	Pendant	Nusil
A072428	mei-19	Pendant	Pendant	Nusil
A072429	aug-19	Pendant	Pendant	Nusil
A072430	aug-19	Pendant	Pendant	Nusil
A072431	aug-19	Pendant	Pendant	Nusil
A072432	aug-19	Pendant	Pendant	Nusil

-*: no data available

nd*: the type of silicone gel in SBI from the same batch was not determined, unless deviations from the technical files were observed.

Table 6.11: The barrier layers in the examined implants according to the experimental analysis and the technical file per analysed implant, and the visual presence of a foam layer.

Order	Expiry date	Experimental	Technical file	Foam layer
A072201	mei-19	diphenylsilicone	diphenylsilicone	none
A072202	jun-19	diphenylsilicone	diphenylsilicone	none
A072203	mei-19	diphenylsilicone	diphenylsilicone	none
A072204	mrt-19	diphenylsilicone	diphenylsilicone	none
A072205	jun-19	diphenylsilicone	diphenylsilicone	none
A072206	mei-18	diphenylsilicone	diphenylsilicone	none
A072207	okt-19	diphenylsilicone	diphenylsilicone	none
A072208	okt-19	diphenylsilicone	diphenylsilicone	none
A072209	okt-19	diphenylsilicone	diphenylsilicone	none
A072210	okt-19	diphenylsilicone	diphenylsilicone	none
A072211	feb-18	diphenylsilicone	diphenylsilicone	none
A072212	dec-18	diphenylsilicone	diphenylsilicone	none
A072213	jul-18	diphenylsilicone	diphenylsilicone	none
A072214	sep-18	diphenylsilicone	diphenylsilicone	none
A072215	sep-17	diphenylsilicone	diphenylsilicone	none
A072216	jun-16	diphenylsilicone	diphenylsilicone	none
A072217	okt-19	diphenylsilicone	diphenylsilicone	none
A072218	okt-19	diphenylsilicone	diphenylsilicone	none
A072219	okt-19	diphenylsilicone	diphenylsilicone	none
A072220	okt-19	diphenylsilicone	diphenylsilicone	none
A072221	okt-19	diphenylsilicone	diphenylsilicone	none
A072222	mrt-19	fluorosilicone	fluorosilicone	none
A072223	apr-09	fluorosilicone	fluorosilicone	none
A072224	apr-19	fluorosilicone	fluorosilicone	none
A072225	jun-19	fluorosilicone	fluorosilicone	none
A072226	feb-19	fluorosilicone	fluorosilicone	none
A072227	mrt-19	fluorosilicone	fluorosilicone	none
A072228	mei-14	diphenylsilicone	diphenylsilicone	present
A072229	mrt-14	diphenylsilicone	diphenylsilicone	present
A072230	jun-19	diphenylsilicone	diphenylsilicone	none
A072231	jun-19	diphenylsilicone	diphenylsilicone	none
A072232	mrt-19	diphenylsilicone	diphenylsilicone	none
A072233	jun-19	diphenylsilicone	diphenylsilicone	none
A072234	okt-17	diphenylsilicone	diphenylsilicone	none
A072235	mei-19	diphenylsilicone	diphenylsilicone	none
A072236	feb-18	diphenylsilicone	diphenylsilicone	none
A072237	feb-18	diphenylsilicone	diphenylsilicone	none
A072238	jun-14	fluorosilicone	fluorosilicone	present
A072239	jul-14	fluorosilicone	fluorosilicone	present
A072240	jun-19	diphenylsilicone	diphenylsilicone	none
A072241	jun-19	diphenylsilicone	diphenylsilicone	none
A072242	aug-19	diphenylsilicone	diphenylsilicone	none
A072243	apr-19	diphenylsilicone	diphenylsilicone	none
A072244	-*	diphenylsilicone	diphenylsilicone	none
A072245	-*	diphenylsilicone	diphenylsilicone	none

