

**FRENCH NATIONAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS SAFETY
INSPECTION DIVISION**

Trials and Vigilances Inspection Department

Dossier followed by

Tél

Fax

E-mail

Réf : MV-Mentor-20102015-C1-15IPV019

PRELIMINARY INSPECTION REPORT

<p>Company inspected</p>	<p style="text-align: center;">MENTOR MEDICAL SYSTEMS B.V</p> <p style="text-align: center;">Zernikedreef 2</p> <p style="text-align: center;">2333 CL Leiden</p> <p style="text-align: center;">The Netherlands</p> <p style="text-align: center;">Phone : +(31) 71 751 3600 Fax : +(31) 71 521 7422</p>								
<p>Activities</p>	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)</td> <td style="width: 50%; border: none;"><input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Medical devices Assembler</td> <td style="border: none;"><input checked="" type="checkbox"/> European Representative</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Importer</td> <td style="border: none;"><input type="checkbox"/> Distributor</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Sub-Contractor</td> <td style="border: none;"><input type="checkbox"/> Other</td> </tr> </table>	<input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)	<input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)	<input type="checkbox"/> Medical devices Assembler	<input checked="" type="checkbox"/> European Representative	<input type="checkbox"/> Importer	<input type="checkbox"/> Distributor	<input type="checkbox"/> Sub-Contractor	<input type="checkbox"/> Other
<input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)	<input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)								
<input type="checkbox"/> Medical devices Assembler	<input checked="" type="checkbox"/> European Representative								
<input type="checkbox"/> Importer	<input type="checkbox"/> Distributor								
<input type="checkbox"/> Sub-Contractor	<input type="checkbox"/> Other								
<p>Date of inspection</p>	<p>20th to 22nd October 2015.</p>								
<p>ANSM Inspector</p>									
<p>References</p>	<p>Reference of the mission : 15IPV019.</p> <p>Mission letter dated 6th October 2015.</p>								

CONTENTS

I. ABBREVIATIONS AND DEFINITIONS	3
I.1 Abbreviations	3
I.2 Definitions	3
II. GENERAL INFORMATION	3
II.1 Presentation of the company and its activities	3
II.2 Regulatory certification	5
II.3 Normative certification	6
II.4 History of the last inspection	6
II.5 Main changes since the last inspection	6
II.6 Main planned changes	6
II.7 Purpose and scope of the inspection	6
II.8 Applicable legal references and guidelines	6
II.9 People attending the opening and closing meetings	6
II.10 Referenced documents (not transmitted to the company)	7
II.11 Annexes	7
III. OBSERVATIONS AND FINDINGS RAISED DURING THE INSPECTION	8
III.1 Medical devices portfolio	8
III.2 Quality Management System (QMS)	8
III.3 Organization of the staff involved or likely to be involved in MV	11
III.4 Interfaces and Contracts	12
III.5 Audits	13
III.6 Management reviews	13
III.7 Traceability	14
III.7.1 Traceability of the materials and components contained in the finished products	14
III.7.2 Traceability of the finished products	14
III.8 Complaints and materiovigilance (MV) management	14
III.8.1 Cases issued from the unsolicited notification (out clinical studies)	14
III.8.2 Cases issued from the solicited notification (within clinical studies)	15
III.9 Product recall	15
III.10 Responses to ANSM requests	16
III.11 Systematic review of experience gained from devices in the post-production phase (PMS)	16
IV. IDENTIFIED RISKS	17
V. SYNTHESIS AND PRELIMINARY CONCLUSION BEFORE ANSWER OF THE INSPECTED COMPANY	20

I. ABBREVIATIONS AND DEFINITIONS

I.1 Abbreviations

AE	Adverse Event.
ALCL	Anaplastic Large Cell Lymphoma.
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French national Agency for medicines and health products safety).
BI	Breast Implant.
CAPA	Corrective Action and Preventive Action.
DHR	Device History Record.
EMEA	Europe, Middle East and Africa.
FSCA	Field Safety Corrective Action.
IRF	Incident Report Form (<i>Manufacturer Incident Report</i>).
MDD	Council Directive 93/42/EEC applicable to medical devices (Medical Devices Directive).
MV	Materiovigilance.
OBL	Own Brand Labeller (Manufacturer that markets, under its own brands, medical devices coming from other manufacturers).
OEM	Original Equipment Manufacturer (Original manufacturer of medical devices).
PMS	Post-Market Survey.
PSR	Periodic Summary Report.
QMS	Quality Management System.

I.2 Definitions

- **Serious incident** (MDD Annex II item 3.1) :

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health. The Manufacturers are required to notify the competent authorities of such incidents immediately on learning of them.

- **Serious deterioration in state of health** :

(MEDDEV 2.12-1 « *Guidelines on a Medical Devices Vigilance System* » items 3.1.2 and 5.1.1)

- Death of a patient, user or other person ;
- Life-threatening illness ;
- Permanent impairment of a body function or permanent damage to a body structure ;
- A condition necessitating medical or surgical intervention (including clinically relevant increase in the duration of a surgical procedure or a condition that requires hospitalisation or significant prolongation of existing hospitalisation) ;
- Foetal distress, foetal death or any congenital abnormality or birth defects.

II. GENERAL INFORMATION

II.1 Presentation of the company and its activities

MENTOR LLC is a worldwide health care company owned by the JOHNSON & JOHNSON Group and headquartered at Irvine, Texas, USA. Its activity covers the design, development, production, marketing and distribution of medical devices intended to breast aesthetics, throughout the world. Those medical devices are silicone gel and saline filled breast implants (BIs), implantable tissues expanders and sizers for BIs.

MENTOR LLC owns several subsidiaries worldwide, the facilities of special interest regarding this inspection being :

- MENTOR MEDICAL SYSTEMS B.V, located in Leiden, Netherlands ;
- MENTOR PEROUSE PLASTIE S.A.S, located in Issy-les-Moulineaux, France.

The main statutes and activities of MENTOR LLC USA and MENTOR MEDICAL SYSTEMS B.V Netherlands can be summarized as follows :

MENTOR LLC Irvine, USA	MENTOR MEDICAL SYSTEMS B.V Leiden, Netherlands
<ul style="list-style-type: none"> • Legal manufacturer of MENTOR silicone gel and saline filled BIs, implantable tissue expanders and sizers for BIs. • Holder of the EC certification of the aforementioned medical devices, issued by the notified body BSI (n° 0086). 	<ul style="list-style-type: none"> • Legal manufacturer of MENTOR silicone gel filled BIs, implantable tissue expanders and sizers for BIs. • Holder of the EC certification of the aforementioned medical devices, issued by the notified body TÜV SÜD (n° 0123). • European authorised representative ¹ of MENTOR LLC Irvine, USA, regarding the saline filled BIs and expanders marketed in Europe.
<p>Production (manufacture, control and release) and marketing of MENTOR BIs intended to the Worldwide market, except from the silicone gel filled BIs intended to the European market.</p>	<p>Production (manufacture, control and release) and marketing of MENTOR silicone gel filled BIs intended to the European market.</p>
<p>Centralization and management of the Worldwide complaint and materiovigilance activities, via <i>MENTOR LLC Customer Quality and Product Evaluation Department</i>.</p>	<p>Centralization and management of the complaint and materiovigilance activities within the region of Europe, Middle East and Africa (EMEA), in collaboration with local subsidiaries and <i>MENTOR LLC Customer Quality and Product Evaluation Department</i>.</p>

The global staff headcount of MENTOR MEDICAL SYSTEMS B.V site is of 378 employees. This subsidiary markets its silicone gel filled BIs in Europe under its own name and under the brands named SILTEX™ and CPG™.

