



CONFIDENTIAL

**RESPONSES TO THE FINAL INSPECTION SUMMARY REPORT FROM
ANSM FOLLOWING THE MATERIOVIGILANCE INSPECTION OF
ALLERGAN LTD COMPANY IN MARLOW, UK
FROM 27th APRIL TO 1st MAY 2015**

6th October 2015

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1. ASSESSMENT OF THE RESPONSES OF THE COMPANY BY THE INSPECTOR

The below aims to clarify, provide further justification and in some cases further corrective actions for the responses deemed unsatisfactory by ANSM.

Annex I provides a list of attachments which shows evidence of the commitments made to ANSM in the first response and which were deemed acceptable by ANSM and attachments for the further comments based on ANSM's final report.

Note that Satisfactory Responses were not included in this report.

2. APPROVAL

Name	Role	Signature	Date
	Associate Director Product Surveillance, EAME		5 th Oct 2015

3. ALLERGAN RESPONSES

1. Quality Management System (QMS)

DEVIATION / REMARK DESCRIPTION	D1 – Other
<p>The management of the skills and habilitations of ALLERGAN Ltd Marlow staff is incompletely described in the documentation system regarding the MV activity (MDD Annex II item 3.2 b, claimed ISO 13485 standard items 4.2.1 c, 6.2.1, 6.2.2), insofar this documentation system does not mention the modalities of:</p> <p>1. Training, familiarization or sensitizing of the following staff :</p> <p><u>Staff in charge of the management of complaints and MV</u></p> <ul style="list-style-type: none"> • MV references and guidelines (MDD, European MEDDEV 2.1211 '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 2.1212 'Post market clinical follow-up studies' ; • ALLERGAN Materiovigilance procedures; • Risks associated to the medical devices marketed by ALLERGAN. <p><u>Marketing and Commercial staff</u></p> <ul style="list-style-type: none"> • Risks associated to the medical devices marketed by ALLERGAN; • Principles of identification of safety and MV cases; • Identification of ALLERGAN MV staff to whom shall be passed on the cases communicated. <p><u>Reception staff in charge of directing the calls towards the staff in charge of the management of complaints and MV.</u></p> <ul style="list-style-type: none"> • Risks associated to the medical devices marketed by ALLERGAN; • Principles of identification of safety and MV cases; • Identification of ALLERGAN MV staff to whom shall be passed on the cases communicated. <p>2. Periodic training, familiarization or sensitizing intended to maintain the habilitations of the aforementioned staff.</p>	
ALLERGAN ORIGINAL RESPONSE	
<p>A complete review of the Allergan medical device vigilance training system was completed in response to the D1 findings. As was discussed during the inspection, Allergan provides global adverse event reporting training to employees during orientation training. Additional job specific training is provided to staff receiving calls/complaints, those investigating complaints, and individuals otherwise involved in MV activities. In addition to these training activities, Allergan has identified several actions that will strengthen associate training and provide greater assurance that requirements are clearly defined, training curricula are complete, and the program is effectively managed. These are described below under each point of the observation.</p> <p>With respect to Point 1, for Product Surveillance staff managing the complaints and vigilance processes, training is managed under procedure SOP10-014, “Quality System Training Requirements.” This procedure controls:</p> <ol style="list-style-type: none"> 1. The management of position training requirements 2. The generation and maintenance of curricula and employee qualification records/training records 3. Training effectiveness assessment 4. Quality System training <p>Training requirements are assigned to staff utilising Allergan’s Learning Management System (LMS) where specific procedures are allocated to an individual’s profile (see below for the core product surveillance procedure listing).</p> <p>During the new employee orientation process, Product Surveillance staff review relevant procedures</p>	

assigned to them via their LMS profile. Each new employee also receives a one-day induction programme that includes presentations from both Regulatory Affairs and Product Surveillance management, covering the legislative framework in operation within EAME countries/region. Product surveillance training is divided into three sections, to cover regulatory/vigilance, procedures and product learning. The details for each part of this training are as follows:

Regulatory/Vigilance Training. Consists of:

- GSE-SIMR-P-001, Policy for Reporting Adverse Events
- EU Product Surveillance Regulatory and Vigilance training module
- External third party courses and regulator sponsored training (on ad hoc basis)

Procedure Training. Consists of training on the following:

Procedure#	Description
DOP-054	Vigilance Reporting
POL-003	Complaint Handling
SOP-026	Vigilance Reporting
SOP12-018	Complaint Processing
SOP-071	Medical Device Reporting
SOP-055	Post Market Surveillance
SOP12-006	Complaint Review
DOP-03719	Management/Specialist Review
DOP-004	Complaint Handbook, Breast Implants
SOP12-019	Complaint Further Investigation

Product Training. Consists of the following for breast implant products:

- Risks associated with Breast Implants – Class room training
- Allergan Medical Breast Implant Product Training

Allergan’s review of the training system indicates that training is assigned by area managers and supervisors. Although the Allergan LMS captures conducted training, the company is planning to implement additional measures within the LMS so that training requirements will be automatically assigned from the LMS. (See Corrective Action D1.1.) This will provide additional assurance that there are no gaps in training requirements.

As an immediate correction measure, on 12th May 2015 EU regulatory and vigilance retraining was provided to the Marlow Product Surveillance team. This training, which is part of the routine curriculum for all staff managing complaints and vigilance, reviewed the European Commission Medical Devices Directive 93/42/EEC and MEDDEV 2.12-1 Rev 8, Guidelines on a Medical Devices Vigilance System and has been formally documented within the Allergan LMS. Enclosed is the list of the Product Surveillance Associates who attended the training (Attachment D1.1). Allergan will be expanding this training module to include the other EC MEDDEV requirements cited in finding D1. (See Corrective Action D1.2.) The company is also scheduling additional refresher training on product risks and information (See Corrective Action D1.3).

For all staff, including Reception staff and commercial/marketing associates, training on the identification and reporting of adverse events as well as to who to report these adverse events is given on annual basis. This training is based on GSE-SIMR-P-001, ‘Policy for Reporting Adverse Events and Other Safety Information which is provided in Attachment D1.2. In addition, product

risks are described in orientation training as well as on-the-job training. As per corrective actions identified in D1.4 and D1.5, this will be enhanced further and additional training documented.

In response to Point 2, Periodic refresher training is triggered by change events within the training system. Employees are automatically notified of the need to train on an amended procedure through the Allergan LMS. Email alerts are sent to the employee when a new training or refresher training activity is required. Training activities are monitored by the system and must be completed within a predetermined time frame. Alerts will be sent to the employees and their managers if the specified time frames are not achieved. Training compliance metrics are monitored during monthly Operational Management Review and remedial actions undertaken as required.

Regulatory surveillance activities are conducted by the Regulatory and Product Surveillance teams. Any changes to the EAME legislative framework or the EC guidance documents are discussed and retraining undertaken, as appropriate. Regular meetings are held within the Product Surveillance group that allow the management team the opportunity to discuss audit/inspection findings, provide ad-hoc guidance, review systemic findings from case audits, and provide clarity on specific areas of post market activities.

From the review of training, Allergan noted that while training is conducted in response to new developments and events, there also should be routine retraining on a periodic basis. The program has been expanded to include mandatory retraining on all modules on an annual basis. (See Corrective Action D1.6.)

The corrective actions discussed above focus on the training requirements for Breast Implant products within EAME region. A separate global project has been initiated to review global complaint intake training for device and drug/biologic products across all markets (See Corrective Action D1.7).

ANSM'S COMMENTS IN THE FINAL REPORT

Acceptable response. It is however reminded that the provisions related to the management of the skills and habilitations of ALLERGAN Ltd Marlow staff, according to points 1 and 2 raised in D1 and to the committed corrective actions mentioned in the response file provided, shall be clearly described in ALLERGAN documentation system, which includes the update of the training procedures accordingly.

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

- D1.1– Associate Director Curricula, Analyst Curricula, Clinical Analyst Curricula, Training and Compliance Curricula
- D1.2 – Vigilance Med Dev Training Record, Vigilance Training July_15
- D1.3 – Breast Training log
- D1.4 – Breast Marketing and Commercial Training Slides, Breast Marketing and Commercial Training Record
- D1.5 – Reception Training Slides, Reception Training Record
- D1.6 – Refer to attachment F_D1.1

FURTHER COMMENTS BASED ON THE FINAL REPORT

Further to the response already provided, Allergan will enhance the training expectation by updating SOP10-014 (Quality System Training Program) section 5.7 which currently implies that the curricula defined in Plateau-LMS is only reviewed by Supervisor/Manager annually at Costa Rica only. This will be amended to make review of curricula applicable to all sites. Marlow Product Surveillance has defined curricula recorded in Plateau-LMS for:

Role	Curricula Title
Associate Director, Product Surveillance, Marlow	GTOPS-WWQA_AGM-ASSOCDIRE-MA
Manager, Product Surveillance, Marlow	GTOPS-WWQA_AGM-MGRPSRA-MA
Analyst, Product Surveillance, Marlow	GTOPS-WWQA_AGM-ANLYPEU-MA
Training and Compliance Associate, Product Surveillance, Marlow	GTOPS-WWQA_AGM-ASSOCPSRA-MA
Clinical Analyst, Product Surveillance, Marlow	GTOPS-WWQA_AGM-ANLPSEUCLPRJ-MA

These curricula were created in line with DOP-02504 (Position Training Requirements). Any modifications to these curricula are recorded on FRM-02204 (Curriculum Creation, Change and Assignment Request) as a means of control.

With regard to management of qualifications that require an annual refresher, each item assignment within Plateau-LMS can have re-training periods specified, if applicable. For example, attachment F_D1.1 shows the items details for the vigilance / MED DEV Theory and Context training which indicates retraining period of 364 days. Therefore, Plateau-LMS has been configured to trigger a re-training notification on an annual basis.

Section 8.0 of SOP10-14 will also be updated to include a statement that each training item can be evaluated for re-training frequency on a case by case basis by the trainer. When uploaded into Plateau-LMS, curricula can be configured to trigger a re-training event. Any re-training frequencies are documented on FRM-02204.

If any update to the training material is required outside of the training frequency defined, it will require an additional training session, for which the attendees are documented on FRM-080108 (Training Record).

Changes to SOP10-014 as above will be completed as soon as possible but no later than by 05Dec15.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

F_D1.1 - Screen shot of meta data in Plateau-LMS for Vigilance and MED DEV Theory Training.