A072401	jun-19	diphenylsilicone	diphenylsilicone	present
A072402	jun-19	diphenylsilicone	diphenylsilicone	present
A072403	jul-18	diphenylsilicone	diphenylsilicone	none
A072404	nov-18	diphenylsilicone	diphenylsilicone	none
A072405	apr-19	diphenylsilicone	diphenylsilicone	none
A072406	mrt-19	diphenylsilicone	diphenylsilicone	none
A072407	jun-19	diphenylsilicone	diphenylsilicone	none
A072408	jan-18	diphenylsilicone	diphenylsilicone	none
A072409	jul-17	diphenylsilicone	diphenylsilicone	none
A072410	sep-17	diphenylsilicone	diphenylsilicone	none
A072411	okt-17	diphenylsilicone	diphenylsilicone	none
A072412	sep-17	fluorosilicone	fluorosilicone	present
A072413	sep-17	nd*	fluorosilicone	present
A072414	sep-17	nd*	fluorosilicone	present
A072415	sep-16	fluorosilicone	fluorosilicone	present
A072416	sep-16	nd*	fluorosilicone	present
A072417	sep-16	nd*	fluorosilicone	present
A072418	sep-17	fluorosilicone	fluorosilicone	present
A072419	sep-17	nd*	fluorosilicone	present
A072420	sep-17	nd*	fluorosilicone	present
A072421	apr-16	fluorosilicone	fluorosilicone	present
A072422	apr-16	nd*	fluorosilicone	present
A072423	apr-16	nd*	fluorosilicone	present
A072424	sep-17	fluorosilicone	fluorosilicone	present
A072425	sep-17	nd*	fluorosilicone	present
A072426	sep-17	nd*	fluorosilicone	present
A072427	mei-19	diphenylsilicone	diphenylsilicone	none
A072428	mei-19	diphenylsilicone	diphenylsilicone	none
A072429	aug-19	diphenylsilicone	diphenylsilicone	none
A072430	aug-19	diphenylsilicone	diphenylsilicone	none
A072431	aug-19	diphenylsilicone	diphenylsilicone	none
A072432	aug-19	diphenylsilicone	diphenylsilicone	none

-*: no data available

nd*: the presence of barrier layers in SBI from the same batch was not determined, unless deviations from the technical files were observed.

6.9 Annex 9: Biocompatibility methods

Materials
In total 10 brands of SBI were identified on the Dutch market. In total 11 different SBIs designated with unique order numbers were evaluated for biocompatibility. From one brand (SBI08) two SBIs were evaluated; one containing and one not containing cyclosiloxanes as observed in the chemical analysis. Biocompatibility was assessed by evaluating the cytotoxic potential of both the silicone gel within the implant and the outer shell of the implant. According to ISO 10993-12 hydrophilic extracts were prepared of the silicone gel and silicone elastomeric shell using tissue culture medium with and without the presence of fetal bovine serum (incubation for 72 ± 2 hours at 37^{o}C). The cytotoxicity assay was performed according to ISO 10993-5 standard describing cytotoxicity assays with hydrophilic (tissue culture medium) extraction vehicles.
Cell cultures of a macrophage cell line (RAW264.7) and a fibroblast cell line (L929) were incubated with undiluted extract for default periods of 24, 48 and 72 hours. After the incubation periods the cell viability was determined by measuring the metabolic activity of the cells by WST-1 conversion.

Cell culture and cytotoxicity assay
RAW264.7 and L929 murine cells were cultured in a 75 cm^2 tissue culture flask to propagate the cells. The tissue culture medium for RAW264.7 macrophages was Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F12, GlutaMAX Supplement, Gibco, Cat No 31331-028) supplemented with 10% fetal bovine serum (FBS, Greiner Bio-One, Cat No 758093), 1% sodium pyruvate (Gibco, Cat No 11360-039) and 100 U/mL penicillin, 100 µg/mL streptomycin (Gibco, Cat No 15140-122). The tissue culture medium for L929 fibroblasts was DMEM Glutamax (Gibco, Cat No 61965-026) supplemented with 10% fetal bovine serum (FBS, Greiner Bio-One, Cat No 758093), 1% Minimum Essential Medium Non-Essential Amino Acids (MEM NEAA, Gibco, Cat No 11140-035) and 100 U/mL penicillin - 100 µg/mL streptomycin (Gibco, Cat No 15140-122).
Cells in the exponential growth phase were isolated, counted and seeded in 96 tissue culture clusters at 1x 10^4 cells per well. Cell viability was determined after 24-48-72 hours of incubation with the extract samples. The cell viability was determined by using the cell proliferation reagent WST-1. The stable tetrazolium salt WST-1 is cleaved to a soluble formazan by a complex cellular mechanism that occurs primarily at the cell surface. As for this cleavage energy is needed the formation of formazan demonstrates the presence of viable cells in the test system. After 1 hour and 2 hours incubation the soluble formazan is detected spectrometrically in a SpectraMax M2 spectrophotometer (Molecular Devices) at 440 nm with as reference at 620 nm. The amount of formazan formed is measured in the spectrometer and the absorbance directly correlates to the number of viable cells.
The cytotoxicity assay was performed in fourfold (i.e. four cell culture wells were incubated with 200 µL extract) using undiluted extracts for the exposure of the cells.

A positive control was used in the cytotoxicity assay to demonstrate cytotoxic activity in tissue culture medium extracts. Extracts were prepared similar to the silicone gel and shell extracts The positive control consisted of a poly(vinylchloride) recepture stabilized with organo-tin (bis(tri-n-butyltin)oxide, tributyltin oxide, TBTO), designated as PVC-Sn. Tributyltin oxide (TBTO) is a highly toxic organotin compound used as a biocide (fungicide and molluscicide). This recepture is known to have a strong cytotoxic effect leading to extensive cell death and lysis, and can be used as a positive control for cell death in the cytotoxicity testing of biomaterial extracts [30]. Cell survival was expressed as percentage growth of the treated cells compared to non-treated control cells.