The design of those BIs is broken down according to :

- 3 grades of silicone gel increasing cohesivity (gels COHESIVE I™, COHESIVE II™ and COHESIVE III™) ;
- 2 types of profiles : round for SILTEX™ brand or anatomical for CPG™ brand ;
- 2 types of surfaces : smooth and textured ;
- Variable volumes from 100 ml to 800 ml.

The raw materials used to manufacture the shell and the silicone gel of those BIs are sourced from the sole supplier named _____, located in _____. The texturing effect is achieved by a process of contact of the shell with a silicone sheet.

MENTOR MEDICAL SYSTEMS B.V has also marketed BIs in Europe under the brand PERTHESE™, but stopped this activity as this brand is no longer produced.

¹ Pursuant to Article 1 point j) of the MDD and as mentioned in the EC Certificate Ref. CE 562288 issued by BSI Notified body to MENTOR LLC.

The latest sales forecasts of BIs established by MENTOR, for year 2015, are summarized as follows :

The corresponding document provided during the inspection is *referenced 2* in this inspection report.

MENTOR MEDICAL SYSTEMS B.V markets its medical devices via a _____, located in _____ and dedicated to the European market. This subsidiary then supplies the other _____ European subsidiaries, distributors and health institutions (public and private hospitals).

MENTOR MEDICAL SYSTEMS B.V processes the complaints and vigilance cases with a computerized database called TRACKWISE™ (in collaboration with MENTOR local subsidiaries and MENTOR LLC *Worldwide Customer Quality and Product Evaluation Department*).

II.2 Regulatory certification

Within the framework of the CE marking procedures set out in article 11 of the MDD, MENTOR LLC and MENTOR MEDICAL SYSTEMS B.V manufacturers have chosen the Annex II (EC Declaration of conformity, Full quality assurance system) point 3 (Quality system) and point 4 (Design examination) of this MDD to ensure the compliance of the medical devices that there are marketing, with the essential requirements of safety and health applicable to those medical devices in the European Union.

These medical devices are covered by the following certificates, *referenced 3 to 6* in this inspection report :

Holder of EC Certification	Medical devices categories	EC Design examination Certificates
MENTOR MEDICAL SYSTEMS B.V	Body contouring implants and accessories.	EC Certificate n° G1 15 05 21103 026 of compliance with Annex II excluding point 4 of the MDD, issued by TÜV SÜD notified body (n° 0123) valid from 7 th July 2015 till 6 th July 2020.
	Breast implants.	EC Certificate n° G7 14 01 21103 025 of compliance with Annex II point 4 of the MDD, issued by TÜV SÜD notified body (n° 0123), valid from 23 rd February 2014 till 22 nd February 2019.
MENTOR LLC	Gel and saline filled breast implants, implantable tissue expanders and sizers for breast implants.	EC Certificate n° CE 562288 of compliance with Annex II excluding point 4 of the MDD, issued by BSI notified body (n°0086), valid from 7 th August 2015 till 9 th August 2020.
	Saline breast implants.	EC Certificate n° CE 562289 of compliance with Annex II point 4 of the MDD, issued by BSI notified body (n°0086), valid from 7 th August 2015 till 9 th August 2020.

II.3 Normative certification

MENTOR MEDICAL SYSTEMS B.V facility is certified ISO 13485. The corresponding certificate is *referenced 7* in this inspection report.

II.4 History of the last inspection

MENTOR MEDICAL SYSTEMS B.V did not undergo a previous ANSM inspection exclusively focused on materiovigilance.

II.5 Main changes since the last inspection

Not applicable.

II.6 Main planned changes

According to the statements collected during the inspection, MENTOR plans to replace, as from the second quarter of year 2016, its current TRACKWISE™ computerized database by another database intended to process the complaints and vigilance cases.

II.7 Purpose and scope of the inspection

Pursuant to article L 5313-1 of the French Public Health Code (CSP), this inspection was intended to assess the compliance of the materiovigilance activities performed by MENTOR MEDICAL SYSTEMS B.V, as set out in article 10 and Annex II section 3.1 of the MDD, insofar this company is the legal manufacturer and holder of the EC certification of the MENTOR BIs which are marketed in Europe.

This inspection was thus scoped on the global organization, interfaces and activity of this company regarding the materiovigilance of the BIs intended to the European market, particularly in France.

II.8 Applicable legal references and guidelines

Mandatory references : MDD, particularly :

- Article 10 and Annex II section 3.1 regarding materiovigilance ;
- Article 3 and Annex I regarding the essential requirements applicable to medical devices ;
- Article 11 regarding the CE marking procedures, particularly Annex II chosen by MENTOR MEDICAL SYSTEMS B.V as manufacturer for the EC Certification of the marketed medical devices.

Guidelines :

- European MEDDEV 2.12/1 '*Guidelines on a Medical Devices Vigilance System*' ;
- European MEDDEV 2.7/3 '*Clinical investigations : Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC*' ;
- European MEDDEV 2.12/2 '*Post market clinical follow-up studies*'.

II.9 People attending the opening and closing meetings

The list of the people attending the opening and closing meetings is attached in *Annex 1* of this report.

II.10 Referenced documents (not transmitted to the company)