DEVIATION / REMARK DESCRIPTION	D2 – Other
<p>The audit scopes of the complaints and MV management activities are not described in ALLERGAN Ltd Marlow documentation system, which does not precisely attest to the provisions for assessing the efficiency of the processes associated with these activities (MDD Annex II items 3.1 and 3.2 b, claimed ISO 13485 standard items 8.2.2 and 8.5.1), particularly in the following scopes :</p> <p>1. Regarding the internal activities:</p> <p>a) Identification of safety and MV cases associated with complaints;</p> <p>b) Management of the individual MV cases in terms of :</p> <ul style="list-style-type: none"> • fluidity and efficacy of the cases collection channels ; • traceability of the input and output documents associated with each case and embedded in TRACKWISE database ; • quality and deadlines of the processing and of the notifications of serious incidents to the concerned local authorities; • quality and deadlines of the responses provided to local authorities requests; • quality and deadlines of the corrective and preventive actions (CAPAs/IFSCAs) implemented; <p>c) Management of the grouped MV cases within the post-market survey (PMS) in terms of :</p> <ul style="list-style-type: none"> • detection and management of the recurrent safety and MV cases, associated with the continuous assessment of the concerned medical devices Benefit Risk ratio and the risk analysis reviews; • quality and deadlines of the periodic summary reports (PSR) transmissions to the concerned local authorities (annual PSR for France) ; <p>2. Regarding the outsourced activities: audits of the subcontractor called Professional Information, in charge of receiving calls, including complaints, safety and in cases, during the hours of closure of Marlow site.</p>	
ALLERGAN'S ORIGINAL RESPONSE	
<p>With respect to Audits and MV management activities, these are covered within two processes;</p> <ol style="list-style-type: none"> a. The Quality Audit Program (AGNM SOP-006), which covers all Quality System elements including MV management, is audited annually internally as seen from the 2014 Internal Audit program discussed during the inspection. b. Monthly auditing of all complaint cases is performed. Cases are challenged according to specific criteria and using a risk based sampling plan. <p>With respect to (a), the Quality System elements are documented in the Quality Manual QM-001 as defined in the main sections of the ISO 13485 (2003) (e.g. 8.1, 8.2, etc.), however, it does not go into further detail to mention section 8.2.2 as this would be defined in each audit scope. The Quality Manual will be revised to include specific requirements around MV activities (Refer to Corrective Action D2.1).</p> <p>With respect to (b), the two procedures outlining the monthly auditing program (DOP-03719 and SOP-027) have been updated to focus on the critical areas of complaint case management, as identified in ANSM finding D2(1b) and including:</p> <ul style="list-style-type: none"> • Confirming that vigilance decisions been determined correctly by Product Surveillance Analysts and that vigilance report submissions been made to National Competent Authorities (NCA's) within the time frames specified within MEDDEV 2.12-1 and/or Member State national law • Confirming that the due diligence follow-ups have been conducted and are correctly documented within the Trackwise records • If an NCA has requested further information following the submission of a vigilance report, confirming that all questions have been answered within the deadline set by the 	

regulator or otherwise in accordance with applicable regulations or internal procedures.

Copies of the revised procedures are presented in attachments D2.1 and D2.2.

In addition, holistic review of complaint management procedures was conducted in response to this finding. While the observation is focused on the scope of the audit program, Allergan also looked at the vigilance reporting and complaint management processes used by all staff members. This will provide better assurance that the day-to-day workflows address the points raised by ANSM, with the audit program being aligned to these areas such that Allergan can more effectively monitor performance.

The following procedures form the core of the vigilance and complaint management vigilance program:

Table 1

Procedure#	Description
DOP-004	Complaint Handbook, Breast Implants
DOP-054	Vigilance Reporting
POL-003	Complaint Handling
SOP-026	Vigilance Reporting
SOP-055	Post Market Surveillance
SOP-071	Medical Device Reporting
SOP12-006	Complaint Review
SOP12-018	Complaint Processing
SOP12-019	Complaint Further Investigation

These procedures broadly cover all of the areas touched on in this observation. The procedures that describe the auditing program for these functions are:

Table 2

Procedure#	Description
DOP-03719	Management/Specialist Review
SOP-027	Complaint Handling Generated Reports
AGNM SOP-006	Quality Audit Program

Allergan has reviewed all of the procedures identified in tables 1 and 2 above, against the items referenced under point 1, which focus primarily on the following areas:

- the need to characterize cases upon intake and be able to properly characterize the safety and vigilance risks presented;
- effectiveness of complaint identification processes in other areas, and how complaints are brought into the complaint intake process;
- traceability of associated required actions (e.g., batch review; returned sample testing) and linkage to or presence of supporting documentation within the Trackwise system;
- timeliness of different actions that are taken throughout the case management process (e.g., escalation to management; initial notification to regulatory authorities; follow up information including CAPAs and any commitments made; periodic safety update reports); and
- The manner in which complaints are assessed and triaged, considering such things as the history of events on the same, similar or related products.

Revisions have already been made to the case auditing procedures and are planning additional revisions to some of the procedures listed in Table 1, to address the points raised by ANSM, as discussed below:

Procedure DOP-054, Vigilance Reporting will be reviewed and updated to address the points raised by ANSM:

- Including specific National Competent Authority (NCA) guidance;
- Updating the MHRA's guidance concerning particular breast implant adverse events;
- Providing more detail to the procedure for managing follow-up NCA's questions;
- Implementing methodologies to ensure that vigilance reports are submitted to regulators within specified time frames (daily vigilance aging reports now made available to Analysts directly).

(See Corrective action D2.2)

Procedure SOP12-018, Complaint Handling will be reviewed and updated to address the points raised by ANSM:

- Focus on the traceability of information associated with due diligence follow-up. Clear references between the case Correspondence Log and the documents attached to the record;
- Due diligence documents must reside with Trackwise and not outside of the database;
- Ensuring that corrective and preventive actions taken are appropriately referenced within the case history
- The Correspondence Log to clearly document what channels are being utilised to collect case information

(See Corrective action D2.3)

Training on all the updated procedures identified above has been assigned and completed through the Allergan Learning Management System (LMS).

With respect to point 2 in this finding, regarding the outsourcing of activities, this is covered in detail in R5.

ANSM'S COMMENTS IN THE FINAL REPORT

Acceptable response regarding D2 item 1. It is however reminded, against item 1 c), that the updates of the audit procedures, as mentioned in the response, shall cover not only the audits of the individual complaints and MV cases but also the audits of the grouped cases and of the Post-Market Survey.

Unsatisfactory response regarding D2 item 2 : It was already noted in the preliminary inspection report that the next audit of the subcontractor 'Professional Information' is planned for Q3 2015, but ALLERGAN Ltd Marlow does not provide, in its response file, documents describing precisely :

- the risk-based methodology used to issue the annual audit schedules, as mentioned in its response file;
- how is monitored this subcontractor, with in this methodology (considering that the last audit of Professional Information was performed in May 2009).

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

D2.1 – QM-001

D2.2 – Vigilance Reporting_DOP-054, Vigilance Reporting SOP-026

D2.3 – Complaint Processing SOP12-018

FURTHER COMMENTS BASED ON THE FINAL REPORT

With respect to D2, item 2, Global R & D Quality (GRDQ), is responsible for defining the process and strategy for audit planning, and audit scheduling, and also for conducting audits per that schedule. This process is described in procedure GRDQ-PV-W-002: Pharmacovigilance & Medical Device Vigilance Audit Planning. (See attachment F_D2.1.) This procedure describes the risk-based methodology that is used to develop the audit plan and schedule. GRDQ annual audit planning is conducted during Q3/Q4 of each year, based upon the outputs from the risk-based assessment. In particular reference to the first point from ANSM, we want to highlight the following:

- All higher risk elements of the Allergan subsidiary and PV system audit universes are expected to be audited within a 3 year period. Elements of a medium or lower risk may have an audit frequency of 3-5 years.
- The GRDQ Pharmacovigilance/ Medical Device Vigilance vendor audit universe has now been defined, and all elements will be audited on a 3 year cyclical basis. Since this frequency is consistent with our audit frequency for higher risk audits, specific risk criteria will not be applied at the strategic audit planning stage; however, these will be considered during operational planning.
- The medical device vigilance system audit universe has also been defined, and all audits will be conducted on a 3 year cyclical basis.

In regard to the second point relating specifically to how this applies to Professional Information (PI), the last audit of PI was conducted in 2009 prior to the formation of the GRDQ organization and the establishment of SOP GRDQ-PV-W-002. Under this new procedure, PI will be audited on a 3 year cyclical basis (treated as higher risk audit, as noted above), beginning this year. This is reflected in the audit schedule which indicates PI was audited on the 28th September 2015. (See attachment F_D2.2.) In addition to auditing by GRDQ, routine oversight of PI also is included in the scope of routine performance monitoring conducted by Medical Information. All PI enquiries and adverse events are included in the weekly 100% reconciliation of medical information enquiries for the UK/Ireland, as explained in the original response. GRDQ also can conduct additional “for cause” audits in the event that routine oversight identifies any negative trend in PI performance.

The same response is also valid for R5.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

F_D2.1 – SOP GRDQ-PV-W-002

F_D2.2 – 2015 PV Audit Schedule

DEVIATION / REMARK DESCRIPTION	D3 – Other
<p>Some deadlines related to the processing of complaints and MV cases mentioned in procedures used by ALLERGAN Ltd Marlow, are not compatible with the European regulatory provisions which state that the manufacturers are required to notify the competent authorities of serious incidents (reminded in Chapter 1.2 of this report) immediately on learning of them (MDD Annex II item 3.1) insofar:</p> <ol style="list-style-type: none"> 1. The Complaint Handling procedure POL-003 mentions (Chapters 4.1.2 and 4.1.3) that the complaints shall be entered in TRACKWISE e database within 5 working days of receipt, then a risk assessment shall be performed within 5 (more) working days of complaint entry into TRACKWISE and if a complaint introduces or increases a risk to the patient, then the case shall be transferred to a Product Surveillance Manager who will present it to management; 2. The Vigilance Reporting procedure SOP-026 defines (Chapter 3 page 4) the wording 'Immediately' and 'without any delay that could not be justified'. The above POL-003 and SOP-026 procedures shall be updated consequently. 	
ALLERGAN ORIGINAL RESPONSE	
<p>Procedure POL-003, Complaint Handling, and procedure SOP-026, Vigilance Reporting are based on the European Commission MEDDEV 2.12-1 Guidance on a Medical Device Vigilance System. MEDDEV 2.12-1 details reporting timelines as follows;</p> <ol style="list-style-type: none"> 1. Serious public health threat – Immediately but not later than 2 days 2. Death or serious deterioration in the state of health – Immediately but not later than 10 days 3. All other reports – Immediately but not later than 30 days <p>The ANSM, the MHRA, and the Italian Ministry of Health have implemented reporting timelines that differ from the guidance provided by MEDDEV 2.12-1. These requirements have been transposed into national law within each Member State.</p> <p>Since Allergan operates within all of these countries and cannot practically have different timeframes by country, the company will modify its procedures to comply with MEDDEV 2.12-1, which are not significantly different from those provided by ANSM.</p> <p>In terms of management of the individual cases at intake, a risk-based approach, where complaints are triaged, will be applied at time of intake. If the complaint is a serious public health threat or is death or serious deterioration in the state of health, this will require immediate action to comply with the required timeframes as stipulated by the MEDDEV 2.12-1 (See Corrective Action D3.2).</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
<p>Acceptable Response</p>	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
<p>D3.1 – Complaint Handling POL-003, Complaint Processing SOP12-018 (Refer to Attachment D2.3), Vigilance Reporting SOP-026 (Refer to Attachment D2.2), D3.2 – Training evidence for ANSM document updates</p>	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
<p>None</p>	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
<p>None</p>	