6.10 Annex 10: Biocompatibility results

Table 6.13: RAW264.7 cells, incubation with silicone extracts with and without FBS.

RAW264.7 cells		24 hr incubation					
		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	109	101	96	90	119	107
	A072416	106	89	96	102	89	108
	A072221	94	nd	nd	108	nd	nd
	A072226	91	nd	nd	112	nd	nd
	A072229	109	nd	nd	152	nd	nd
	A072405	102	nd	nd	150	nd	nd
	A072411	94	nd	nd	87	nd	nd
	A072234	93	nd	nd	96	nd	nd
	A072245	96	nd	nd	108	nd	nd
	A072205	98	nd	nd	97	nd	nd
	A072216	104	nd	nd	100	nd	nd
Shell	A072238	92	111	nd	95	cont	nd
	A072416	101	119	nd	cont	cont	nd
	A072221	103	nd	nd	122	nd	nd
	A072226	109	nd	nd	128	nd	nd
	A072229	100	nd	nd	138	nd	nd
	A072405	113	nd	nd	147	nd	nd
	A072411	103	nd	nd	104	nd	nd
	A072234	110	nd	nd	99	nd	nd
	A072245	116	nd	nd	98	nd	nd
	A072205	99	nd	nd	75	nd	nd
	A072216	107	nd	nd	83	nd	nd

Nd = not determined, cont = contaminated.

NOTE. All data are the mean of n=4 measurements.

RAW264.7 cells 48 hr incubation

		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	100	101	109	100	91	104
	A072416	99	96	105	123	90	102
	A072221	100	nd	nd	92	nd	nd
	A072226	99	nd	nd	93	nd	nd
	A072229	107	nd	nd	81	nd	nd
	A072405	100	nd	nd	83	nd	nd
	A072411	97	nd	nd	92	nd	nd
	A072234	92	nd	nd	99	nd	nd
	A072245	100	nd	nd	93	nd	nd
	A072205	98	nd	nd	98	nd	nd
	A072216	97	nd	nd	96	nd	nd
Shell	A072238	99	118	nd	103	cont	nd
	A072416	98	118	nd	cont	cont	nd
	A072221	112	nd	nd	102	nd	nd
	A072226	98	nd	nd	75	nd	nd
	A072229	115	nd	nd	81	nd	nd
	A072405	110	nd	nd	66	nd	nd
	A072411	108	nd	nd	95	nd	nd
	A072234	115	nd	nd	102	nd	nd
	A072245	101	nd	nd	84	nd	nd
	A072205	96	nd	nd	85	nd	nd
	A072216	89	nd	nd	74	nd	nd

Highlighted: cellular survival below 80%. Nd = not determined, cont = contaminated.
NOTE. All data are the mean of n=4 measurements.

RAW264.7 cells 72 hr incubation

		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	120	96	96	119	75	104
	A072416	141	99	100	133	89	1068
	A072221	100	nd	nd	101	nd	nd
	A072226	99	nd	nd	102	nd	nd
	A072229	95	nd	nd	131	nd	nd
	A072405	104	nd	nd	131	nd	nd
	A072411	108	nd	nd	115	nd	nd
	A072234	107	nd	nd	113	nd	nd
	A072245	106	nd	nd	108	nd	nd
	A072205	112	nd	nd	106	nd	nd
	A072216	105	nd	nd	105	nd	nd
Shell	A072238	93	98	na	88	cont	nd
	A072416	88	91	na	cont	cont	nd
	A072221	97	nd	nd	100	nd	nd
	A072226	93	nd	nd	81	nd	nd
	A072229	98	nd	nd	112	nd	nd
	A072405	92	nd	nd	99	nd	nd
	A072411	112	nd	nd	114	nd	nd
	A072234	104	nd	nd	115	nd	nd
	A072245	105	nd	nd	92	nd	nd
	A072205	102	nd	nd	95	nd	nd
	A072216	102	nd	nd	82	nd	nd

Highlighted: cellular survival below 80%. Nd = not determined, cont = contaminated.
NOTE. All data are the mean of n=4 measurements.

Table 6.14: L929 cells, incubation with silicone extracts with and without FBS.

