CONFIDENTIAL

RESPONSES TO THE PRELIMINARY REPORT FROM ANSM FOLLOWING THE MATERIOVIGILANCE INSPECTION OF ALLERGAN LTD COMPANY IN MARLOW, UK FROM 27TH APRIL TO 1ST MAY 2015

16th June 2015

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1. INTRODUCTION

Following the inspection of Allergan Ltd in Marlow, the preliminary report referenced above was issued giving a review of the materiovigilance activities performed by Allergan as well as the changes in components and/or manufacturing processes of breast implants.

This document aims to provide a point by point response to ANSM's deviations and remarks, together with a schedule for the corrective actions.

This document also identifies a number of points in the ANSM report that need to be corrected as Allergan would like to clarify some imprecisions.

2. CORRECTIONS

Situation	Page 4/34
ANSM preliminary report	- The marketing and distribution, under its own name and brands, of breast implants, breast sizers and tissue expanders, intra-gastric rings, intra-gastric balloons, surgical scaffolds, dermal fillers, eye products
Allergan correction	- The marketing and distribution, under its own name and brands, of breast implants, breast sizers and tissue expanders, surgical scaffolds, dermal fillers, eye products
Justification	Intra-gastric rings and intra-gastric balloons, has been sold to the company APOLLO on 29 October 2013

Situation	Page 4/34
ANSM preliminary report	ALLERGAN Inc generates an annual global average turnover of about 20 billion dollars. Its global staff headcount is around 10000 employees worldwide
Allergan correction	ALLERGAN Inc generates an annual global average turnover of about . Its global staff headcount is around **30000** employees worldwide
Justification	The headcount of 10000 employees corresponds to the headcount of legacy Allergan. Due to the acquisition by Actavis, the global headcount is now around 30000

3. APPROVALS

Name	Role	Signature	Date
	Associate Director Product Surveillance, EAME		16th June 2015

4. RESPONSES

1. Quality Management System (QMS)

DEVIATION / REMARK DESCRIPTION	R1 – Other
During the inspection, the question regarding the existence of a back-up procedure for complaints and MV processing, in case of breakdown or dysfunction of TRACKWISE database, remained unanswered. ALLERGAN Ltd Marlow shall mention, in its response to this report the provisions planned in such a situation.	
RESPONSE	
There are two parts to this observation, first being Allergan's process for backup and recovery of the Trackwise system in the event of a system breakdown, and second, the process Allergan follows in the event Trackwise is offline. In respect to the Trackwise system itself, a technical agreement (14-01-01-QAD) is in place between Allergan Information Services in Irvine, California and Marlow. A copy of this agreement is provided in Attachment R1.1. This agreement describes the implementation, validation, maintenance and decommissioning of the Trackwise system. Allergan Information Services is also responsible for backup and restoration, problem management and data retention. In the event that Trackwise is not operational, procedure DOP-04526, "Trackwise Product Surveillance Instructions" section 4.1.2.1 outlines the process Allergan would follow. In short, the complaint intake would be recorded manually using a paper form, DOP-004.1 "Call In Log" (Attachment R1.3), and attached to the Trackwise system once it is operational again. A copy of the procedure is provided in Attachment R1.2.	
COMMITTED CORRECTIVE ACTION	
N/A	
SCHEDULE	
N/A	
ATTACHMENTS	
Attachment R1.1 - 14-01-01-QAD, Attachment R1.2 - DOP-04526, Attachment R1.3 - DOP-004_1	

DEVIATION / REMARK DESCRIPTION	D1 – Other

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:

1. Training, familiarization or sensitizing of the following staff :

Staff in charge of the management of complaints and MV

• 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.

Marketing and Commercial staff

• 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.

Reception staff in charge of directing the calls towards the staff in charge of the management of complaints and MV.

• 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.

2. Periodic training, familiarization or sensitizing intended to maintain the habilitations of the Aforementioned staff.

RESPONSE

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.

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:

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

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).

During the new employee orientation process, Product Surveillance staff review relevant procedures 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

Allegan'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).

COMMITTED CORRECTIVE ACTION

D1.1

Specific curricula for EU vigilance activities will be developed within LMS for Product Surveillance Associates.