- Référence 1 General presentation made at the beginning of the inspection (16 pages) ;
- Référence 2 Latest sales forecasts of BIs established by MENTOR, for year 2015 (1 page) ;
- Référence 3 EC Certificate n° *G1 15 05 21103 026* of compliance with Annex II excluding point 4 of the MDD, issued by TÜV SÜD notified body (n° 0123) to MENTOR MEDICAL SYSTEMS B.V for *Body contouring implants and accessories*, valid from 7th July 2015 till 6th July 2020 (3 pages) ;
- Référence 4 EC Certificate n° *G7 14 01 21103 025* of compliance with Annex II point 4 of the MDD, issued by TÜV SÜD notified body (n° 0123) to MENTOR MEDICAL SYSTEMS B.V for *Breast implants*, valid from 23rd February 2014 till 22nd February 2019 (4 pages) ;
- Référence 5 EC Certificate n° *CE 562288* of compliance with Annex II excluding point 4 of the MDD, issued by BSI notified body (n°0086) to MENTOR LLC for *Gel and saline filled breast implants, implantable tissue expanders and sizers for breast implants*, valid from 7th August 2015 till 9th August 2020 (4 pages) ;
- Référence 6 EC Certificate n° *CE 562289* of compliance with Annex II point 4 of the MDD, issued by BSI notified body (n°0086) to MENTOR LLC for *Saline breast implants*, valid from 7th August 2015 till 9th August 2020 (3 pages) ;
- Référence 7 ISO 13485 certificate issued by TÜV SÜD notified body (n° 0123) to MENTOR MEDICAL SYSTEMS B.V (1 page) ;
- Référence 8 Work Instruction *Processing of a complaint file and investigation guidelines Ref. DOP-QA-4002* (16 pages) ;
- Référence 9 Issy-les-Moulineaux site procedure for *Complaint Handling Ref. PR-FR-3-3003* (10 pages) ;
- Référence 10 Issy-les-Moulineaux site procedure for *Vigilance and field actions Ref. PR-FR-3-0002* (12 pages).
- Référence 11 MENTOR *Product Evaluation Department* Head's delegation form (1 page).
- Référence 12 E-mail of notification, to MENTOR MEDICAL SYSTEMS B.V staff, of the new training intended to address the identification of the staff in charge of MV and to whom shall be passed on any complaint or MV case communicated (1 page) ;
- Référence 13 Record of presence of the Head of the *Product Evaluation Department* since the beginning of the year 2015 (1 page) ;
- Référence 14 Updated incident report related to the ALCL case *Ref.* (6 pages) ;
- Référence 15 MENTOR BIs PMS report covering the period from November 2013 to December 2014 (17 pages).
- Référence 16 Presentation written by MENTOR Worldwide LLC Medical Director and a consultant for MENTOR Worldwide LLC, regarding the ALCL questions (13 pages).

II.11 Annexes

- Annex 1 List of the people attending the inspection opening and closing meetings.
- Annex 2 Findings raised along the review of the procedure *Regulatory agency reporting Ref. SOP-TX-113*.
- Annex 3 Findings raised along the review of the individual complaints and MV cases realized during the inspection.

III. OBSERVATIONS AND FINDINGS RAISED DURING THE INSPECTION

The *Deviations*, preceded by the symbol 'D', are non-compliances notified with regard to legal references applicable to medical devices, particularly the MDD. Deviations are followed in brackets by the concerned legal references and, when applicable, by claimed standards or recommendations likely to support the aforementioned legal references.

The *Remarks*, preceded by the symbol 'R', although not related to non-compliances with regard to legal references, highlight either more or less serious defects raised during the inspection and inducing a risk of public health, either non-compliances with claimed standards or recommendations (guidelines).

Deviations and remarks call a written response from the inspected facility and are ranked into three levels : 'Critical', 'Major' and 'Other'.

The first two levels are mentioned next to the corresponding number of the deviation or remark. The absence of mention of one of those two levels means that the deviation or remark is ranked as 'Other'.

The definitions adopted for the aforementioned levels are the following :

- Is 'Critical' a breach in the system, the processes and the practices of materiovigilance which causes important effects going against the right, the safety or the well-being of the patients or induces a risk of public health or refers to a serious violation of the current legal provisions.
- Is 'Major' a breach in the system, the processes and the practices of materiovigilance which may cause important effects going against the right, the safety or the well-being of the patients or may induce a risk of public health or refers to a major deviation to the current legal provisions.
- Is 'Other' a failure in the system, the processes and the practices of materiovigilance which should not cause any harmful effect against the right, the safety or the well-being of the patients.

Findings that are not ranked as major when considered individually may represent, once accumulated, a major grouping.

The European guides and recommendations mentioned in this report are accessible via the European Commission Website ec.europa.eu/health/medical-devices/documents/guidelines.

III.1 Medical devices portfolio

The availability and validity of the EC certificates covering the medical devices marketed in Europe by MENTOR MEDICAL SYSTEMS B.V were checked during this inspection.

The management of the medical devices portfolio is satisfactory.

III.2 Quality Management System (QMS)

The QMS inspection focused on the processes regarding the management of :

- Documentation (procedures, records and archiving) ;
- Competencies and habilitations of the staff involved or likely to be involved in complaints and MV ;
- Audits of the complaints and MV processing activity ;
- Complaints and MV processing activity ;
- Correctives/Preventives actions (CAPAs/FSCAs) ;
- Products recalls ;
- Systematic review of experience gained from devices in the post-production phase (Post Market Survey).

Regarding the management of MENTOR's documentary system (procedures, records and archiving), the following documents were reviewed during the inspection :

- Procedure *Document Management Process in the ADAPTIV System* (Ref. PR-0011367) ;
- Procedure *Document change control and authorization / Mentor Leiden approval matrix* (Ref. SOP-1000) ;
- *Franchise procedure for management of inactive and historical records & information* (Ref. PR-0000654) ;
- *Franchise procedure for the records retention schedule* (Ref. PR-0000018) ;
- *Work Instruction Quality System Archiveren* (Ref. QI-0031) ;
- *Franchise Records Retention Schedule* (Ref. 100095458).

The documentation (procedures, instructions) is centralized by an electronic document management system, called 'ADAPTIV'. The broadcasting and implementation of MENTOR's new documents and updates of the existing documents involve a training of all the addressees of these documents, via a module (called 'Compliance Wire') integrated into this electronic document management system.

R1 MENTOR shall update and complete its procedures regarding the management of its documentary system (procedures, records and archiving), so that they clearly mention :

1. The management of the training of all the addressees concerned by the new documents and updates of the existing documents ;
2. A period of archiving at least equivalent to that laid down by the European legislation in force (MDD Annex II point 6.1), regarding the EC Declarations of conformity, EC Certificates of the medical devices, decisions and reports from the notified body, which shall be at least :
 - 15 years after the last product has been manufactured, in the case of implantable devices ;
 - 5 years after the last product has been manufactured, for the other devices.
3. The restrictions of access to the complaints and MV documents in paper, to the only authorized staff.

Regarding the management of the skills and habilitations of MENTOR staff, the following documents were reviewed during the inspection :

- *Franchise procedure for Ethicon training process* (Ref. PR-0000372) ;
- *Procedure Quality System Training* (Ref. SOP-1007) ;
- *Procedure Quality System Training* (Ref. TV-SOP-01837) ;
- *Procedure Formation du personnel d'ETHICON à l'environnement réglementaire et aux standards qualité des dispositifs médicaux – Issy-les Moulineaux – ETHICON SAS.*

R2 MENTOR MEDICAL SYSTEMS B.V shall update and complete its procedures regarding the management of the skills and habilitations of its staff, insofar the documentation system does not mention the modalities of initial and periodic trainings to the risks associated to the BIs, intended to the staff involved or likely to be involved in the communications of complaints and MV cases (staff in charge of the management of complaints and MV, any other staff that may direct such communications to the staff in charge of the management of complaints and MV...).