DEVIATION / REMARK DESCRIPTION	R2 – Major
<p>The Complaint Processing procedure SOP12-018, which mentions (Chapter 9.5) that further investigations associated with Device History Records (DHR) shall be carried out in cases of death or serious injury allegedly related to the BIs and not indicated in the labelling, shall be corrected so that the processing of each complaint and/or MV case, when the batch number or serial number of the medical device involved is known, shall include a systematic review of the DHR.</p>	
ALLERGAN’S ORIGINAL RESPONSE	
<p>Procedure SOP12-018, Complaint Processing was reviewed in response to finding R2. The Further Investigation/Device History Record section of the procedure was found to lack specific guidance for Complaint Analysts, around the management of cancer and lymphoma adverse events. Evidence from the inspection appeared to suggest that manufacturing records were not always reviewed when cancer and lymphoma adverse events were notified to Allergan.</p> <p>Procedure SOP12 -018, paragraph 9.5.1.2 Complaint Processing has been updated and released in order to mandate that a review of manufacturing records is conducted for adverse event categories previously stated in the procedure and now also includes cancer, cancer-breast, lymphoma and lymphoma-ALCL cases, where the batch number or serial number of the medical device involved is known. (See attachment D2.1.)</p> <p>PS Marlow Product Surveillance training to the updated procedure SOP12 -018, Complaint Processing has been assigned and completed through the Allergan Learning Management System (LMS).</p>	
ANSM’S COMMENTS IN THE FINAL REPORT	
<p>Unsatisfactory response, in the absence of transmission of the updated Complaint Processing procedure SOP12-018 stating that the processing of each complaint and/or MV case (not limited to cancers, cancer breast, lymphoma and ALCL cases), when the batch number or serial number of the medical device involved is known, shall include a systematic review of the DHR.</p>	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
None	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
<p>Complaint investigations are governed by two separate, but related procedures. The basic process for complaint handling is described in SOP12-018 - “Complaint Processing” which includes the following activities: initial risk assessment, materiovigilance reporting, initial investigation, device laboratory analysis, and also determination of whether further investigation is required. SOP12-019 – “Complaint Further Investigation” describes the process for conducting further investigations, which includes review of the Device History Record (DHR), review of complaints from the same manufacturing lots, review of the product labelling, and review of training, where appropriate.</p> <p>The further investigation process starts with QA review of the complaint file and laboratory analysis prior to conducting a review of the DHR. Review of the DHR includes evaluation of non-conforming material reports associated with the production lot, sterilization run, and environmental monitoring. Additional records may be requested by QA based on the results of the DHR review.</p> <p>In response to the comment from ANSM, the short term actions include an updated SOP12-018 - “Complaint Processing” to reflect that when the batch number or the serial number of the medical</p>	

device involved is known, 100% of production batch records (DHR) shall be systematically reviewed using the methods described in procedure SOP12-019 – “Complaint Further Investigation.” (See attachments F_R2.2 and F_R2.3.) Furthermore, for every new complaint a DHR review will be completed for all Breast Implant product family complaints with known serial/batch number will be implemented by 30th November 2015.

The long term solution includes further revising procedures SOP12-019 and SOP12-018 to reflect a more in-depth systematic, risk-based review and investigational methodology for all Breast Implant product family complaints. A schematic showing the proposed process flow is provided in attachment F_R2.1.

Note that the long term solution is an improvement on the short term solution, in that all complaints for Breast Implants with known serial/batch number will include the complaint information, reportability statement, complaint term codes and risk analysis. All Breast Implant product family complaints will be evaluated as a technical and medical event, and triaged to determine if the event is a new failure mode and/or novel event. If the event is a new failure mode or novel event it will be sent to the medical device safety physician for review within TrackWise Database System to quantify the health risk impact to the patient. Once the health risk impact is known (complaint related to a known failure mode or through physician review), this information will be reviewed to determine reportability eligibility per local country requirements.

The investigation then will proceed, with the depth of review being commensurate with the complaint risk per the risk management file (e.g., Clinical Hazard Lists and FMEAs) and the signal detection process pertaining to the breast implant product family. A query will be generated to identify all possible serial numbers associated with the incident to determine the lots of devices shipped to the reported user facility during a specified time frame related to the investigation. Documentation to be reviewed during the investigation per the health risk impact to the patient will include (but not be limited to): DHR reviews, release lot reviews, nonconforming material reports (NCMRs), change controls, deviations, CAPAs or additional related documentation for every event. Based on the results of the complaint investigation, a review will be conducted of the risk management file to determine if the risk associated with the complaint is commensurate with the assigned risk as documented in the device’s risk assessment.

The risk assessment review will concentrate on the following areas as documented in the device’s risk assessment: overall residual risk level, identified patient effects and identified hazards and hazard causes. If the review of the device’s risk assessment shows that a new hazard, root cause, or patient effect is identified that may potentially have an unacceptable risk or a significant increase in the complaint rate from the expected occurrence rate; an escalation of the complaint will be conducted according to the AGNM SOP-002 – Quality Board Review Procedure and will be a data stream into the AGNM SOP-010 – Quality System Management Review Procedure.

We expect that the above updates will be effective by 29th April 2016, to allow for the selection and training of staff to support the systematic reviews for all Breast Implant product family complaints and updates to the Clinical Hazards Lists, Adverse Event Term Codes, Risk Management Files and FMEAs for the Breast Implant product family.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

F_R2.1 - Schematic Process Flow - Process flow to reflect a more in-depth systematic, risk-based review and investigational methodology for all Breast Implant product family complaints

F_R2.2 - SOP12-018 - “Complaint Processing” Version 56.0 – Effective, September 30, 2015 (refer to Attachment D2.3)

F_R2.3 - SOP12-019 - “Complaint Further Investigation” Version 25.0 – Effective, July 7, 2015

DEVIATION / REMARK DESCRIPTION	R3 – Other
<p>The AGNM SOP-001 Corrective and Preventive Action (CAPA) and SOP12-001 Field Corrective Action procedures should be completed so that they mention provisions regarding the transmissions 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) (Meddev 2.12/1 point 5.4.4) ; • likely to induce substantial changes to the manufacturing processes of the devices covered (MDD Annex II item 3.1) ; • Likely to induce any change to the design of the class III devices covered (MDD Annex II item 4.4). 	
ALLERGAN'S ORIGINAL RESPONSE	
<p>A review was conducted and confirmed the need to revise AGNM SOP-001 Corrective and Preventive Action (CAPA) and SOP12-001 Field Corrective Action procedures to incorporate MEDDEV 2.12/1 point 5.4.4 and Annex II item 3.1 and item 4.4 of the MDD. The review was completed on June 9, 2015. Based upon the review the aforementioned SOPs will be revised to include the requirements in MEDDEV 2.12/1 point 5.4.4 and Annex II item 3.1 and item 4.4 of the MDD (See Corrective Action R3.1).</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
<p>Acceptable response, considering the commitment of ALLERGAN Ltd. to update its SOP-001 Corrective and Preventive Action (CAPA) and SOP12-001 Field Corrective Action procedures by 31st July 2015, so that those procedures shall incorporate the appropriate references of MEDDEV 2.12/1 and Annex II of the MDD. However, an error has been noted in the wording of the second point of R3, in the preliminary inspection report: the wording 'likely to induce substantial changes to the manufacturing processes of the devices covered (MDD Annex II item 3.1)' must be replaced by the wording 'likely to induce substantial changes to the design and/or manufacturing processes of the devices covered (MDD Annex II item 3.4)'.</p>	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
R3.1 - AGNM SOP-001	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
None	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
None	

DEVIATION / REMARK DESCRIPTION	D4 – Other
<p>The batch recall process description in ALLERGAN Ltd Marlow documentation system (particularly the SOP12-001 Field Corrective Action) shall be completed insofar it does not mention that any medical device batch recall motivated by a technical or medical reason related to a serious incident shall be reported immediately to the European authority on the territory of which the recall is to be conducted (MDD Annex II item 3.1)</p>	
ALLERGAN'S ORIGINAL RESPONSE	
<p>The procedure referenced in the observation (SOP12-001) is a global procedure that provides guidelines for field actions worldwide for medical devices. Detailed instructions are outlined in regional procedure (Europe, Africa & Middle East) EAME-API-003, "EAME API Recall Implementation," including the process for communication to relevant authorities of any medical device recalls. This was also reviewed in the Inspection and is attached for verification in attachment D4.1. In order for there to be a clear cross linkage between the global procedure SOP12-001 and the procedure used in the EAME for recall, SOP12-001 will be updated as indicated in Corrective Action D4.1</p> <p>Specifically, Table 2 of EAME-API-003 sets out a matrix of responsibilities for different functional areas in relation to any medical device recalls. Among the responsibilities listed, is that Product Surveillance Marlow will be responsible for liaising with the European Authority on the territory of which the recall is to be conducted, and Medical Device Regulatory Affairs will be responsible for informing the notified body.</p> <p>Although EAME-API-003 states that "traceability of product should be initiated immediately to allow for rapid implementation", it does not specifically refer to timelines regarding notification of serious incidents to European Authorities. See Corrective Action D4.2.</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
Acceptable Response.	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
D4.1 – SOP12-001 D4.2 – EAME-API-003, EAME-API-003_F_02, EAME-API-003_F_03	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
None	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
None	

DEVIATION / REMARK DESCRIPTION	R4 – Other
<p>The batch recall process description in ALLERGAN Ltd Marlow documentation system (particularly the SOP12-001 Field Corrective Action) should be completed with clear provisions regarding a systematic recall full balance sheet recapitulating the quantities of units of each batch :</p> <ul style="list-style-type: none"> • 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). 	
ALLERGAN'S ORIGINAL RESPONSE	
<p>As is noted in the response for D4, procedure EAME-API-003 'EAME API Recall Implementation' provides detailed instructions relating to medical device recalls conducted in Europe. Specifically, Table 2 of this procedure states that QA Supply Chain, under the instruction of QA Management is responsible to quarantine affected product both by physical means (for product remaining in stock or returned by customers) and within the SAP system. QA Supply Chain is also responsible for</p> <ul style="list-style-type: none"> • Issuing a recall report, stock movement report and completing initial stock reconciliation review. This recall report will contain the destination and quantities of all product distributed related to the affected batch(es), including all used and unused stock as well as any samples. • Following up with Customer Service on the status of customer returns • Ensuring Goods return process and stock inventory • Communicating with Customers after QA direction <p>The above can be verified by reviewing Attachment D4.1.</p> <p>The procedure will be updated to include additional detail related to the documentation associated with any recall. See Corrective Action R4.1.</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
Acceptable Response	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
See attachments for D4.	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
None	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
None	