D1.2

The EU Product Surveillance regulatory and vigilance training module discussed in the response above will be updated to include a review of the following EC guidance documents: -

- European Commission MEDDEV 2.7-3 – Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC.
- European Commission MEDDEV 2.12-2 – Post market Clinical follow-up studies.

The Marlow Product Surveillance Associates will be trained in the amended module. This training will be formally documented within the LMS database and will form part of mandatory curricula for this role.

D1.3

The Marlow Product Surveillance Associates will be retrained in the following areas:-

- Risks associated with Breast Implants – Classroom training will be conducted by the Marlow PS Management (with the assistance of Medical Safety and Quality Management personnel as necessary) to review the Breast Implant Clinical Hazards List and the DOP-004 Complaint Handbook Breast Implants.
- Breast Implant product training - The Marlow Product Surveillance Associates will be retrained in the current Breast Implant training module.

This training will be formally documented within the LMS database and form part of mandatory curricula for this role in the future.

D1.4

Breast Marketing & Commercial Associates – EAME Region

- Risks associated with Breast Implants – Classroom training will be conducted by the Marlow PS Management (with the assistance of Medical Safety and Quality Management personnel as necessary) to review the Breast Implant Clinical Hazards List and the DOP-004 Complaint Handbook Breast Implants.
- Principles of safety and vigilance cases – Class room training will be conducted by Marlow PS Management (with the assistance of Medical Safety and Quality Management personnel as necessary) to review Breast Implant safety and vigilance. A new training module will be developed for the purposes of this training.
- Identification of the Allergan Product Surveillance team – Identification of the Marlow Product Surveillance team will be included in the new training module discussed above to include the methods of contacting the department.

This training will be formally documented within the LMS database and form part of mandatory curricula for this role.

D1.5

Reception Associates - Marlow

- Risks associated with Breast Implants – Class room training will be conducted by the Marlow PS Management (with the assistance of Medical Safety and Quality Management personnel as necessary) to review the Breast Implant Clinical Hazards List and the DOP-004 Complaint Handbook Breast Implants.
- Principles of safety and vigilance cases – Classroom training will be conducted by the Marlow PS Management (with the assistance of Medical Safety and Quality Management personnel as necessary) to review Breast Implant safety and vigilance. A new training module will be developed for the purposes of this training.
- Identification of the Allergan Product Surveillance team – Identification of the Marlow Product Surveillance team will be included in the new training module discussed above to include the methods of contacting the department.

This training will be formally documented within the LMS database and form part of mandatory curricula for this role.

D1.6

All the training modules discussed above will be retrained annually to all affected Associates. The Allergan LMS will be utilised to trigger the retraining activities. The curricula with specify retraining frequency requirements. All of the executed training exercises will be recorded in LMS.

D1.7

To complete review of global complaint intake training for device and drug/biologic products across all markets.

SCHEDULE

D1.1– 31st July 2015
D1.2 – 31st July 2015
D1.3 – 31st August 2015
D1.4 – 30th September 2015
D1.5 – 31st August 2015
D1.6 – 30th September 2015
D1.7 – 31st December 2015

ATTACHMENTS
Attachment D1.1 – EU Product Surveillance associate training list for training conducted on the 12th May 2015. Attachment D1.2 - GSE-SIMR-P-001

DEVIATION / REMARK DESCRIPTION	D2 – Other

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 :

1. Regarding the internal activities:

a) Identification of safety and MV cases associated with complaints;

b) Management of the individual MV cases in terms of :

• 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 (CAPAslFSCAs) implemented;

c) Management of the grouped MV cases within the post-market survey (PMS) in terms of :

• 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) ;

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.

RESPONSE

With respect to Audits and MV management activities, these are covered within two processes;

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.

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).

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:

- 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.

COMMITTED CORRECTIVE ACTION

D2.1
QM-001 will be updated to include MV activities in the Quality System elements list in Annex 2.

D2.2
Procedure DOP-054, Vigilance Reporting, will be updated in order to provide Product Surveillance Analysts with clearer guidance when making vigilance determinations. The update of this procedure will also cover the points raised in the response section above.

D2.3
Procedure SOP12-018, Complaint Handling, will be updated to cover the points raised in the response section.

SCHEDULE
D2.1 – 31st July 2015 D2.2 – 31st July 2015 D2.3 – 31st July 2015
ATTACHMENTS
Attachment D2.1 – DOP-03719 Attachment D2.2 – SOP-027

DEVIATION / REMARK DESCRIPTION	D3 – Other

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 (MOD Annex II item 3.1) insofar:

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.