Such modalities shall include :

- periodic and nominative training plans of the staff ;
- nominative records attesting the trainings followed by the staff and the assessment of the effectiveness of such trainings.

Regarding the management of the complaints and MV processing activity, the following documents used by MENTOR MEDICAL SYSTEMS B.V were reviewed during the inspection :

- *Procedure Product complaint handling system* (Ref. SOP-TX-112) ;
- *Procedure Regulatory agency reporting* (Ref. SOP-TX-113) ;
- *Work Instruction Processing of a complaint file and investigation guidelines* (Ref. DOP-QA-4002), which is *referenced 8* in this inspection report.

The following documents used by MENTOR French affiliate were also reviewed during the inspection :

- Issy-les-Moulineaux site procedure for *Complaint Handling PR-FR-3-3003*, which is *referenced 9* in this inspection report ;
- Issy-les-Moulineaux site procedure for *Vigilance and field actions PR-FR-3-0002*, which is *referenced 10* in this inspection report.

The review of the procedure *SOP-TX-113* raises the findings detailed in *Annex 2* to this inspection rapport.

D1 The processing of the MV cases, as described in the corresponding procedure used by MENTOR MEDICAL SYSTEMS B.V, is not completely compliant with the European legislation in force (MDD Annex II point 3.1) considering the findings detailed in *Annex 2* to this inspection rapport, which implies to update this procedure so that :

1. Any serious incident or risk of serious incident, whether expected/foreseeable or not, shall be reported to the concerned competent authority ;
2. Any serious incident or risk of serious incident, regardless of its likelihood of occurrence, shall be reported to the concerned competent authority (as an example, this shall apply to ALCL cases) ;
3. In case of doubt on the causality of the medical devices and thus on the reportability of an event, there should be a pre-disposition to report

The Work Instruction *DOP-QA-4002* mentions which data are needed for the assessment of the causality of the medical devices involved in the reported incidents, but does not precise the methodology with which the final decision of causality is made and supported.

R3 The procedures and/or work instructions used by MENTOR MEDICAL SYSTEMS B.V in the processing of the complaints and MV cases should be completed so that they precise clearly the methodology with which the final decision of causality of the medical devices involved in the reported incidents is made and supported.

Neither MENTOR MEDICAL SYSTEMS B.V procedures nor those of the French affiliate mention the reporting process agreed between MENTOR and ANSM regarding the BIs related incidents occurred in France.

D2 The description of the MV cases processing, in MENTOR MEDICAL SYSTEMS B.V and/or MENTOR French affiliate documentation system, is not complete (MDD Annex II point 3.2, claimed ISO 13485 standard points 4.2.1 d et 4.2.2 b) insofar the documentation system :

1. Does not mention the reporting process agreed between MENTOR and ANSM regarding the BIs related incidents occurred in France, which concerns :
 - the individual cases prone to immediate notification ;
 - the clustered cases prone to periodic (yearly) notification :
 - via the *Periodic summary reports (PSRs)* ;
 - via the *Trend reports* in case of detection of drift, simultaneously to the aforesaid PSRs.
2. Does not include any procedure of preparation and submission of the PSRs to ANSM.

Regarding the management of the *corrective and preventive actions (CAPAs/FSCAs)* and product recalls, the following documents used by MENTOR MEDICAL SYSTEMS B.V were reviewed during the inspection :

- *Franchise procedure for corrective and preventive action (CAPA) (Ref. PR575-001)* ;
- *Franchise procedure for field action (Ref. PR-0000109)*.

R4 The description of the *corrective and preventive actions (CAPAs/FSCAs)* management, in MENTOR MEDICAL SYSTEMS B.V documentation system, should be completed so that it mentions provisions regarding the communications to the notified body of the *CAPAs/FSCAs* :

1. Implemented on medical devices design and/or manufacturing processes and/or labelling, further to each serious incident (to prevent its recurrence) (Meddev 2.12/1 point 5.4.4) ;
2. Likely to induce substantial changes to all the medical devices concerned, not only on class III medical devices (MDD Annex II point 3.4).

Regarding the product recall process, the Franchise procedure *PR-0000109* mentions (point 5.2 a) that '*Competent Authority / Health Authorities / Regulatory Agencies / Notified Bodies (if applicable) – should be contacted per local regulations/timelines*'.

- R5 The product recall process description, in MENTOR MEDICAL SYSTEMS B.V documentation system, should be clarified and completed, at least regarding the medical devices marketed in France, so that it :
1. Mentions that any medical device recall motivated by a technical or medical reason related to a serious incident shall be reported immediately to the European competent authorities on the territory of which the recall is to be conducted (MDD Annex II item 3.1) or that any message intended to the concerned competent authorities and to the patients and/or users, within the framework of such a situation, should be communicated in advance (48 h for example) to the concerned competent authorities ;
 2. Precisely the reconciliation intended to document the efficiency of the recall, with a systematic recall full balance sheet recapitulating the quantities of product units :
 - produced and/or in production ;
 - present in stocks ;
 - likely to be outside stocks (samples sent for analysis, samples given to the staff for demonstration... for examples) ;
 - marketed and recallable (unused) ;
 - marketed and not recallable (used).
 3. Plans the evaluation of the efficiency of the recall process by simulations of recall involving the distribution stakeholders until the final clients.

Regarding the management of the systematic review of experience gained from devices in the post-production phase (*Post Market Survey*), the procedure *Post Market Surveillance (Ref. SOP-CO-046)* was reviewed during the inspection. This procedure mentions the source data that shall be collected within the framework of this survey (complaint and MV data, clinical data...).

- R6 The Post Market Surveillance (PMS) process described in MENTOR documentation system and related to experience gained from devices in the post-production phase should be completed, so that it lays down provisions related to the construction and update of a consolidated survey report for each category of BIs since their first marketing, with a presentation of :
1. The incidents outcomes broken down by :
 - Typologies of incidents ;
 - Regions of occurrence of the incidents (Worldwide / Europe / local countries) ;
 - Years of occurrence ;
 - Years of sales and/or implantation ;
 - Sales volumes or numbers of BIs implanted per year (in order to assess the significance of the reported cases) ;
 - Surface (smooth or textured) of the BIs (in order to allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs) ;
 2. An exhaustive list of the typologies of reported incidents, from the most frequent to the rarest ones ;
 3. A methodology of identification of the key points, issues and stakes stemming from these data.

III.3 Organization of the staff involved or likely to be involved in MV

The verification of MENTOR staff organization focused on :

- The staff organization chart ;
- The presence of an MV correspondent or responsible person and of his deputy(ies) ;
- The job descriptions of the staff involved in MV ;
- The management of the competences, skills and habilitations of the staff involved or likely to be involved in MV ;
- The continuity of the MV activity.

MENTOR LLC *Product Evaluation Department* is in charge of the centralization and management of the Worldwide complaints and MV activities. The Head of this Department authorized three members of his staff as delegates to conduct some activities on his behalf. The corresponding delegation form was presented during the inspection and is *referenced 11* in this inspection report. This form is signed by the Head of the Department but is not signed by the delegates themselves, which does not certify that they know and accept these delegations.