DEVIATION / REMARK DESCRIPTION	D5 – Other
<p>The Post Market Survey (PMS) process description in ALLERGAN Ltd Marlow documentation system, related to experience gained from devices in the post-production phase, does not mentions provisions allowing the company to have complete and relevant indicators and metrics regarding the BIs, in order to demonstrate the continuous compliance of those medical devices with the applicable essential requirements (MDD Annex II item 3.1, claimed ISO 134B5 standard items 7.2.3, B.2.1, B.4 and B.5), insofar the PMS process does not provide a methodology for the detection and analyses of trends of the recurring incidents broken down by :</p> <ul style="list-style-type: none"> • regions of occurrence of the incidents (Worldwide / Europe / local countries) ; • sale volumes or numbers of BIs implanted per year, which does not allow to identify the significance and risks related to the reported cases; • year of implantation, which does not allow to identify possible trends and drifts over time; • surface (smooth or textured) of the BIs, which does not allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs, particularly important to update and consolidate the clinical data. 	
ALLERGAN'S ORIGINAL RESPONSE	
<p>Allergan conducted a comprehensive review of all of the data points collected as part of the Post-Market Survey (PMS) program. These data and metrics are reviewed at a global level through the identification of device-related occurrences in the field; assessment of the risk of occurrences; and responding to the risk through corrective and preventive actions. In terms of the process, current Operations Management Reviews (OMR) performed at each regional site monitor specific rates and trends emerging from these data at a regional level. For example, Marlow's OMR process includes adverse event trending for the EAME region (Europe, the Middle East and Africa). Quality System Management Review evaluates reports from both a regional and worldwide perspective. These reports include trending, prevalence /cohort tracking of adverse event counts and rates. Historically, evaluation of rates and trends at the country level had not been deemed necessary, as the environment of use was considered to be similar between countries.</p> <p>In September 2014, Allergan initiated a project to augment present trending with a signal detection element. This project already has defined what will be the new business process, with the new signal detection element. At its core, the revised business process has a Signal Detection Panel comprised of global functions such as Product Development, Medical Device Safety, Epidemiology, Regulatory Affairs, Medical Affairs, Clinical Development, Quality and Marketing that will review specific signal detection reports generated by a statistical application that is designed to identify triggers and prioritize signals. The Panel will assess these reports and monitor trends, disposition findings (where appropriate) for further investigation, and also ensure that identified signals feed into a defined escalation process, based on signal priority. The business process will be closely connected to the risk management process.</p> <p>The original signal detection project scope included regional signal detection and trending. Allergan has further expanded the scope of the project in May 2015 to include by-country signal detection and trending. At the same time, as part of the scope expansion an additional requirement to monitor key product contrasts, including surface type, has been added as part of the defined dataset. This new signal detection SOP and associated collection of reports will also ensure both long-term and short-term trending needs are addressed. (See Corrective Action D5.1.) With respect to the different factors listed in this observation, as discussed above, both regions of occurrence/incidents and surface texture are now defined parts of the signal detection process.</p> <p>With respect to sales Information, data from 2008 to the present include the country in which the device was sold. Global, regional and "to-country" sales data for any device implanted after 2008 can be reliably queried in the SAP system (in use since late 2007). For data prior to 2007, much of the country-specific information is not available due the types of legacy databases that were in use</p>	

at that time. To address this, a project was initiated to estimate “country specific” sales from 1995 through 2007. (See Corrective Action D5.2.) With respect to year of implantation, Allergan has not historically used implant year globally because implantation dates are not provided for all implants. Thus, there is not an appropriate denominator for complaints by implant year. Based upon how these products are used in the field, the majority of devices are used very shortly after they are sold. Therefore, Allergan believes that evaluating complaints as a function of year sold is adequate for evaluating trends and drift over time.

ANSM’S COMMENTS IN THE FINAL REPORT

Unsatisfactory response, in the absence of transmission of the updated Post Market Surveillance procedure stating clearly that the assessment of the trends and of the Bls Benefit/Risk ratio shall integrate the reported incidents broken down by :

- regions of occurrence of the incidents (WorldWide / Europe / local countries), as included in the signal detection project scope according to page 17 of the response file provided :
- years of sales;
- sale volumes per year, as mentioned on page 18 of the response file provided (which can be reliably required in SAP system used by ALLERGAN, according to page 17 of this response file) ;
- surface (smooth or textured) of the Bls, as included in the signal detection project scope according to page 17 of the response file provided.

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

- D5.1 – AGNM SOP-014_Signal Detection Procedure
- D5.2 – Sales Data Reconciliation Project_QPCR0051, Sales data_PRJ102544-VSR-02

FURTHER COMMENTS BASED ON THE FINAL REPORT

In response to the above observation, the following procedures were updated to address the points raised by ANSM:

Table D5-1: Documents Updated/Created to Address ANSM Requirements

Document	Description	Change/Comment	ECO #
AGNM SOP-010	Quality System Management Review (QSMR)	Updated	ECO-AGNM-12
AGNM SOP-012	Post Market Surveillance Procedure	Updated. Top level Post Market Survey procedure.	ECO-AGNM-13
AMED-002	Risk Management Process for Medical Devices and Combination Products	Updated	DCR-00072295
AGNM SOP-014	Signal Detection	New	ECO-AGNM-13

These procedures now have integrated the following elements specifically requested by ANSM in the process for assessing trends and also in evaluating benefit/risk ratios:

- Region of occurrence (World-wide, Europe, local countries, etc.) as included in the signal detection metrics
- Years of sales for BIs
- Sales volumes per year; sale volumes of BIs implanted (invoiced) per year in order to identify the significance and risks related to the reported casesType of product – product key features (e.g. Breast Implant surface texture (smooth, Microcell, and Biocell textured) of the BIs to enable analysis of the textured BIs versus smooth BIs

Two (2) Quality Plans were initiated to develop the new and revised processes detailed in Table D5-1, and drive the transition to the new processes. The first Quality Plan, QPCR 0063, “Postmarket Surveillance Updates Including Introduction of Signal Detection” is related to the evaluation and structure of post market data. (See attachment F_D5.1.) It details the new/updated processes and action plan to achieve conformance with the ANSM requirements. The second Quality Plan, QPCR0051, “Sales Reconciliation Project Quality Plan, QPCR0051”, outlines the actions to restore country level traceability of Breast Implant sales from 1995 to the present. (See attachment D5.2.)

Quality Plan QPCR0063 contains both a short term and long term plan to address the postmarket surveillance updates. The completed short term actions associated with QPCR0063 include release of the new Signal Detection Procedure, AGNM SOP-014 and updates to the Postmarket Surveillance Procedure, AGNM SOP-012 along with associated procedures. (See attachments D5.1 and F_D5.2.) The Signal Detection Procedure includes the creation of the Signal Detection Panel. The Signal Detection Panel encompasses a cross functional team whose goal is to assess all post market data, evaluate any signals and alerts identified, and escalate as required. The SOP updates and implementation plan for the changes (QPCR0063) outline exactly how compliance with ANSM requested review will be carried out. The long term solution includes the release of the new Signal Detection Trending Software to augment the identification of post-market surveillance signals. Note that the long term solution is an improvement on the short term solution in that all ANSM required contrasts outlined previously will remain. The Signal Detection Trending Software is a custom application, which is described in the released SOP and quality plan (QPCR0063) which automates the detection and prioritization of signals using risk management principles. The quality plan describes its integration into the quality system, including the validation requirements.

Quality Plan QPCR0051 specifically addresses the need for historical country specific breast implant sales through a Sales Reconciliation Project. Completion of the Sales Reconciliation Project will provide access to worldwide, regional, and country specific breast implant sales data back as far as 1995. The updated sales data will be used for trending of the Breast Implant devices going forward.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

F_D5.1 - Quality Plan QPCR0063

F_D5.2 – Postmarket Surveillance Procedure (AGNM SOP-012), Version 2.0

2. Organization of the staff involved or likely to be involved

DEVIATION / REMARK DESCRIPTION	D6 – Other
<p>The management of the competences, skills and habilitations of the staff involved or likely to be involved in safety and/or MV cases is incomplete, considering the findings detailed in Annex 3 of this report, which induces a risk that MV cases may not all be processed and reported with due diligence (MDD Annex II items 3.1 and 3.2 b, claimed ISO 13485 standard item 6.2), insofar ALLERGAN Ltd Marlow does not have all the documentation 3 attesting to training (or) familiarization (or) sensitizing given to all the above staff according to its level of involvement in cases likely to be communicated, regarding:</p> <ul style="list-style-type: none"> • the MV references and guidelines (MDD, European MEDDEV 2.12/1 'Guidelines on a Medical Devices Vigilance System', European MEDDEV 2.713 'Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC, European MEDDEV 2.1212 'Post market clinical follow-up studies') ; • the risks associated to the medical devices marketed by ALLERGAN • the principles of identification of safety and MV cases ; • The identification of ALLERGAN staff in charge of MV and to who shall be passed on the cases communicated. 	
<p>ALLERGAN'S ORIGINAL RESPONSE</p>	
<p>Please see D1 for a discussion concerning the current training program, the retraining that has been completed since the inspection, and further training that is planned through corrective actions.</p>	
<p>ANSM'S COMMENTS IN THE FINAL REPORT</p>	
<p>Acceptable Response</p>	
<p>ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED</p>	
<p>None</p>	
<p>FURTHER COMMENTS BASED ON THE FINAL REPORT</p>	
<p>None</p>	
<p>ATTACHMENTS TO SUPPORT FURTHER COMMENTS</p>	
<p>None</p>	

3. Audits

DEVIATION / REMARK DESCRIPTION	R5 – Other
<p>ALLERGAN Ltd Marlow should tighten the frequencies of the audits of his subcontractor 'Professional Information', unless being able to justify them.</p>	
ALLERGAN'S ORIGINAL RESPONSE	
<p>The vendor in charge of receiving calls, including complaints, safety and MV cases out of hours (Professional Information, PI) is included on the internal GRDQ (Global Research and Development Quality) audit plan for 2015. (See Attachment and Corrective Action R5.1.) Annual audit planning is conducted during Q3/Q4 of each year, using a risk-based methodology, and the outputs create the audit schedule for the following year. (See Corrective Action R5.2.) The risk-based audit strategy utilizes data representing business, quality and compliance factors and audit frequency is determined by the outputs.</p> <p>In addition, oversight of PI, is included in the scope of routine performance monitoring conducted by Medical Information. All PI enquiries and adverse events are included in the weekly 100% reconciliation of medical information enquiries for the UK/Ireland. This is documented in the Medical Information Quality Assessment Form, which is in line with the MI-W-016-UK-IE Medical Information Adverse Event Reconciliation Process. (See attachments R5.2 and R5.3.)</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
<p>Unsatisfactory response : It was already noted in the preliminary inspection report that the next audit of the subcontractor 'Professional Information' is planned for 032015, but ALLERGAN Ltd Marlow does not provide, in its response file, documents describing precisely :</p> <ul style="list-style-type: none"> o the risk-based methodology used to issue the annual audit schedules, as mentioned in its response file o how is monitored this subcontractor, within this methodology (considering that the last audit of Professional Information was performed in May 2009) 	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
None	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
Please refer to response for D2.	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
None	