RESPONSE

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;

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

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.

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.

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).

COMMITTED CORRECTIVE ACTION

D3.1
Procedures POL-003, Complaint Handling, procedure SOP-026, Vigilance Reporting will be updated in order to allow for compatibility with the timelines specified in MEDDEV 2.12-1

D3.2
To develop a triage procedure to be applied at time of case intake that escalates complaints requiring immediate action and aligns with POL-003 and SOP-026.

SCHEDULE

D3.1 - 31st July 2015
D3.2 - 31st July 2015

ATTACHMENTS
None

DEVIATION / REMARK DESCRIPTION	R2 – Major
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 Bls 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.	
RESPONSE	
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. 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.) 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).	
COMMITTED CORRECTIVE ACTION	
N/A	
SCHEDULE	
Complete	
ATTACHMENTS	
Refer to Attachment D2.1	

DEVIATION / REMARK DESCRIPTION	R3 – Other

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 :

• 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).

RESPONSE

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).

COMMITTED CORRECTIVE ACTION

R3.1

The AGNM SOP-001 Corrective and Preventive Action (CAPA) and SOP12-001 Field Corrective Action procedures will be revised to incorporate MEDDEV 2.12/1 point 5.4.4 and Annex II item 3.1 and item 4.4 of the MDD.

SCHEDULE

31st July 2015

ATTACHMENTS

N/A

DEVIATION / REMARK DESCRIPTION	D4 – Other

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)

RESPONSE

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

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.

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.

COMMITTED CORRECTIVE ACTION

D4.1
SOP12-001 Field Corrective Action will be updated to refer to EAME-API-003 for recalls conducted in Europe, Africa & Middle East.

D4.2
EAME-API-003 will be updated to include reporting timelines for serious incidents to European Authorities as per MDD Annex II 3.1

SCHEDULE

D4.1 - 31st July 2015
D4.2 – 31st July 2015

ATTACHMENTS

Attachment D4.1 – EAME-API-003

DEVIATION / REMARK DESCRIPTION	R4 – Other

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 :

- 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).

RESPONSE

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

- 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

The above can be verified by reviewing Attachment D4.1.

The procedure will be updated to include additional detail related to the documentation associated with any recall. See Corrective Action R4.1.

COMMITTED CORRECTIVE ACTION

R4.1

SOP EAME-API-003 'EAME API Recall Implementation' will be updated to include wording to reflect that a full reconciliation must always take place covering all applicable aspects of distribution such as Quantity manufactured, Quantity shipped, stock in warehouse, samples, returns and destroyed.

SCHEDULE

R4.1 - 31st July 2015

ATTACHMENTS

Refer to attachment D4.1

DEVIATION / REMARK DESCRIPTION	D5 – Other

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 Bls, 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 :

- regions of occurrence of the incidents (Worldwide / Europe / local countries) ;
- sale volumes or numbers of Bls 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 Bls, which does not allow the inter-comparison of the Benefit/Risk ratio of the textured Bls versus smooth Bls, particularly important to update and consolidate the clinical data.

RESPONSE

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.

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.

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.

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 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.

COMMITTED CORRECTIVE ACTION

D5.1

Implement signal detection SOP along with a collection of signal detection reports.

(a) The SOP will consist of a standing Signal Detection Panel that will meet on a quarterly basis. Specific reports with identified triggers and prioritized signals will be reviewed. Signals will be dispositioned for investigation and trends will be monitored. The signals will be data inputs into a defined escalation process based on signal priority and will be a data stream into the risk management process. Furthermore, the data stream will be utilized to expand the Customer feedback and Post-Market Performance Data Stream as a data input into the quality system management review (QSMR) process.

(b) Collection of signal detection reports: The signal detection system will consist of a trending application and various defined reports. The trending application will prioritize signals by risk (severity and occurrence) and "signal strength" (which will consider both the magnitude and statistical significance of the change in trend). The trending application will support signal evaluation at a worldwide level, regional level and country level. The trending application will also be supplemented with reports to ensure all required contrasts (including, but not limited to, smooth versus textured BIs) will be reviewed.