Moreover, the job description of MENTOR MEDICAL SYSTEMS B.V Plant Quality Assurance Manager does not mention his activities related to complaints and MV.

- R7 MENTOR LLC and MENTOR MEDICAL SYSTEMS B.V should complete the job descriptions and the documentation related to the delegations of its staff, insofar :
1. The delegation form related to activities under the responsibility of the Head of the *Product Evaluation Department* is not signed by the delegates themselves, which does not certify that they know and accept these delegations ;
 2. The job description of MENTOR MEDICAL SYSTEMS B.V Plant Quality Assurance Manager does not mention his activities related to complaints and MV.

Regarding the management of the competences, skills and habilitations of the staff involved or likely to be involved in complaints and/or MV cases, the trainings in place within MENTOR organization, depending on the degree of involvement of the staff concerned, is satisfactory with regards to the knowledge of the MV legal references and guidelines and with regards to the knowledge of the risks associated to the BIs.

Moreover and considering that any staff is likely to receive a communication related to a complaint or MV case, MENTOR MEDICAL SYSTEMS B.V implemented on 21st October 2015 a new training intended to all its staff, via the module '*Compliance Wire*' integrated into the electronic document management system, that addresses the identification of the staff in charge of MV and to whom shall be passed on any complaint or MV case communicated. The corresponding notification by e-mail to MENTOR MEDICAL SYSTEMS B.V staff is *referenced 12* in this inspection report.

Regarding the continuity of the MV activity, a record of presence of the Head of the *Product Evaluation Department*, since the beginning of the year 2015, was presented during the inspection and is *referenced 13* in this inspection report. Nevertheless, the records certifying the presence of the *Product Evaluation Department* Head's delegates within the same period are not implemented, which does not allow to document the continuity of the MV activity.

- D3 The continuity of the MV activity within MENTOR organization is not enough documented, which induces a risk that MV cases may not all be processed and reported with the required due diligence (MDD Annex II items 3.1 and 3.2 b), in the absence of records demonstrating the continuous presence of the *Product Evaluation Department* Head's or of his delegates.

III.4 Interfaces and Contracts

The verification of the provisions implemented by MENTOR regarding the organization and interfaces of the complaints and MV circuits related to the medical devices marketed covered :

- The internal organization and interfaces of the staff involved or likely to be involved in complaints and MV cases, within MENTOR LLC, MENTOR MEDICAL SYSTEMS B.V and local affiliates ;
- The external organization and interfaces between MENTOR, its partners and customers.

The internal organization and interfaces of the staff involved or likely to be involved in complaints and/or MV cases, within MENTOR LLC, MENTOR MEDICAL SYSTEMS B.V and local affiliates, does not raise any particular comment.

The verification of the external organization and interfaces focused on the written agreements concluded between :

- - MENTOR MEDICAL SYSTEMS B.V as legal medical devices manufacturer and distribution subsidiary ;
- distribution subsidiary and :
 - subsidiary ;
 - subsidiary.

The aforementioned agreements are satisfactory, insofar they include provisions which cover :

- Guarantees of traceability, by the distributors, of the devices made available to the end users ;
- The implementation of the product recall process ;
- Mutual communications of the incidents related to the concerned medical devices ;
- The identification of the party who is responsible for communicating any serious incident to the concerned European competent authority.

III.5 Audits

Each process of MENTOR MEDICAL SYSTEMS B.V's QMS is audited at least once a year. The demonstration of audits performed in 2014 and 2015, which scope covered the process '*Complaint handling, Vigilance reporting and PMS*', was provided during the inspection.

- R8 MENTOR should complete the audits covering its complaints and MV management, so that their scope cover the assessment of the quality and timeliness of :
- the MV serious incidents communications to the concerned European competent authorities (which would notably reduce the risk of non-compliances such as point 1 of the Major Deviation D4 mentioned in this inspection report) ;
 - the responses to the requests of the competent authorities.

III.6 Management reviews

MENTOR MEDICAL SYSTEMS B.V's management reviews are held twice a year. The reports of the management reviews held on 15th January 2015 (covering the whole year 2014) and on 29th July 2015 (covering the first half of year 2015), were presented during the inspection.

These reports include the audits results, outcomes and trends of products non-compliances, complaints, MV cases and CAPAs/FSCAs, as well as the follow-up of the actions implemented further to the previous management reviews and global reviews of the QMS indicators.

- R9 MENTOR MEDICAL SYSTEMS B.V's management reviews should be completed in order to :
1. Cover the assessment of the quality and timeliness of :
 - the MV serious incidents communications to the concerned European competent authorities (which would notably reduce the risk of non-compliances such as point 1 of the Major Deviation D4 mentioned in this inspection report) ;
 - the responses to the requests of the competent authorities.
 2. Develop the key points, issues and stakes stemming from the PMS data regarding the question of ALCLs related to BIs (see also R12 in this inspection report).

III.7 Traceability

III.7.1 Traceability of the materials and components contained in the finished products

The materials and components traceability check focused on the lots of shell and filling gel used in the manufacture of a textured BI corresponding to the reference SILTEX™ Round moderate profile, lot 6982189.

The references of articles, batch numbers, name of the supplier, delivery dates and certificates of control of the lots of shell and filling gel contained in this BI are properly traced. The other batches of BIs manufactured with these lots of shell and filling gel are also traced. This traceability test is thus satisfactory.

III.7.2 Traceability of the finished products

The finished products traceability check focused on the lot 6982189 of BI targeted in the abovementioned test. This traceability test is also satisfactory insofar it demonstrated the reconciliation between the numbers of BI units produced, BI units in stock and BI units marketed, with the identification of their recipients.

III.8 Complaints and materiovigilance (MV) management

III.8.1 Cases issued from the unsolicited notification (out clinical studies)

The details of the findings raised along the review of the individual complaints and MV cases realized during the inspection are mentioned in *Annex 3* of this report. Each finding mentioned in this Annex is followed by a number in italics (*point 1, point 2, point n ...*) to which the Major Deviation D4 below refers to.