4. Management reviews

DEVIATION / REMARK DESCRIPTION	R6 – Other
<p>The management reviews should develop the <i>PMS</i> data, stakes and challenges on the basis of complete and relevant indicators and metrics regarding the Bls (see D5 and D11 Major - item 1, in this report).</p>	
ALLERGAN'S ORIGINAL RESPONSE	
<p>A review was conducted on Jun 10, 2015 and AGNM SOP-010 Quality System Management Review (QSMR) Revision 2 will be revised to expand the Customer feedback and Post-Market Performance Data Stream. The expansion will capture all risk management indicators and metrics to ensure a holistic review of all clinical hazards, failure modes, and trends for safety and compliance analysis. (See Corrective Action R6.1.)</p> <p>The Signal Detection Process SOP will be formalized and provide the risk management indicators and metrics identified above (See Corrective Action D5.1.) This SOP will also describe monitoring of complaint (medical and non-medical) data including customer feedback and Post-Market Performance Data Streams. These sources will be data inputs into the QSMR.</p>	
ANSM'S COMMENTS IN THE FINAL REPORT	
<p>Unsatisfactory response, in the absence of :</p> <ul style="list-style-type: none"> o clear commitment that the last management review conducted on June 10th 2015 integrated the trends of the reported incidents broken down by : <ul style="list-style-type: none"> - categories of incidents; - regions of occurrence of the incidents (Worldwide/ Europe/local countries) ; - years of sales; - sale volumes per year; - surface (smooth or textured) of the Bls. - communication of the stakes, challenges and conclusions issued from this management review. 	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
<p>R6.1 – AGNM SOP-010</p>	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
<p>Procedure AGNM SOP-010 Quality System Management Review (QSMR) Version 3.0 was reviewed on June 10, 2015.</p> <p>To clarify, Allergan's initial response referred to the review of the governing procedure for the Quality System Management Review (AGNM SOP-010), which was completed on June 10, 2015. Please note that this was not a reference to the conduct of a specific management review meeting. The QSMR occurs quarterly and the meeting for Q2 2015 was conducted on August 12, 2015. The August 12, 2015 management review did not include the new data inputs because actions were still underway to standardize sales volumes. However, during the QSMR on August 12, 2015, draft updated slides were presented to demonstrate aggregate rates for both long-term (e.g., rupture and capsular contracture) and short-term (e.g., hematoma, infection) complaint term codes. Furthermore, for both long-term and short-term complaint term codes, rates, counts and sales volumes were presented for the specific breast implant product family. In addition, pareto charts were presented and rates were utilized for the appropriate denominator for short- term versus long-term trending. The Quality System Management Review Procedure has been revised to expand the Customer feedback and Post-Market Performance Data Stream. (See attachment R6.1.)</p>	

The expansion captures all risk management indicators and metrics ANSM has requested in the observations from this inspection to ensure a holistic review of all clinical hazards, potential manufacturing related failure modes, and trends for safety and compliance analysis. Furthermore, any previously unrecognized hazards (i.e., unrecognized hazards/causes, failure modes, patient effects and either an unacceptable risk or a significant increase in the complaint rate from the expected occurrence rate) identified are escalated according to AGNM SOP-002 – Quality Board Review Process. (See attachment F_R6.1.) During the Quality Board Review, the issue(s) identified will be presented and evaluated for inclusion in the recognized clinical hazards list and corrective actions to be taken. Final recommendations will be provided at the Quality System Management Review (QSMR). In addition, the QSMR will include the integration of the trends of the reported incidents broken down by :

- categories of incidents;
- regions of occurrence of the incidents (Worldwide / Europe / Local Countries) ;
- years of sales;
- sale volumes per year;
- surface (smooth or textured) of the BIs.

Prior to the next QSMR on the 11th November 2015, Allergan will convene a cross-functional Signal Detection Panel meeting on the 2nd October 2015 and all breakouts and trending requested by ANSM will be presented and reviewed. During the Signal Detection Panel meeting, Allergan will assess signal detection reports and monitor trends, disposition findings for further investigation, and ensure that identified signals feed into a defined escalation process, based on signal priority.

Furthermore, this will include but not be limited to the following:

Prevalence/ Cohort Trending

- Regional breakouts (Worldwide versus EU versus France)
- Adverse Events Cohort Rates (for specific adverse events as opposed to aggregating across all events) for
 - Top 5 adverse events by event count as indicated by Pareto charting, plus
 - All high severity events (S = 9 and 10)
- Smooth versus Biocell textured versus Microcell textured breast implants.

Aggregate Rate Trending for Short versus Long-Term Events

- Aggregate Rates with the appropriate long-term versus short-term rate denominators
- Diagnostic slides with event counts and sales volumes

In addition, a risk management review meeting was held on the 18th September 2015 and the slides presented during the QMSR on the 12th August 2015 were reviewed. All subsequent Risk Management review meetings beyond the 18th September 2015 meeting will include slides from the Signal Detection Panel that include regional breakouts (Worldwide versus EU versus select country), smooth versus textured BI's and prevalence/cohort trending of adverse event rates against sales volumes.

At the next QSMR scheduled for the 11th November 2015, the review of the complete slide deck will include slides presented from both the Signal Detection Panel meeting on the 2nd October 2015 and from the 18th September 2015 Risk Management Review meeting.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

F_R6.1_ AGNM SOP-002 – Quality Board Review Process

In response to point 3 (control of sodium chloride residual):

1. Ref: McCabe, W., Smith, J., & Harriot, P. (2007). Operaciones unitarias en ingeniería química (7th ed.). México D.F.: Mc-Graw Hill.

In response to point 4 (sodium chloride 0.155 g):

ANSM'S COMMENTS IN THE FINAL REPORT
Acceptable response given the availability of the documents provided, regardless the assessment of those documents which is out of the scope of the inspection .
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED
D7.1 – FMEA-04653 rev 1.0
FURTHER COMMENTS BASED ON THE FINAL REPORT
None
ATTACHMENTS TO SUPPORT FURTHER COMMENTS
None

6. Complaints And Materiovigilance (Mv) Management :

6.1 Cases Issued From the Unsolicited Notification (Out Clinical Studies)

DEVIATION / REMARK DESCRIPTION	D8 – Critical
<p>The management of the individual complaints and MV cases by ALLERGAN Ltd Marlow is not satisfactory, which compromises the proper processing and notification of the serious incidents occurred in France to ANSM, regarding particularly the cases of Cancers-Lymphoma-ALCL (MDD Annex II item 3.1 , claimed ISO 13485 standard items 7.2.3, 8.2.1, B.4 and B.5, Meddev 2.1211 points 5.1.7 et 5.3), in terms of :</p> <p>1. Assessment of the gravity and causality of the incidents regarding the Bls involved, insofar :</p> <ul style="list-style-type: none"> • The <i>Incident Report Forms (IRFs)</i> issued by ALLERGAN : <ul style="list-style-type: none"> - rank those serious cases in the fields '<i>All other reportable incident</i> and '<i>No threat of public health</i>' (<i>points 3, 7, 12, 14, 15, 19,27</i>) ; - do not always take into account the conclusions of the physician notifiers and anatomopathological reports, when available, in terms of causality of some cases regarding the Bls involved (<i>point 12</i>) ; • TRACKWIDE database does not always: <ul style="list-style-type: none"> - clearly mention the seriousness (<i>point 11</i>) and causality (<i>points 20, 24</i>) of some cases regarding the Bls involved; - take into account the conclusions of the physician notifies and anatomopathological reports, when available, in terms of causality of some cases regarding the Bls involved (<i>point 12</i>) ; • ALLERGAN Ltd Marlow does not always request to notifiers : <ul style="list-style-type: none"> - for returning the Bls (in order to proceed to their analysis and expertise) and for the identification of their batch number, so that the causality of the concerned cases regarding the Bls involved cannot be assessed (<i>point 18</i>) ; - the reasons why some Bls are not returned, which compromises again the assessment of the causality of the concerned cases regarding those Bls, considering particularly that some notifiers are physicians involved in clinical trials (<i>point 26</i>) ; • The processing of cases that do not involve an ALLERGAN BI in place at the time of the diagnosis of the patient even if the BI concerned has been worn by the patient for only few months and implanted to replace an ALLERGAN BI worn for several years by this same patient, is such that ALLERGAN excludes the causality and risk assessment related to the ALLERGAN BI (<i>point 16</i>) ; <p>2. Control of the deadlines regarding the processing and notification of those cases to ANSM, insofar :</p> <ul style="list-style-type: none"> • 5 cases occurred in France, concerning patients bearing Bls manufactured by ALLERGAN, were notified by ALLERGAN Ltd Marlow to ANSM within periods ranging from more 1 month to almost 4 months after acquiring knowledge thereof, although such cases shall be notified immediately (<i>points 8, 13, 21, 28, 31</i>) ; • ALLERGAN Ltd Marlow sent an information request to its R&D team in order to assess the causality of a case, regarding the BI involved, more than 3 months after acquiring knowledge of this case, without documented Justification explaining this delay (<i>point 5</i>) ; <p>3. Traceability of input documents, output documents and records related to intermediate investigations, such as (<i>points 2, 6, 9, 10, 17, 22, 25, 30</i>) :</p> <ul style="list-style-type: none"> • acknowledgements of receipts confirming the actual dates of receipts of cases by ALLERGAN staff ; • dates when some <i>Risk assessments</i> began; • identity of the staff who led some <i>Risk assessments</i>; • conclusions of some <i>Risk assessments</i>; • responses provided to ALLERGAN requests and possible relaunch(es) sent to get answers; • responses provided by ALLERGAN Ltd Marlow to ANSM requests and written exchanges which followed; • decision taken by ALLERGAN Ltd Marlow with their rationales; • closure letter to notifiers, with their actual date of shipment and conclusions ; • written exchanges (Request form, relaunch of notifiers and responses of the notifiers by mails or letters ...) that are not attached in TRACKWIDE database; <p>4. Accuracy and consistency of the information brought in the cases documentation, insofar :</p> <ul style="list-style-type: none"> • TRACKWISE " database mentions that one case was reported to ALLERGAN on 11 March 2015, whereas this case was reported to ALLERGAN by ANSM in June 2014 (<i>point 1</i>) ; • an <i>IRF</i> issued by ALLERGAN mentions that the device will be returned to the Costa Rica facility (for analysis 	

and expertise) but the BI has not been returned by the physician to date (*point 4*) ;

- some *Risk assessments* performed by ALLERGAN are not consistent with the information brought in TRACKWISE database (*point 19*) ;
- a response provided by ALLERGAN to ANSM states that ALLERGAN cannot provide all the requested information and that investigations are ongoing, whereas (*Point 29*) :
 - no investigation has been conducted because the BI explanted was not returned for expertise and production batch records (*DHR*) have not been challenged;
 - the inspection raised that this case is closed by ALLERGAN, notwithstanding the foregoing ;

5. The production batch records (*DHR*) are never reviewed and challenged in the processing of complaints and MV cases, which excludes any assessment of the production impacts.