D5.2

Complete "to-country" sales data estimations from 1995 to 2007 at the catalogue (SKU) level so that sales can be consistently queried for trending, reporting and signal detection work.

SCHEDULE

D5.1 - 30th August, 2015
D5.2 – 30th August, 2015

ATTACHMENTS

N/A

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

DEVIATION / REMARK DESCRIPTION	D6 – Other
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: • 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.	
RESPONSE	
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.	
COMMITTED CORRECTIVE ACTION	
Please see corrective actions D1.1, D1.2, D1.3, D1.4, D1.5 and D1.6	
SCHEDULE	
Please see D1	
ATTACHMENTS	
None	

3. Audits

DEVIATION / REMARK DESCRIPTION	R5 – Other

ALLERGAN Ltd Marlow should tighten the frequencies of the audits of his subcontractor 'Professional Information', unless being able to justify them.

RESPONSE

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.

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.)

COMMITTED CORRECTIVE ACTION

R5.1
Complete audit of PI according to 2015 audit schedule
R5.2
Complete annual planning for 2016 schedule based on ongoing data review and risk based factors

SCHEDULE

R5.1 – 31st December 2015
R5.2 – 31st December 2015

ATTACHMENTS

Attachment R5.1 - GRDQ audit plan for 2015
Attachment R5.2 - MI-W-016-UK-IE
Attachment R5.3 - Medical Information Quality Assessment Form

4. Management reviews

DEVIATION / REMARK DESCRIPTION	R6 – Other
The management reviews should develop the *PMS* 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).	
RESPONSE	
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.) 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.	
COMMITTED CORRECTIVE ACTION	
R6.1 AGNM SOP-010 – Quality System Management Review, Revision 2 will be revised to expand the Customer feedback and Post-Market Performance Data Stream.	
SCHEDULE	
R6.1 – 30th August 2015	
ATTACHMENTS	
N/A	

5. Resumption of the breast implants production by ALLERGAN Costa Rica site and review of potential production variations since them

DEVIATION / REMARK DESCRIPTION	D7 – Major
ALLERGAN Ltd Marlow, as the legal manufacturer of Bls marketed in Europe, does not take all the necessary actions to keep under control the residues that may be contained in those Bls, which may compromise their biocompatibility and consequently their compliance with the essential requirements applicable to medical devices (MDD Annex I item 7.2, Annex II items 3.2 band 3.2 e), insofar: 1. The water temperature, during the soaking step of the Bls integrated to the texturation, is never reported in the batch records *(DHR) ;* 2. The control of the manufactured Bls is limited to a visual inspection and some control points, the results of which may impact the safety of the Bls, are neither integrated in the validation records of the manufacturing processes, nor in routine production control, particularly regarding the controls of : • *Xylene* residues, in accordance to specifications that should be established ; • *Surface topography,* in accordance to specifications which should also be established. 3. The control of texturing *salt residues* after the soaking step, within justified and documented limits, is not evidenced in a validation file regarding the microtextured Bls (MICROCELL TN) ; 4. The control of texturing *salt residues* after the soaking step, regarding the textured Bls (BIOCELL 1M), is subjected to a validation file which mentions a biocompatible acceptance threshold of 0,155 g *NaCl* residues, but the devices used as reference in this validation are re-usable gauzes impregnated with *NaCl,* without demonstration of the relevance of this reference of devices versus Bls which are Class III devices intended to be implanted for several years.	
RESPONSE	
In response to point 1 (water temperature during soaking): In response to point 2 (control of xylene residuals and surface topography):	

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):

COMMITTED CORRECTIVE ACTION [JUST FORMAT AND ALIGN AS OTHERS]

D7.1

Water Temperature during soaking: Update router and work instructions to record soak tank water temperature.

D7.2

Controls of xylene residuals:

Perform xylene residual analysis and incorporate xylene residual monitoring for every dispersion lot and evaluate routine monitoring frequency after a year.

D7.3

As a short term corrective action, establish an alert limit on xylene residuals based on historical data analysis

D7.4

Assess existing xylene specifications after significant body of data is collected from xylene monitoring program and as applicable apply new specification limits

D7.5

Complete the pFMEA 04653 in accordance with AMED 002 and any additional control measures will be implemented as the results from the pFMEA's outcome.