D4 Major

The management of the individual complaints and MV cases by MENTOR is not satisfactory, which compromises the proper processing and notification of the serious incidents occurred in France to ANSM, (MDD Annex II item 3.1, claimed ISO 13485 standard items 7.2.3, 8.4 and 8.5, Meddev 2.12/1 points 5.1.7 and 5.3), insofar :

1. MENTOR reported an MV case of *silicone granuloma* to ANSM more than 8 months after its reception by the French affiliate, whereas *silicone granulomas* correspond to serious incidents prone to immediate notification (*point 2*) ;
2. The evaluation of the ALCL cases is limited to the analysis of the medical and scientific literature which states that risks of ALCLs on patients bearing BIs are not to be excluded, without further investigations (*point 1*) ;
3. The production batch records (*DHR*) are not systematically reviewed and challenged in the processing of the complaints and MV cases, particularly when these cases refer to known and anticipated incidents, which excludes any assessment of the production impacts (*points 1, 4, 6*) ;
4. TRACKWISE™ database does not provide the traceability of :
 - the source documents attesting the actual dates of receipts of the complaints and MV cases communicated to MENTOR staff, with the notifiers details ;
 - the documents attesting the reporting of the serious incidents to the concerned competent authorities ;
 - requests and/or reminders which should be addressed to the notifiers in order to collect information on the complaints and MV cases, which may jeopardize the proper evaluation of the incidents gravity and of the causality of the BIs involved (*point 3*).
5. TRACKWISE™ database decision tree may be empty of any information (*point 9*) or may refer to decisions which are not consistent with the European legislation and guidelines in force regarding the gravity and the reportability of some MV cases, insofar silicone granulomas and surgical interventions related to explantations, which are serious incidents prone to immediate notification, are not ranked as such in this database, which may jeopardize the reporting of the serious incidents with the required due diligence to the concerned European competent authorities (*point 5, 7*).

R10 MENTOR should implement :

1. Appropriate actions so that its complaints and MV management database includes fields that shall summarize the information and the evaluations made with regards to each key point of the processing of each case, with the attached supporting documents or references, concerning :
 - The *date and mode of reception of the source document* related to the case notification to MENTOR (letter, fax, e-mail, report of phone call...), with the identification of the notifier and MENTOR staff addressee ;
 - The *gravity* of the case (serious / non serious) ;
 - The *causality* of the medical device(s) involved (established, possible, excluded or unknown) ;
 - The *risk(s)* related to the patient ;
 - Potentialities of *use error* ;
 - Potentialities of *misuse* ;
 - The *reportability* of the incident to the concerned competent authorities ;
 - The *reference of the notification of the incident* (is serious) to the concerned competent authorities ;
 - The *final evaluation, conclusion and decision* related to the case ;
 - The *criteria triggering the closure of the case*.
2. A quality control of the data entered in this database.

III.8.2 Cases issued from the solicited notification (within clinical studies)

The only clinical study involving MENTOR BIs is a post-market study concerning BIs manufactured in the USA and intended to the US market. The last enrollment was done in 2008, with a follow-up of patients over 10 years.

No BI manufactured by MENTOR MEDICAL SYSTEMS B.V is currently involved in clinical studies.

Therefore, this chapter does not raise any particular comment.

III.9 Product recall

R11 MENTOR MEDICAL SYSTEMS B.V should assess the efficiency of its recall process and the proactivity of its partners (customers and distributors) in this matter by conducting periodic recall simulations, documented with :

1. Reconciliations that shall summarize the quantities of product units :
 - produced and/or in production ;
 - present in stocks ;
 - likely to be outside stocks (samples sent for analysis, samples given to the staff for demonstration... for examples) ;
 - marketed and recallable (unused) ;
 - marketed and not recallable (used).
2. Conclusions and potential areas of improvements that may be deemed necessary, following such simulations.

III.10 Responses to ANSM requests

MENTOR's responses to ANSM requests were reviewed during the session dedicated to the management of the individual complaints and MV cases.

The incidents reports sent by MENTOR to ANSM, related to the 3 cases of ALCLs occurred in France (see Annex 3 of this inspection report), initially mentioned that '*MENTOR did not consider these cases as MDV reportable according to MEDDEV. ALCL are known complications associated with these products and are referenced in the product insert data sheet. Therefore, these complaints will not be reported by MENTOR*'. MENTOR modified these incident reports during the inspection by correcting these statements, then sent back to ANSM the updated reports. A copy of the updated incident report related to the case Ref. (taken as an example) is *referenced 14* in this inspection report

This chapter does not raise any other particular comment.

III.11 Systematic review of experience gained from devices in the post-production phase (PMS)

MENTOR performs an annual review of its BIs post-market survey (PMS). The BIs PMS report covering the period from November 2013 to December 2014 was presented during the inspection and is *referenced 15* in this inspection report.

Regarding the ALCL questions, a presentation written by MENTOR Worldwide LLC Medical Director and a consultant for MENTOR Worldwide LLC was provided during the inspection. This document is *referenced 16* in this inspection report. It appears from this document, from the statements gathered during the inspection and from the cases review detailed in Annex 3 of this inspection report that :

- 23 ALCL cases have been identified Worldwide, related to patients who wore BIs from several manufacturers including MENTOR, among which :
 - 22 cases concern patients who wore BIs manufactured by MENTOR LLC USA ;
 - 1 case concerns a patient who wore a BI manufactured by MENTOR MEDICAL SYSTEMS B.V Leiden.
- 5 ALCL cases have been identified Worldwide, related to patients who wore only MENTOR BIs ;
- 3 ALCL cases have been identified in France :
 - 2 cases involve PERTHESE™ gel filled BIs manufactured by Mauritius site :
 - the first case concerns a PERTHESE™ BI implanted in February 2013 to replace a BI marketed by another manufacturer, followed by an ALCL diagnosis in the end of year 2014 ;
 - the second case concerns a PERTHESE™ BI implanted in November 2012 to replace a BI marketed by another manufacturer, followed by an ALCL diagnosis in March 2013.
 - 1 case involves a SILTEX™ saline filled BI manufactured by MENTOR LLC USA, borne by the patient from 2000 to 2006, then replaced by a BI marketed by another manufacturer, followed by an ALCL diagnosis in January 2015.

R12 MENTOR should complete its BIs post-market survey, so that the PMS reports present :

1. An analysis of the incidents outcomes broken down by BI surfaces (smooth and textured), in order to allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs ;
2. An exhaustive list of the typologies of reported incidents, from the most frequent to the rarest ones ;
3. An in depth analysis of the key points, issues and stakes stemming from the data related to ALCL cases, including the demonstration of the preservation of the BIs' Benefit/Risk ratio.

IV. IDENTIFIED RISKS

The risks associated to the main findings raised during this inspection shall be distributed as follows :

Incomplete organization of the staff involved in MV		
Findings		Classification
D3	Continuity of the MV activity within MENTOR organization not enough documented, in the absence of records demonstrating the continuous presence of the <i>Product Evaluation Department</i> Head's or of his delegates.	Other

Efficiency of the complaints and MV management process incompletely assessed		
Findings		Classification
R8	Incomplete scopes of the audits covering the complaints and MV management activity, regarding the assessment of the quality and timeliness of : <ul style="list-style-type: none"> • the MV serious incidents communications to the concerned European competent authorities ; • the responses to the requests of the competent authorities. 	Other
R9	Incomplete management reviews regarding the assessment of : <ul style="list-style-type: none"> • the quality and timeliness of the MV serious incidents communications to the concerned European competent authorities ; • the quality and timeliness of the responses to the requests of the competent authorities ; • the development the key points, issues and stakes stemming from the PMS data regarding the question of ALCLs related to BIs. 	Other