The rate of returns, to ALLERGAN, of the BIs related to confirmed Lymphoma-ALCL cases is approximately 17,3 % worldwide, as mentioned in a document entitled '*ALLERGAN breast implants reports of confirmed Lymphoma-ALCL returned devices rate table*', provided during the inspection and attached in *Reference 15* of this report.

The procedures *POL-003 'Complaint Handling'* (§ 6.1) and *SOP12-006 'Complaint review'* mention that the complaints and vigilance data shall be reviewed periodically. According to Marlow staff statements during the inspection, the complaints and vigilance data are reviewed monthly but those reviews are recorded and documented only if problems are identified.

ALLERGAN'S ORIGINAL RESPONSE

With respect to points 1 to 5, Allergan conducted a complete review of its procedures in response to these findings. As discussed within the response to observation D2, this includes an assessment of vigilance reporting and complaint management processes used by the staff members to ensure day-to-day workflows address the points raised by ANSM.

The following procedures form the core of the vigilance and complaint management program related specifically to the findings within this observation D8:

Procedure#	Description
POL-003	Complaint Handling
SOP12-018	Complaint Processing
DOP-054	Vigilance Reporting
SOP-026	Vigilance Reporting
DOP-03719	Management/Specialist Review

Allergan has reviewed the procedures above, against the items referenced under points 1 to 5, which focus primarily on the following areas:

- Classify reportable events appropriately within IRF's (SOP-054 and SOP-026)
- Manage the receipt of follow-up information to ensure that risk assessments and vigilance decisions are reviewed robustly on the basis of new data (DOP-054 and SOP-026)
- Clearly document, review and assess information supplied by HCP's (SOP-12-018)
- The need to clearly document each attempt to obtain device samples and make finite conclusions when it has not been possible to obtain devices (SOP12-018)
- Ensure that appropriate risk assessments are made in situations where a patient's history indicates that multiple operations have occurred with BI's from different manufacturers, including Allergan (SOP12-018)
- Ensure the dates of all actions are captured accurately within the Trackwise record and that all supporting evidence is available within the database (SOP12-018)
- Decisions that are taken concerning the management of each complaint record are documented clearly with the case Correspondence Log (SOP12-018)

- Closure letters are sent and accurately reflect the conclusions of the case investigation (SOP12-018)
- Maintain a case auditing program to ensure a high level of compliance to regulatory requirements. Ensure audit evidence is maintained for all aspects of the analysis (DOP-03719)

Allergan has already made changes to several procedures (SOP12-018, DOP-03719 and SOP-027) as detailed within the D2 response. An update to DOP-054, Vigilance Reporting is also proposed in responses D2 and D9. SOP12-018 requires further updates to address further considerations addressed in this observation, D8.

The points raised in D8 are partially covered in the responses to D2, D9 and D10. Updating SOP12-018, Complaint Processing will align the Allergan post market surveillance activities per the ANSM's expectations.

Additionally, a holistic review of medical device complaint records from the last 2 years will be conducted. Any required remediation actions determined during this review will be completed per the established procedures and reported to the ANSM, as required in the revised MV procedure. (See Corrective Action D8.2.)

ANSM'S COMMENTS IN THE FINAL REPORT

Acceptable response regarding 08 items 1 to 4, considering particularly that on 31st July 2015, ALLERGAN Ltd will have reviewed, corrected and documented all of the cases (thus including ALCL cases) and points referenced within *Annex 4* of the preliminary inspection report, taken into account the conclusions of the physician notifiers and anatomopathological reports, when available, in terms of causality of some cases regarding the BIs involved.

Unsatisfactory response regarding 08 item 5, in the absence of :

- clear commitment that the production batch records (*DHR*) shall, from now on, systematically be reviewed and challenged in the processing of each complaint and MV case;
- transmission of the updated Complaint Processing procedure *SOP12-018* stating that the processing of each complaint and MV case (not limited to cancers, cancer-breast, lymphoma and ALCL cases), when the batch number or serial number of the medical device involved is known, shall include a systematic review of the *DHR* (see R2 Major).

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

D8.1 – Case Plan Review_Annex IV

FURTHER COMMENTS BASED ON THE FINAL REPORT

As noted in response R2, Allergan plans to implement a risk-based approach to batch record review. Until this implementation is complete, the company plans to conduct batch record review of all complaints when a serial or lot number is known.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

Refer to R2

DEVIATION / REMARK DESCRIPTION	R8 – Other						
The periodic reviews of the complaints and vigilance data should be systematically recorded and documented, in order to trace and certify their effective realization.							
ALLERGAN'S ORIGINAL RESPONSE							
<p>This response is associated with the D2 response. Periodic reviews of the complaints and vigilance data are covered by the monthly case auditing programme. Complaints and vigilance data are analysed during monthly Marlow Operational Management Review (OMR) and quarterly Quality System Management Review (QSMR).</p> <p>For the audit programme, the two procedures outlining the monthly auditing program (DOP-03719 and SOP-027) have been updated to focus on the critical areas within the complaint management system including:</p> <ul style="list-style-type: none"> • Confirming that vigilance decisions been determined correctly by Product Surveillance Analysts and that vigilance report submissions been made to National Competent Authorities (NCA's) within the time frames specified within MEDDEV 2.12-1 and/or Member State national law • Confirming that the due diligence follow-ups have been conducted and are correctly documented within the Trackwise records • If an NCA has requested further information following the submission of a vigilance report, confirming that all questions have been answered within the deadline set by the regulator or otherwise in accordance with applicable regulations or internal procedures. <p>Copies of the two revised procedures are provided as attachments in D2.</p> <p>Training on all the updated procedures identified above has been assigned and completed through the Allergan Learning Management System (LMS).</p> <p>The procedures covering the management review process are as follows:</p> <table border="1"> <thead> <tr> <th>Procedure #</th> <th>Description</th> </tr> </thead> <tbody> <tr> <td>SOP-02907</td> <td>Marlow Operations Management Review</td> </tr> <tr> <td>AGNM- SOP-010</td> <td>Quality System Management Review (QSMR)</td> </tr> </tbody> </table> <p>Vigilance data is reviewed on a monthly basis during the Marlow Operational Management review and Corporate Quality System Management Review (QSMR). Vigilance metrics are discussed and actions captured within meeting minutes.</p>		Procedure #	Description	SOP-02907	Marlow Operations Management Review	AGNM- SOP-010	Quality System Management Review (QSMR)
Procedure #	Description						
SOP-02907	Marlow Operations Management Review						
AGNM- SOP-010	Quality System Management Review (QSMR)						
ANSM'S COMMENTS IN THE FINAL REPORT							
<p>Acceptable response. It is reminded that the periodic reviews of the complaints and vigilance data should be systematically recorded and documented, even in the cases where no problem is identified.</p>							
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED							
None							
FURTHER COMMENTS BASED ON THE FINAL REPORT							
None							
ATTACHMENTS TO SUPPORT FURTHER COMMENTS							
None							

7. Responses To ANSM Requests

DEVIATION / REMARK DESCRIPTION	D10 – Major
<p>The quality and deadlines of the responses provided by ALLERGAN Ltd Marlow to ANSM requests are not always satisfactory (MDD Annex II items 3.1), insofar :</p> <p>1. An ANSM request sent to ALLERGAN. on 2nd February 2015, for providing an incident report (<i>IRF</i>) within 60 days, remains unanswered to date (<i>point 23</i>) ;</p> <p>2. A response provided by ALLERGAN to another ANSM request states that ALLERGAN cannot provide all the requested information and that investigations are ongoing. whereas (<i>point 29</i>) :</p> <ul style="list-style-type: none"> • no investigation has been conducted because the BI explained was not returned for expertise and production batch records (DHR) have not been challenged; • the inspection raised that this case is closed by ALLERGAN, notwithstanding the foregoing 	
ALLERGAN'S ORIGINAL RESPONSE	
<p>In response to point 1, the quality and responsiveness of the complaint handling and management process has been assessed as part of Allergan's holistic evaluation of these procedures as described in the response and corrective actions under observation D2.</p> <p>In response to point 2, All of the legacy ANSM cases referenced within Annex 4 of ANSM report MV-Allergan-have been reviewed for by dedicated Analysts within global Product Surveillance team.</p> <p>In response to the ANSM's findings, a final review of the Annex 4 cases will be undertaken. Any corrections will be completed per the ANSM guidance provided below:-</p> <ul style="list-style-type: none"> • The classification of the case from a vigilance perspective and type of vigilance report that was submitted. Some cases will need reclassification and the submission of an amended vigilance report; • The due diligence follow-up for case details and whether a sample device has been returned and analysed; • The pathology reports that may have been received from the HCP ad whether these have been appropriately documented within the case; and • The closure of the case and whether the final conclusions have been communicated to the customer (See Corrective Action D10.1). 	
ANSM'S COMMENTS IN THE FINAL REPORT	
<p>Acceptable response, considering that on 31st July 2015, ALLERGAN Ltd will have :</p> <ul style="list-style-type: none"> • reviewed, corrected and documented all of the cases and points referenced within Annex 4 of the preliminary inspection report ; • documented to ANSM the responses that remain outstanding so that, regarding 010 item 1, the incident report (<i>IRF</i>) regarding the case referenced by ALLERGAN and by ANSM (<i>point 23</i> of the preliminary inspection report) is to be sent to ANSM by 31st July 2015. 	
ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED	
D10.1 – Refer to attachment D8.1	
FURTHER COMMENTS BASED ON THE FINAL REPORT	
None	
ATTACHMENTS TO SUPPORT FURTHER COMMENTS	
None	