D7.6

Surface topography: Implement a monitoring process for pore size, pore depth, and pore density and establish process control limits using the data from TR-1103, Characterization of Surface Morphology: BIOCELL Gel-filled Breast Implants and Tissue Expanders to gain additional information on these characteristics

D7.7

As a short term corrective action, based on the data from the monitoring program of surface topographgy (Corrective action D7.6), evaluate and determine if an internal alert limit can be established.

D7.8
Assess all data collected from the monitoring program and all data from current surface morphology processes and the determine what additional controls and specifications can be applied.

D7.9
Control of texturing sodium chloride residual: Perform an evaluation to demonstrate that the NaCl residue is <0.155 g / Shell for the texturing application process after soaking.

SCHEDULE

D7.1 - 31st December 2015
D7.2 - 31st Decemeber 2015
D7.3 – 31st December 2015
D7.4 – 30th June 2015
D7.5 - 30th June 2015
D7.6 - 31st December 2015
D7.7 - 30th June 2015
D7.8 - 31st December 2015
D7.9 - 30th June 2015

ATTACHMENTS

Attachment D7.1 - Residual Salt Risk Memo_BI and TE_Jan2015

DEVIATION / REMARK DESCRIPTION	R7 – Other

ALLERGAN Ltd Marlow should take all the necessary actions to ensure a consistent and homogenous traceability of the production operations reported in all the batch records, insofar some of the reviewed batch records do not report :

- the *Dispersion mixing step* (batch records # *1408999,* # *1420443,* # 1468911, # *1530070,* # *17709511)* ;
- The reference of the salt (that shall be *200,024)* used for the texturation (batch record # *17709511).*

RESPONSE

In response to this observation, Allergan reviewed the batch records associated with the lots cited.

With respect to the Dispersion mixing step, Silicone Shells (envelopes) for batch records # 1408999, # 1420443, # 1468911, # 1530070, # 1770958 were manufactured in Arklow, Ireland, during 2007 and 2008. The effective procedure at that time (MP057 Preparation of Dispersions), required recording of the dispersion mixing step in form FRM143 (Barrier, Balloon or Standard Dispersion Mixing Record). With the closure of Arklow, executed manufacturing records were transferred from Arklow to Santa Barbara and then to Irvine. At the time of the inspection, the specific records documenting the dispersion mixing step were not located, because FRM143 documents were archived in a different location than batch records. The search has been broaded to additional locations to trace these records, but to date they have not been recovered.

For all manufacturing conducted at the Costa Rica facility since product transfer in 2007, the completed form FRM 143 documenting the dispersion mixing step has been included in the batch record. Please note that all of the batch records from the Costa Rica shell fabrication process which were presented during the inspection included the completed Form FRM143 documenting the

dispersion mixing step. In respect to the identification of the salt used in the texturization step, batch record 1770958, used silicone shell lot 1678800. The reference for the salt (part number 200024, and lot number 120002212) used as part of the process is recorded on the Dip Run Report in attachment R7.2. A copy of the assembly batch record is also provided in attachment R7.1.
COMMITTED CORRECTIVE ACTION
N/A
SCHEDULE
N/A
ATTACHMENTS
Attachment R7.1 - Assembly DHR Report Attachment R7.2 - Dip Run DHR report

6. Complaints And Materiovigilance (Mv) Management :

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

DEVIATION / REMARK DESCRIPTION	D8 – Critical

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 :

1. Assessment of the gravity and causality of the incidents regarding the Bls involved, insofar :

• The *Incident Report Forms (IRFs)* issued by ALLERGAN :

- rank those serious cases in the fields *'All other reportable incident* and *'No threat* of *public health' (points* 3, 7, 12, 14, 15, 19,27) ;
- 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 *(point* 12) ;

• TRACKWIDE database does not always:

- clearly mention the seriousness *(point* 11) and causality *(points 20,* 24) of some cases regarding the Bls involved;
- take into account the conclusions of the physician notifies and anafomopathological reports, when available, in terms of causality of some cases regarding the Bls involved *(point* 12) ;

• ALLERGAN Ltd Marlow does not always request to notifiers :

- 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 *(point* 18) ;
- 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 *(point* 26) ;

• 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 th is same patient, is such that ALLERGAN excludes the causality and risk assessment related to the ALLERGAN BI *(point* 16) ;