Management of the individual complaints and MV cases not satisfactory		
Findings		Classification
D1	1. In the QMS (documentation system) : <ul style="list-style-type: none"> a) Incomplete provisions regarding the reporting of the serious incidents or risks of serious incidents to the concerned competent authorities : <ul style="list-style-type: none"> • whether expected/foreseeable or not ; • regardless of their likelihood of occurrence (this shall apply to ALCL cases) ; • even in case of doubt on the causality of the medical devices involved. 	Other
D2	<ul style="list-style-type: none"> b) No mention of the reporting process agreed between MENTOR and ANSM regarding the BIs related incidents occurred in France, which concerns the individual cases prone to immediate notification and the clustered cases prone to periodic (yearly) notification ; c) No procedure of preparation and submission of the PSRs to ANSM. 	Other

Management of the individual complaints and MV cases not satisfactory (continued)

Findings		Classification
D4	<p>2. In practice :</p> <ul style="list-style-type: none"> • MV case of <i>silicone granuloma</i> reported to ANSM more than 8 months after its reception by the French affiliate, whereas <i>silicone granulomas</i> correspond to serious incidents prone to immediate notification ; • Evaluation of the ALCL cases limited to the analysis of the medical and scientific literature, without further investigations ; • Production batch records (<i>DHR</i>) not systematically reviewed and challenged in the processing of the complaints and MV cases, particularly when these cases refer to known and anticipated incidents, which excludes any assessment of the production impacts ; • Lack of traceability in TRACKWISE™ database regarding : <ul style="list-style-type: none"> - the source documents attesting the actual dates of receipts of the complaints and MV cases communicated to MENTOR staff, with the notifiers details ; - the documents attesting the reporting of the serious incidents to the concerned competent authorities ; - requests and/or reminders which should be addressed to the notifiers in order to collect information on the complaints and MV cases, which may jeopardize the proper evaluation of the incidents gravity and of the causality of the BIs involved ; • TRACKWISE™ database decision tree not systematically updated with relevant information or not consistent with the European legislation and guidelines in force regarding the gravity and the reportability of some MV serious incidents prone to immediate notification, which may jeopardize the reporting of the serious incidents with the required due diligence to the concerned European competent authorities. 	Major

Incomplete management of the corrective et preventive actions (CAPAs/FSCAs).

Findings		Classification
R4	<p>Incomplete provisions in the QMS, regarding the communications to the notified body of the CAPAs/FSCAs :</p> <ul style="list-style-type: none"> • Implemented on medical devices design and/or manufacturing processes and/or labelling, further to each serious incident (to prevent its recurrence) ; • Likely to induce substantial changes to all the medical devices concerned (not only on class III medical devices). 	Other

Incomplete product recall process		
Findings		Classification
R5	<p>1. In the QMS (documentation system) :</p> <p>Incomplete provisions regarding :</p> <p>a) The immediate reporting of any medical device recall motivated by a technical or medical reason related to a serious incident, to the European competent authorities on the territory of which the recall is to be conducted <u>or</u></p> <p>The communication in advance, to the concerned competent authorities, of any message intended to these authorities and to the patients and/or users, within the framework of such a situation.</p> <p>b) The evaluation of the efficiency of the recall process by simulations of recalls involving the distribution stakeholders until the final clients.</p> <p>2. In practice :</p>	Other
R11	No periodic simulations of recalls involving the distribution stakeholders until the final clients.	Other

Incomplete review of experience gained from devices in the post-production phase (PMS)		
Findings		Classification
R6	<p>1. In the QMS (documentation system) :</p> <p>Incomplete provisions in the QMS, regarding the construction and update of a consolidated survey report for each category of BIs since their first marketing, with a presentation of :</p> <ul style="list-style-type: none"> • The incidents outcomes broken down by : <ul style="list-style-type: none"> - Typologies of incidents ; - Regions of occurrence of the incidents ; - Years of occurrence ; - Years of sales and/or implantation ; - Sales volumes or numbers of BIs implanted per year ; - Surface (smooth or textured) of the BIs ; • An exhaustive list of the typologies of reported incidents, from the most frequent to the rarest ones ; • A methodology of identification of the key points, issues and stakes stemming from these data. <p>2. In practice :</p>	Other
R12	<p>Incomplete BIs post-market survey reports regarding :</p> <ul style="list-style-type: none"> • the analysis of the incidents outcomes broken down by BI surfaces (smooth and textured), in order to allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs ; • the exhaustive list of the typologies of reported incidents, from the most frequent to the rarest ones ; • the in depth analysis of the key points, issues and stakes stemming from the data related to ALCL cases, including the demonstration of the preservation of the BIs' Benefit/Risk ratio. 	Other

V. SYNTHESIS AND PRELIMINARY CONCLUSION BEFORE ANSWER OF THE INSPECTED COMPANY

The inspection carried out from 20th to 22nd October 2015 at MENTOR MEDICAL SYSTEMS B.V site located Zernikedreef 2, 2333 CL, Leiden, The Netherlands, allowed to collect the information related to the organization and to the activity of this company regarding materiovigilance.

This inspection raised 4 deviations among which 1 is major and 12 remarks.

All those findings shall be prone to corrective and preventive actions in response to this report

The conclusions regarding the conformity of the medical devices materiovigilance activities carried out by this company, with the applicable regulations, will be determined after evaluation of the corrective and preventive actions and associated timeframes proposed by this company, in response to the findings raised.

The inspection is a report produced following interviews and document reviews by sampling during the mission. Therefore, the exhaustiveness of the activities and documents is not examined. The findings raised are issued from the activities and documents inspected. The company shall ensure the compliance of all its activities and products and shall implement, where necessary, the appropriate corrective and preventive actions.

Saint-Denis (France), 29th October 2015.

ANSM Inspector

Annex 2 Findings raised along the review of the procedure Regulatory agency reporting Ref. SOP-TX-113.

Items	Comments
<p>Point 6.3.2.1.1 of this procedure mentions, among examples of typical events linked to the incidents occurred within Europe and that are considered reportable to the concerned competent authorities : 'Unanticipated adverse reaction or unanticipated side effect'.</p>	<p>Any serious incident or risk of serious incident, whether expected/foreseeable or not, shall be reported to the concerned competent authority (MDD Annex II point 3.1).</p>
<p>MDD reportability flowchart in Attachment 1 of this procedure mentions :</p>	<p>In case of doubt on the causality of the medical device and thus on the reportability of an event, there should be a pre-disposition to report (MEDEV 2.12-1 « Guidelines on a Medical Devices Vigilance System » points 5.1 and 5.4.4).</p>
<p>Did the device cause or contribute to the event ?</p>	<p>_____ No _____→ Do not report</p>
<p>Expected and foreseeable side effect (referenced in IFU) ?</p>	<p>_____ Yes _____→ Do not report</p>
<p>Negligible likelihood occurrence (has incident been reported previously) of death or serious deterioration in state of health ?</p>	<p>_____ Yes _____→ Do not report</p> <p>Any serious incident or risk of serious incident, regardless of its likelihood of occurrence, shall be reported to the concerned competent authority (MDD Annex II point 3.1). As an example, this applies to ALCCL cases.</p>

Annex 3 (1/3) Findings raised along the review of the individual complaints and MV cases realized during the inspection.