8.0 Systemic Review Of Experience Gained From Devices In The Post Production Phase. Post-Market Survey (PMS)

DEVIATION / REMARK DESCRIPTION	D11 – Major
<p>The global management of the post-market survey by ALLERGAN Ltd Marlow, regarding the BIs marketed in Europe, is not satisfactory, which might question the continuous compliance of those BIs with the essential requirements applicable to medical devices (MDD Annex I, Annex II item 3.1, claimed ISO 13485 standard items 7.2.3, 8.2.1, 8.4 and 8.5), insofar:</p> <ol style="list-style-type: none"> 1. The global complaints and MV data are classified by types of incidents (ruptures, capsular contractures ...) but are not broken down according to : <ul style="list-style-type: none"> • the sale volumes or numbers of BIs implanted per year, which does not allow to identify the significance and risks related to the reported cases; • the year of implantation, which does not allow to identify possible trends and drifts over time; • the surface (smooth or textured) of the BIs, which does not allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs, particularly important to update and consolidate the clinical data. 2. The <i>Risk management review summary report</i> dated September 2014 concludes that the Benefit/Risk ratio of all ALLERGAN products remains acceptable but: <ul style="list-style-type: none"> • does not include any of the above criteria in terms of sale volumes, years of implantation and BI surface (smooth or textured) ; • mentions only the best known and most common incidents, which uncovers the cases of cancer, lymphomas, ALCL and other rare incidents that ALLERGAN Ltd Marlow is however aware of. 3. The '<i>Clinical hazards list for Silicone filled implants</i>' presented during the inspection does not mention either the risks of cancer, lymphomas, ALCL. 4. ALLERGAN Ltd Marlow did not submit a complete documentation demonstrating its analysis of the cases of cancer, lymphomas and ALCL involving some of its marketed BIs, of the resulting issues, challenges and stakes that may be identified and of an investigation plan mentioning, for example: <ul style="list-style-type: none"> • the appointment of a Project Pilot ; • the different routes of investigations and the periodicities of project progress reviews; • the implementation of actions within the scope of BIs production, particularly in terms of residue controls (salt, Xylene, 04/05 short molecules, others ...) and surface topography, associated with adequate specifications, considering especially that: <ul style="list-style-type: none"> - 195 cases of ALCL are diagnosed worldwide to date on patients bearing BIs, among which 130 cases concern patients bearing BIs manufactured by ALLERGAN, with 90 cases confirmed (including 66 cases involving BIOCELL TM textured BIs) and 40 cases suspected : - 3 batches of BIs manufactured by ALLERGAN 4 may appear as a special route of investigation, insofar each of them include 2 BIs involved among the aforementioned cases, while 1 batch represents an average of only 6 BI units. 5. The risk analysis of ALLERGAN BIs does not include the risks and risk reduction measures inherent in the production (ISO 14971 item 6.2 b). 	
ALLERGAN'S ORIGINAL RESPONSE	
<p>In relation to point 1 of this observation, please note that the process is being expanded to include additional data points as part of the analysis, including yearly sales, in country data analysis, and BI surface texture. Please refer to the response and corrective actions under observation D5.</p> <p>As a general response to points 2 through 5, all of these relate to the manner in which data were analyzed, how this affected the different reports cited, and Allergan's internal quality systems management review process. Before specifically addressing each of the different numbered points, Allergan notes that prior to the changes the company is now implementing, available data were pooled and assessed on a global basis looking for overall incidence rate against the total number of units distributed historically. In this context, it becomes clearer that potential additional risks, which might have been more prominent if analyzed locally or taking into account other factors (such as number of units sold annually per country), were not characterized as significant, given the</p>	

overall posture of the clinical experience. Overall, the data continue to suggest that cancer, lymphoma and ALCL cases associated with breast implants are relatively rare occurrences. That said, the need to further enhance Allergan's processes in this entire area was recognised, including how data is collected, characterized and analyzed. This commitment is reflected in other responses provided in this document, particularly the specific steps that were outlined in Allergan's response and corrective actions under observation D5.

In addition, Allergan has formed a cross-functional team that is tasked with gaining a comprehensive understanding of ALCL data, ensuring that risks are communicated to all stakeholders, and proactively monitoring patient safety. This team is led by Medical Safety and includes members from Epidemiology, Product Development, Regulatory Affairs, Medical Affairs, and Clinical Development. To date, the group has spent most of its time reviewing the data and convening experts to determine the best diagnosis and treatment practices, in addition to gathering and assessing theories for the root cause of ALCL. Analyses of the data included evaluating rates by production year and sales year. To ensure that the impact of production materials and processes on the risk of ALCL are appropriately assessed, the team will be expanded to include Manufacturing and Quality Assurance. (See Corrective Action D11.1.)

In specific reference to the cases reported in France, a project also was initiated to review complaints from France for ALCL to gain a better understanding. This review was initiated by the internal cross-functional team, which looked specifically at the cases from France, and also data available from the RAMBI study. No root cause or common attribute was found from this review. However, the review revealed that in most cases in France, there was no antimicrobial soak of the device just prior to implantation and the surgical pocket was not washed with antibiotic solution and/or povidone-iodine prior to implantation. All of this information will be within the scope of work for the independent review to be conducted by Research Triangle Institute (RTI), described below.

Allergan also initiated a partnership with Research Triangle Institute, Inc. (RTI) to provide an independent review and epidemiological analysis. RTI's work will include an analysis of data and also providing advice on the next steps with respect to characterizing a possible causal relationship between ALCL and manufacturing, implant characteristics, patient characteristics, and surgical procedure characteristics. In addition, RTI also will be evaluating the significance of the findings of the RAMBI case study data, and also the initial review of the cases reported in France. RTI will summarize its conclusions and recommendations in a final report. (See Corrective Action D11.2.)

In response to points 2, 3, 4 and 5, the manner in which data historically have been analyzed directly relates to the risk management review summary referenced in point 2. The additional reviews that are being conducted as described in the preceding paragraph are aimed at better defining potential risk, using the data (e.g., sales volumes; surface texture). These reviews will become part of Allergan's routine data review process as described in response to observation D5, and also as described below.

In response to point 3, a full review was completed on June 12, 2015 of AMED-002 Allergan Risk Management Process For Medical Devices and Combination Products, as well as the Clinical Hazards List (CHL) and HACCP (Hazard Analysis and Critical Control Point) for the Silicone Breast Implant Products. AMED-002 will be revised to ensure risk management reviews will include the key data variables for each associated breast implant product family: sales volumes and surface texture. Furthermore, the risk management reviews will cover all reported clinical hazards and failure modes, not just the common incidents. The risk management review output will be provided to the legal manufacturer (Marlow) for Marlow's Operational Management Review. (See Corrective Action

D11.3). The Clinical Hazards List (CHL) for the Silicone Breast Implant products will be revised to include all clinical hazards known to Allergan based on peer-reviewed literature and product experience. If a new harm or hazard is identified in an FMEA (Failure Mode and Effect Analysis) that is not in the CHL, then the CHL will be updated to include and evaluate the new harm or hazard. (See Corrective Action D11.4)

In response to points 4 and 5, all of the activities described in the other sections of this response, taken together with the investigation plan that were described in this response to D11 (including the internal cross-functional team, more in-depth analysis of cases within France, and the independent assessment to be performed by RTI) all are directed at ensuring that Allergan thoroughly understands the historical performance of BIs, and has the tools established to monitor and detect signals such that case analysis is complete and comprehensive. With regards to any risk potentially introduced by the manufacturing process, the HACCP for the Silicone Breast Implants will be converted into PFMEA – 04653 (See Corrective Action D7) per AMED-003, Failure Modes and Effects Analysis (FMEA) Process. The PFMEA (Process Failure Modes and Effects Analysis) will systematically identify failure modes and their corresponding effects for each step in a particular manufacturing process (including process residuals) to aid in the identification of critical control points, (ISO 14971, sec. 6.2 b). Furthermore, the PFMEA for silicone breast implants will list any additional preventive measures and/or controls in the medical device itself or in the manufacturing process that need to be investigated to reduce risk further per (ISO 14791, sec 6.2 b). Furthermore, the verification of control measures will be implemented within the PFMEA to capture the control verification protocol, and/or test report providing the evidence of effectiveness of control measures. (See Corrective Action D11.5.)

ANSM'S COMMENTS IN THE FINAL REPORT

Responses noted, regarding:

- the committed corrective actions referenced D11 .1 to D11.5 in the response file provided ;
 - D11 item 1 second point: the implementation of a cross-functional team reviewing the post-market data including incident rates by production year and sales year, as mentioned in page 34 of the response file provided;
 - D11 item 2: the risk management reviews which will cover, from now on, all reported clinical hazards and failure modes, not just the common incidents, as mentioned in page 34 of the response file provided.
- Regarding the committed corrective action referenced D11.5 and related to HACCP and PFMEA, it is reminded that the risk analysis of ALLERGAN BIs (in the sense of ISO 14971 standard) shall be regularly updated in order to include all the output data from HACCP and PFMEA with the risks and risk reduction measures inherent in the production.

The global response is however **not satisfactory** regarding the implementation of actions within the scope of BIs production, considering the absence of response in terms of investigation on the 3 batches of BIs, each of them including 2 BIs involved among the cases of ALCL diagnosed worldwide on patients bearing BIs manufactured by ALLERGAN, while 1 batch represents an average of only 6 BI units.

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

D11.1 - 2015-07-14 ALCL Core Team Meeting Final Minutes, 2015-08-05 ALCL Core Team Meeting Final Minutes & ALCL Core Team_Project Plan_Jan 20 2014
D11.2 - Summary_of_assumptions from independent sub-contractor 01-oct-2015
D11.3 – AMED-002
D11.4 – CHL-02269
D11.5 – Refer to attachment D7.5

FURTHER COMMENTS BASED ON THE FINAL REPORT

At the outset, Allergan would like to correct the information that was previously provided to ANSM, and which relates to the three lots (1267625, 1435534, and 1511957) being incorrectly identified as having 2 ALCL cases each. Upon further review of the TrackWise database, there is only 1 ALCL case per each lot. These cases are as follows:

Lot 1267625, case
Lot 1435534, case
Lot 1511957, case

The reason for the error is the manner in which ALCL cases are managed within the TrackWise system. For each ALCL complaint, there is a main complaint record. To this main complaint record, additional information is added including sub-records (documenting such things as implant history) and also ALCL-specific information that is not part of other complaint records. Under the procedure SOP-04549, ALCL Data Collection, the Product Surveillance Analyst must link each piece of additional information to the main complaint record. If that linkage is not done correctly between the additional information record and the main complaint record, the data will appear as a unique event, as occurred for these specific three lots. This has been corrected in the system, which now accurately reflects that there are three ALCL cases (one per each lot), as noted above.

A CAPA investigation (288724) was in progress at the time of the inspection to improve reporting of adverse events for ALCL related complaints, and a CAPA plan was defined. In addition to correcting the database so that it now is accurate (July 31, 2015), SOP-04549 has been revised to more clearly describe the process for linking records. The revised SOP was released and applicable training was provided to analysts by May 26, 2015.

In relation to the three lots for which ANSM is seeking additional information, as is noted above, each of these three of these lots is associated with 1 ALCL case. This is consistent with the product experience we have obtained to date, which shows that no single released lot has had more than one ALCL case associated with it. Thus, there is no different trend or signal in each of the lots, compared to other production lots.

A review of the information relating to each finished good lot also was conducted. A brief summary of the findings for each lot is set out below.

Lot 1267625

This lot was assembled in Costa Rica in May 2006, using shells that were fabricated . Twenty seven (27) units of Style 115, 378 CC Implant (part 115-378) were released. According to the complaint record, the Device History Record (DHR) for the finished good lot was completed on September 26, 2013. As part of this response, we also reviewed the shell fabrication lots associated with the finished good lot. Five (5) gel textured biocell shell lots (348958, 358594, 358824, 359606, 361351) were manufactured in Arklow, Ireland and were used in manufacture of finished good lot 1267625. There were no reported deviations for any of these shell lots. As per the completed DHR review and product release documentation, no units were rejected during the assembly process and all 27 units met the specifications defined in the manufacturing tests and quality controls and were released accordingly.

Lot 1435534

This lot was fabricated and assembled in May 2007. Six (6) units of Style TRF (part number TRF 345) were released. As part of this response, the DHR for the finished lot was reviewed along with the shell fabrication lots associated with the finished good lot. One gel textured biocell shell lot (1431326) was used in manufacture of finished good lot 1435534. There were no reported deviations for this shell lot. As per the completed DHR review and product release documentation, no units were rejected during the assembly process and all 6 units met the specifications defined in the manufacturing tests and quality controls and were released accordingly.