2. Control of the deadlines regarding the processing and notification of those cases to ANSM, insofar :

• 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 *(points 8, 13, 21, 28, 31)* ;

• 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 *(point* 5) ;

3. Traceability of input documents, output documents and records related to intermediate investigations, such as *(points* 2, 6, 9, *10,* 17, 22, 25, *30)* :

• acknowledgements of receipts confirming the actual dates of receipts of cases by ALLERGAN staff ;
• dates when some *Risk assessments* began;
• identity of the staff who led some *Risk assessments;*
• conclusions of some *Risk assessments;*
• responses provided to ALLERGAN requests and possible relaunche(s) 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;

4. Accuracy and consistency of the information brought in the cases documentation, insofar:

• 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 *(point* 1) ;
• an *IRF* 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.

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.)

COMMITTED CORRECTIVE ACTION

D8.1
Update SOP12-018, Complaint Processing to cover points raised in D8. See also D1.3.

D8.2
Conduct holistic assessment of medical device complaint records from the last 2 years and complete required remediation per updated MV procedures, if needed.

SCHEDULE

D8.1 – 31st July 2015
D8.2 – 31st December 2015

ATTACHMENTS

N/A

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.	
RESPONSE	
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). 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: • 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 two revised procedures are provided as attachments in D2. Training on all the updated procedures identified above has been assigned and completed through the Allergan Learning Management System (LMS). The procedures covering the management review process are as follows: **Procedure #** | **Description** SOP-02907 | Marlow Operations Management Review AGNM- SOP-010 | Quality System Management Review (QSMR) 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.	
COMMITTED CORRECTIVE ACTION	
None	
SCHEDULE	
N/A	
ATTACHMENTS	
N/A	

6.3 Cases Issued From The Solicited Notification (Within Clinical Studies)

DEVIATION / REMARK DESCRIPTION	D9 – Critical
ALLERGAN Ltd Marlow did not report, to the Spanish competent authority. the *Breast cancer* case identified in Spain in *RANBI* clinical study (MDD Annex II item 3.1).	
RESPONSE	
The RANBI study was a retrospective multi-centre, post-marketing study to evaluate the incidence and aetiology of reoperations with Natrelle Breast Implants in primary augmentation. The case concerned was Trackwise reference which was first notified to Allergan on 1st August 2014. The patient ID was 0145 and the case originated from Madrid, Spain. The date of primary bilateral breast augmentation was 29th June 2007. The date of reoperation was 28th May 2011. The reason for implant removal was indicated as breast cancer. The doctor completing the case notes indicated that no adverse effects had occurred. The case was reviewed for potential vigilance reporting to the Spanish National Competent Authority (NCA) by a Marlow Product Surveillance Analyst. A determination was made by the Analyst not to report the case to the NCA. This case has now been reopened in Trackwise and been reported to the Spanish competent authority on 15th June 2015. (See attachment D9.1.) By making amendments to DOP-054, we will mandate that cancer and lymphoma cases are reported to EU regulators (See Corrective Action D9.1.) Since the beginning of 2015 the clinical study adverse event reconciliation process has been revised for all device clinical studies. Reconciliation activities have been transferred to a dedicated Clinical Product Surveillance team in Austin, Texas. The results of the study reconciliation reviews are sent to the Marlow Product Surveillance management team daily. New and updated adverse events detailed in the reconciliation notifications from Austin, Texas are assessed daily for potential vigilance reporting by the Marlow management team.	
COMMITTED CORRECTIVE ACTION	
<u>D9.1</u> Procedure DOP-054, Vigilance Reporting will be reviewed and updated in order to mandate the submission of vigilance reports for specific adverse events both within standard post market surveillance activities or within clinical studies, to include cancer, cancer-breast, lymphoma and lymphoma ALCL. This granularity is not currently documented within the procedure.	
SCHEDULE	
D9.1– 31st August 2015	
ATTACHMENTS	
Attachment D9.1 - PR1162308 Vigilance Report	