Case Identification	Summary	Findings
<p>Ref. MENTOR</p> <p>Ref. ANSM</p>	<p>ALCL case.</p> <p>MENTOR LLC (Irvine) SILTEX™ saline filled BI implanted in 2000, explanted in 2006 due to deflation and replaced by a BI marketed by ALLERGAN Company. 15th January 2015 : diagnosis of ALCL.</p> <p>Case communicated by ANSM to MENTOR on 27th February 2015. Date of receipt of this case entered in TRACKWISE™ : 3rd March 2015. ANSM asked MENTOR to provide the incident report within 60 days.</p> <p>Incident report communicated by MENTOR to ANSM on 6th March 2015.</p>	<ul style="list-style-type: none"> As the source notification documents are not attached, no traceability through TRACKWISE™ of : <ul style="list-style-type: none"> the notifier details (ANSM) ; the date of receipt of the source document related to the case Ref. TRACKWISE™ mentions that ALCL cases will not be reported as complaints and each incident report initially mentioned that 'MENTOR did not consider this case as MDV reportable according to MEDDEV. ALCL are known complications associated with these products and are referenced in the product insert data sheet. Therefore, these complaints will not be reported by MENTOR'. MENTOR modified these incident reports during the inspection by correcting these statements, then sent back to ANSM the updated reports. The updated incident report related to the case Ref. is referenced 14 in this inspection report. Evaluation of these cases by MENTOR limited to the analysis of the medical and scientific literature which states that risks of ALCLs on patients bearing BIs are not to be excluded. No review of the concerned BIs batch records, nor other investigation (point 1).
<p>Ref. MENTOR</p> <p>Ref. ANSM</p>	<p>ALCL case.</p> <p>Further to a shell rupture of a BI manufactured by ALLERGAN Company and implanted in the right breast, replacement by a PERTHESE™ BI on 4th February 2013.</p> <p>18th February 2014 : diagnosis of granuloma with swelling of the right breast of the patient. End of year 2014 : diagnosis of ALCL. BI not returned to MENTOR.</p> <p>Case communicated by ANSM to MENTOR on 18th February 2015. Date of receipt of the source document properly entered in TRACKWISE™. ANSM asked MENTOR to provide the incident report within 60 days.</p> <p>Incident report communicated by MENTOR to ANSM on 27th February 2015.</p>	
<p>Ref. MENTOR</p> <p>Ref. ANSM</p>	<p>ALCL case.</p> <p>14th November 2012 : Mc GHAN BIs manufactured by ALLERGAN Company, removed after 10 years of implantation and replaced by PERTHESE™ BIs.</p> <p>15th March 2013 : diagnosis of ALCL. BIs not returned to MENTOR.</p> <p>Case communicated by ANSM to MENTOR on 11th March 2015. Date of receipt of the source document properly entered in TRACKWISE™. ANSM asked MENTOR to provide the incident report within 8 days.</p> <p>Incident report communicated by MENTOR to ANSM on 17th March 2015.</p>	

Annex 3 (2/3) Findings raised along the review of the individual complaints and MV cases realized during the inspection.

Case Identification	Summary	Findings
<p>Ref. MENTOR</p>	<p>Case of Silicone granuloma + Capsular contracture. Case received by the French affiliate on 13th February 2013. Bis implanted on 13th February 1998. Baker grade of the capsular contracture not mentioned. The French affiliate asked the notifier to return the concerned Bis to MENTOR USA (Irvine), but the Bis were not returned. MENTOR's review of anteriorities concludes that no similar incidents have been reported regarding these specific lots.</p>	<ul style="list-style-type: none"> • Case reported by the French affiliate to ANSM on 30th October 2013, more than 8 months after its reception by the French affiliate, whereas <i>silicone granulomas</i> correspond to serious incidents prone to immediate notification (<i>point 2</i>). • No traceability of any relaunch from MENTOR to the notifier, in order to collect more information on this case (<i>point 3</i>), particularly : <ul style="list-style-type: none"> - the reason why the concerned Bis were not returned ; - the grade of the capsular contracture ; - the confirmation that the Bis have been explanted or not ; - details regarding the state of the patient. • No review of the concerned Bis batch records (<i>point 4</i>). • TRACKWISE™ decision tree mentions 'Did the event lead or might have led to death or a serious deterioration in the state of health ? No', without documented rationale of this decision and whereas <i>silicone granulomas</i> correspond to serious incidents (<i>point 5</i>).
<p>Refs. MENTOR</p>	<p>Case of Silicone granuloma + Capsular contracture + Rupture + Explantation. Case is a duplicate of the case . Received by the French affiliate on 24th October 2013. Left SILTEX™ BI : Capsular contracture + Rupture. Right SILTEX™ BI : Silicone granuloma + Capsular contracture + Rupture. Bis returned to MENTOR on 27th November 2013. Case reported by the French affiliate to ANSM on 31st October 2013. Analysis and expertise of the returned Bis performed by MENTOR.</p>	<ul style="list-style-type: none"> • MENTOR's evaluation of this case states that '<i>capsular contracture and formation of silicone granulomas are known complications (...) and referenced in the instructions for use</i>'. • No review of the concerned Bis batch records (<i>point 6</i>).

Annex 3 (3/3) Findings raised along the review of the individual complaints and MV cases realized during the inspection.

Case Identification	Summary	Findings
<p>Ref. MENTOR</p>	<p>Case of Capsular contractures Baker II and III + Explantation. Case received by the French affiliate on 17th March 2014. Bis explanted on 26th March 2014. Case reported by the French affiliate to ANSM on 17th March 2014.</p>	<p>Fields integrated into TRACKWISE™ decision tree not filled with information, particularly with regards to the decision of reportability of this case, whereas surgical interventions related to explanations correspond to serious incidents prone to immediate notification (point 7).</p>
<p>Ref. MENTOR</p>	<p>Case of Rupture + Explantation. Case received by the French affiliate on 1st August 2014. BI explanted on 27th August 2014. BI returned to MENTOR on 11th September 2014. Case reported by the French affiliate to ANSM on 1st August 2014 (before explanation). Analysis and expertise of the returned BI performed by MENTOR state that the root cause could not be determined.</p>	<p>TRACKWISE™ decision tree mentions 'Did the event lead or might have led to death or a serious deterioration in the state of health ? No' and 'MDV Reportable ? Not reportable', without documented rationale of these decisions and whereas surgical interventions related to explanations correspond to serious incidents prone to immediate notification (point 8).</p>
<p>Ref. MENTOR</p>	<p>Case of Rupture during the surgical intervention (not reportable). Case received by the French affiliate on 28th August 2015.</p>	<p>Fields integrated into TRACKWISE™ decision tree not filled with information (point 9).</p>