Lot 1511957

This lot was fabricated and assembled in November 2007. Six (6) units of Style 150SH (part number 27-150626) were released. Style 150 is a Double Lumen shaped Biocell texture, composed of a silicon filled outer lumen and a saline filled adjustable inner lumen. According to the complaint record, the Device History Record (DHR) for the finished good lot and shell fabrication lots were completed on December 13, 2012. Two (2) Gel Smooth Shell Bladder (inner lumen) shell lots (1498301, 1502885) and two (2) Gel Textured Biocell Shell (outer lumen) shell lots (1507551, 1508596) were used in manufacture of finished good lot 1511957. There were no reported deviations for all shell lots, with the exception of lot 1498301, Gel Smooth Shell Bladder (inner lumen). Deviation ERIR070157 was opened due to a temperature out of specification during the dipping process. The temperature excursion was at 47°C for 6 minutes out of the 35 minutes of the curing cycle for one of the six layers that compose the shell (temperature range 48-52°C, shell curing time 30-40 minutes for each layer). The documentation associated with the deviation determined that there was no impact on the product, based on a technical evaluation that was conducted (and documented in Technical Report TR-0979). This inner lumen shell is not in direct contact with the patient. As per the completed DHR review and product release documentation, no units were rejected during the assembly process and all 6 units met the specifications defined in the manufacturing tests and quality controls and were released accordingly.

ATTACHMENTS TO SUPPORT FURTHER COMMENTS

None

8. Biocompatibility And Preclinical Data

DEVIATION / REMARK DESCRIPTION	D12 – Other
<p>The biocompatibility and preclinical data presented by ALLERGAN Ltd Marlow during the inspection are not sufficient to guarantee the biocompatibility of its BIs marketed in Europe (MDD Annex I item 7.2), insofar :</p> <p>1. The '<i>Biocompatibility review of gel filled mammary implants manufactured by ALLERGAN</i>' and '<i>Gap analysis for biocompatibility assessment of ALLERGAN Medical breast products testing : An expert opinion</i>' reports, which document the <i>Cytotoxicity (ISO 10993-5)</i>, <i>Systemic toxicity (ISO 10993-11)</i>, <i>Immunotoxicity (ISO 10993-11)</i>, <i>Mutagenicity (ISO 10993-3)</i>, <i>Chronic toxicity (ISO 10993-3)</i>, <i>Carcinogenicity (ISO 10993-3)</i>, <i>Degradation products (ISO 10993-13)</i> and <i>Chemical characterization (ISO 10993-18)</i> ;</p> <ul style="list-style-type: none"> • mention that most of these preclinical trials have not been conducted on the sterilized BIs as finished products ready for sale, but on raw materials or manufacturing intermediates, which does not allow to take into account the risks associated to the manufacturing processes ; • do not provide additional preclinical data regarding the risks of cancer, lymphomas and ALCL, compared to the data mentioned in its previous reports since 2007 ; • do not assess the residues of salts and Xylene, neither short molecules such as D4, D5 etc., in the part devoted to the chemical characterization of materials. <p>2. The in vitro preclinical study on immune cells in contact with BloCELL™ texture particles does not take into account the chemical characterization of these particles.</p>	
ALLERGAN'S ORIGINAL RESPONSE	
<p>Testing on sterilized finished product</p> <p>As outlined in <i>Biocompatibility Review of Gel-Filled Mammary Implants Manufactured by Allergan</i>, BR-0001 Rev. 18, Allergan has conducted a complete battery of tests on components used in its breast implants. Although these tests were not performed on finished, sterile product, Allergan believes that the finished sterile product and its manufacturing methods are represented by the components used, which were manufactured and sterilized by the same methods as finished devices:</p> <ul style="list-style-type: none"> • For an intact device, the primary patient exposure is to the exterior of the shell and the patch. All components representative of a finished shell were tested for biocompatibility: <ul style="list-style-type: none"> ○ Sterilized shells were subjected to cytotoxicity, dermal sensitization, acute systemic toxicity, intracutaneous reactivity, pyrogenicity, mutagenicity, 90-day implantation with histopathology, chronic toxicity, carcinogenicity, haemolysis, developmental toxicity, degradation and immunotoxicity. Sub chronic toxicity testing was not performed separately but was, instead, covered by 90-day implantation and chronic toxicity testing. Toxic kinetics and chemical characterization tests were not performed on sterile shells as they were not necessary due to the fact that the materials passed all other tests. ○ Finished and sterilized saline implants, which are representative of a complete, patched silicone breast implant shell, were subjected to cytotoxicity, dermal sensitization, acute systemic toxicity, intracutaneous reactivity, pyrogenicity, mutagenicity, haemolysis, and immunotoxicity. ○ Additionally, sterile patch assemblies were subjected to sub chronic toxicity, 90-day implantation with histopathology, chronic toxicity, carcinogenicity, and immunotoxicity. This testing was representative of finished, sterile devices and also applicable to the silicone implants, as the shell and patch assembly materials and processes are identical to the silicone implants. The only difference between the saline implants and silicone implants is the use of silicone gel as a fill material, which was tested separately. 	

- In the event of a rupture, a patient could be exposed to the gel filling material. Therefore, sterilized gel filling, without the external shell preventing tissue contact, was tested for biocompatibility as a toxicological worst case as listed below:
 - Sterile gel was subjected to cytotoxicity, dermal sensitization, acute systemic toxicity, intracutaneous reactivity, pyrogenicity, sub chronic toxicity, mutagenicity, 90-day implantation, chronic toxicity, carcinogenicity, haemolysis, developmental toxicity, toxic kinetics, chemical characterization, and immunotoxicity.

All testing performed was in compliance with the standards and guidance in place at the time. Additional review of the testing against current standards indicates that testing conducted was adequate. Although finished and sterilized silicone breast implants were not tested, the testing of sterilized components described above was representative of the finished, sterilized devices, as the components tested were made using the same manufacturing process and sterilization techniques and therefore do reflect the risks from the manufacturing process. These components, representative of finished devices, were chosen based on their tissue contact, with the body being exposed to the external shell only under normal conditions and to the silicone gel in the event of rupture. As a result, further biocompatibility testing on finished devices in animals would not be warranted per ISO 10993-2, as this would not provide additional safety information. Additionally, Allergan’s breast implants and their materials of construction have a long history of safe clinical use, even when considering the observed ALCL cases. Per ISO 10993-1, the preclinical studies presented above should be evaluated in context with the safety demonstrated during clinical use, further supporting the biocompatibility of the products as determined above.

Additional preclinical data regarding risks of cancer, lymphoma, and ALCL

Allergan did not conduct additional biocompatibility testing regarding risks of cancer, lymphoma, and ALCL because there were no changes to materials or processing since the initial biocompatibility testing that would have changed the carcinogenicity results established during the previously described testing. To begin to evaluate the potential for development of lymphoma and ALCL, Allergan conducted the immune cell activation study on particles. The company will continue to add to these data by obtaining leachables and extractables from finished, sterile devices and evaluating their immune cell activation *in vitro*. (See Corrective Action D12.1.)

Chemical characterization – Xylene, Salt, and small molecules

Although salt and xylene residuals were not included as part of chemical characterization, Allergan has conducted residuals testing and provided results to ANSM. Additional salt and xylene residuals test from current production product is addressed in the response to D7. Furthermore, xylene and salt residues as well as other molecules will be evaluated in the leachable and extractable study discussed above. (See Corrective Action D12.1.)

Chemical characterization – Particles

Allergan acknowledges that the original immune cell activation study did not include chemical characterization of the particles; this was not the intent of the study. However, in the planned immune cell activation study, described above, chemical characterization will be performed on finished, sterile devices and thus will include chemical characterization of particles.

ANSM’S COMMENTS IN THE FINAL REPORT

Acceptable response given the availability of the documents provided, regardless the assessment of those documents which is out of the scope of the inspection.

ATTACHMENTS FOR EVIDENCE OF COMMITMENTS COMPLETED

None at this time

FURTHER COMMENTS BASED ON THE FINAL REPORT
None
ATTACHMENTS TO SUPPORT FURTHER COMMENTS
None

4. ANNEX 1 – LIST OF ATTACHMENTS

Deviation 1

D1.1– Associate Director Curricula, Analyst Curricula, Clinical Analyst Curricula, Training and Compliance Curricula

D1.2 – Vigilance Med Dev Training Record, Vigilance Training July_15

D1.3 – Breast Training log

D1.4 – Breast Marketing and Commercial Training, Breast Marketing and Commercial Training record

D1.5 – Reception Training Slides, Reception Training Record

D1.6 – Refer to attachment F_D1.1

F_D1.1 - Screen shot of meta data in Plateau-LMS for Vigilance and MED DEV Theory Training.

Deviation 2

D2.1 – QM-001

D2.2 – Vigilance Reporting_DOP-054, Vigilance Reporting SOP-026

D2.3 – Complaint Processing SOP12-018

F_D2.1 – SOP GRDQ-PV-W-002

F_D2.2 – 2015 PV Audit Schedule

Deviation 3

D3.1 – Complaint Handling POL-003, Complaint Processing SOP12-018 (Refer to Attachment D2.3), Vigilance Reporting SOP-026 (Refer to Attachment D2.2)

D3.2 – Training evidence for ANSM document updates

Remark 2

F_R2.1 - Schematic Process Flow - Process flow to reflect a more in-depth systematic, risk-based review and investigational methodology for all Breast Implant product family complaints

F_R2.2 - SOP12-018 - "Complaint Processing" Version 56.0 – Effective, September 30, 2015 (Refer to Attachment D2.3)

F_R2.3 - SOP12-019 - "Complaint Further Investigation" Version 25.0 – Effective, July 7, 2015

Remark 3

R3.1 - AGNM SOP-001

Deviation 4

D4.1 – SOP12-001

D4.2 – EAME-API-003, EAME-API-003_F_02, EAME-API-003_F_03

Deviation 5

D5.1 – AGNM SOP-014_Signal Detection Procedure

D5.2 – Sales Data Reconciliation Project_QPCR0051, Sales data_PRJ102544-VSR-02

F_D5.1 - Quality Plan QPCR0063

F_D5.2 – Postmarket Surveillance Procedure (AGNM SOP-012), Version 2.0

Remark 6

R6.1 – AGNM SOP-010

F_R6.1_ AGNM SOP-002 – Quality Board Review Process

Deviation 7

D7.1 – FMEA-04653 rev 1.0

Deviation 8

D8.1 – Case Plan Review_Annex IV

Deviation 10

D10.1 – Refer to attachment D8.1

Deviation 11

D11.1 - 2015-07-14 ALCL Core Team Meeting Final Minutes, 2015-08-05 ALCL Core Team Meeting Final Minutes & ALCL Core Team_Project Plan_Jan 20 2014

D11.2 - Summary_of_assumptions from independent sub-contractor draft 16 Sept

D11.3 – AMED-002

D11.4 – CHL-02269

D11.5 – Refer to attachment D7.1