L929 cells		24 hr incubation					
		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	92	99	100.0	112	106	100
	A072416	97	108	102.6	110	107	103
	A072221	109	nd	nd	129	nd	nd
	A072226	101	nd	nd	116	nd	nd
	A072229	102	nd	nd	101	nd	nd
	A072405	107	nd	nd	103	nd	nd
	A072411	106	nd	nd	105	nd	nd
	A072234	105	nd	nd	105	nd	nd
	A072245	95	nd	nd	101	nd	nd
	A072205	89	nd	nd	99	nd	nd
	A072216	103	nd	nd	100	nd	nd
Shell	A072238	99	101	nd	95	cont	nd
	A072416	98	99	nd	105	90	nd
	A072221	106	nd	nd	130	nd	nd
	A072226	106	nd	nd	104	nd	nd
	A072229	100	nd	nd	105	nd	nd
	A072405	102	nd	nd	102	nd	nd
	A072411	103	nd	nd	98	nd	nd
	A072234	105	nd	nd	110	nd	nd
	A072245	95	nd	nd	96	nd	nd
	A072205	97	nd	nd	96	nd	nd
	A072216	93	nd	nd	101	nd	nd

Nd = not determined, cont = contaminated.

NOTE. All data are the mean of n=4 measurements.

L929 cells 48 hr incubation

		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	92	97	102	101	100	99
	A072416	94	102	100	99	101	107
	A072221	107	nd	nd	103	nd	nd
	A072226	105	nd	nd	98	nd	nd
	A072229	102	nd	nd	104	nd	nd
	A072405	101	nd	nd	116	nd	nd
	A072411	107	nd	nd	112	nd	nd
	A072234	110	nd	nd	107	nd	nd
	A072245	102	nd	nd	104	nd	nd
	A072205	97	nd	nd	98	nd	nd
	A072216	100	nd	nd	99	nd	nd
Shell	A072238	99	99	nd	97	cont	nd
	A072416	98	97	nd	104	98	nd
	A072221	105	nd	nd	100	nd	nd
	A072226	106	nd	nd	103	nd	nd
	A072229	102	nd	nd	113	nd	nd
	A072405	102	nd	nd	109	nd	nd
	A072411	111	nd	nd	111	nd	nd
	A072234	112	nd	nd	114	nd	nd
	A072245	100	nd	nd	107	nd	nd
	A072205	99	nd	nd	98	nd	nd
	A072216	97	nd	nd	99	nd	nd

Nd = not determined, cont = contaminated.

NOTE. All data are the mean of n=4 measurements.

L929 cells 72 hr incubation

		% survival extraction in medium - serum			% survival extraction in medium + serum		
	Implant	Exp 1	Exp 2	Exp 3	Exp 1	Exp 2	Exp 3
Gel	A072238	104	102	100.5	99	102	102
	A072416	96	101	97.1	101	101	103
	A072221	107	nd	nd	111	nd	nd
	A072226	110	nd	nd	113	nd	nd
	A072229	105	nd	nd	110	nd	nd
	A072405	105	nd	nd	110	nd	nd
	A072411	98	nd	nd	102	nd	nd
	A072234	101	nd	nd	101	nd	nd
	A072245	97	nd	nd	104	nd	nd
	A072205	98	nd	nd	108	nd	nd
	A072216	100	nd	nd	98	nd	nd
Shell	A072238	103	100	nd	102	cont	nd
	A072416	102	101	nd	102	101	nd
	A072221	112	nd	nd	104	nd	nd
	A072226	112	nd	nd	109	nd	nd
	A072229	106	nd	nd	107	nd	nd
	A072405	106	nd	nd	104	nd	nd
	A072411	101	nd	nd	99	nd	nd
	A072234	101	nd	nd	102	nd	nd
	A072245	105	nd	nd	114	nd	nd
	A072205	98	nd	nd	115	nd	nd
	A072216	97	nd	nd	102	nd	nd

Nd = not determined, cont = contaminated.

NOTE. All data are the mean of n=4 measurements.

Table 6.15: Cytotoxicity of organotin stabilized PVC as measured in multiple assays.

L929 cells	% cell survival			L929 cells	% cell survival		
	Extraction in medium without serum				Extraction in medium with serum		
	24 h	48 h	72 h		24 h	48 h	72
Undiluted	2	0	1		0	0	0.3
1/4 diluted	30	16	12		0	0	0.1
1/5 diluted	50	43	34		0	0	0.1
1/5 diluted	50	33	43		0	0	0
1/5 diluted	51	45	35		0	0	0
1/5 diluted	50	51	29		0	0	0
RAW264.7 cells	% cell survival			RAW264.7 cells	% cell survival		
	Extraction in medium without serum				Extraction in medium with serum		
	24 h	48 h	72 h		24 h	48 h	72
Undiluted	1	0	0		0.5	0	0.2
1/4 diluted	74	49	30		0	0	0
1/5 diluted	78	53	51		0	0	0
1/5 diluted	89	55	57		0	0	0.1
1/5 diluted	86	67	46		0	0.7	0
1/5 diluted	69	69	53		0.5	0	0

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