7. Responses To ANSM Requests

DEVIATION / REMARK DESCRIPTION	D10 – Major
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 : 1. An ANSM request sent to ALLERGAN. on 2nd February 2015, for providing an incident report *(IRF)* within 60 days, remains unanswered to date *(point* 23) ; 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 *(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	
RESPONSE	
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. 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. 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:- • 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).	
COMMITTED CORRECTIVE ACTION	
<u>D10.1</u> All of the ANSM cases referenced within Annex 4 of ANSM report MV-Allergan- will be reviewed by the Marlow Product Surveillance team. All of the points listed by the ANSM will be corrected or an action plan for correction will be documented within the case. Any responses that remain outstanding will be documented to the ANSM.	
SCHEDULE	
D10.1 – 31st July 2015	
ATTACHMENTS	
N/A	

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

DEVIATION / REMARK DESCRIPTION	D11 – Major

The global management of the post-market survey by ALLERGAN Ltd Marlow, regarding the Bls marketed in Europe, is not satisfactory, which might question the continuous compliance of those Bls with the essential requirements applicable to medical devices (MOO Annex I, Annex II item 3.1, claimed ISO 13485 standard items 7.2.3,8.2.1,8.4 and 8.5), insofar:

1. The global complaints and MV data are classified by types of incidents (ruptures, capsular contractures ...) but are not broken down according to :

• the sale volumes or numbers of Bls 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 Bls, which does not allow the inter-comparison of the Benefit/Risk ratio of the textured Bls versus smooth Bls, particularly important to update and consolidate the clinical data.

2. The *Risk management review summary report* dated September 2014 concludes that the Benefit/Risk ratio of all ALLERGAN products remains acceptable but:

• 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 unclears the cases of cancer, lymphomas, ALCL and other rare incidents that ALLERGAN Ltd Marlow is however aware of.

3. The *'Clinical hazards list for Silicone filled implants'* 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 Bls, of the resulting issues,
challenges and stakes that may be identified and of an investigation plan mentioning, for example:

• 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 Bls production, particularly in terms of residue controls (salt, Xylene, 04/05 short molecules, others ...) and surface topography, associated with adequate specifications, considering especially that:

- 195 cases of ALCL are diagnosed worldwide to date on patients bearing Bls, among which 130 cases concern patients bearing Bls manufactured by ALLERGAN, with 90 cases confirmed (including 66 cases involving BIOCELL TM textured Bls) and 40 cases suspected :

- 3 batches of Bls manufactured by ALLERGAN 4 may appear as a special route of investigation, insofar each of them include 2 Bls involved among the aforementioned cases, while 1 batch represents an average of only 6 BI units.

5. The risk analysis of ALLERGAN Bls does not include the risks and risk reduction measures inherent in the production (ISO 14971 item 6.2 b).

RESPONSE

In relation to point 1 of this observation, please note that are 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.

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 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 g 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 it 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 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 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 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)

COMMITTED CORRECTIVE ACTION

D11.1

The assembly of 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. Furthermore, 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.

D11.2

Sub-contractor to carry out an independent review on ALCL cases which also includes an assessment of lifetime risk of ALCL associated with textured implants and a detailed strategy for analysis of data.

D11.3

AMED-002 Allergan Risk Management Process For Medical Devices and Combination Products will be revised to ensure risk management reviews will have key data variables: sales volumes, and implant texture.

D11.4

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.

D11.5

The HACCP will be converted into PFMEA – 04653 (See Corrective Action D7) per AMED-003, Failure Modes and Effects Analysis (FMEA) Process. PFMEA for the silicone breast implants per AMED-003, Failure Modes and Effects Analysis (FMEA) Process. The PFMEA will systematically identify failure modes and their corresponding effects for each step in a particular manufacturing process to aid in the identification of critical control points, (ISO 14971, sec. 6.2 b).

SCHEDULE
D11.1 - 30th September, 2015 D11.2 - 30th September , 2015 D11.3 – 30th August , 2015 D11.4 – 30th July, 2015 D11.5 – 30th July , 2015
ATTACHMENTS
N/A

8. Biocompatibility And Preclinical Data

DEVIATION / REMARK DESCRIPTION	D12 – Other

The biocompatibility and preclinical data presented by ALLERGAN Ltd Marlow during the inspection are not sufficient to guarantee the biocompatibility of its Bls marketed in Europe (MDD Annex I item 7.2), insofar :
1. The *'Biocompatibility review of gel filled mammary implants manufactured by ALLERGAN' and 'Gap analysis for biocompatibility assessment of ALLERGAN Medical breast products testing : An expert opinion'* reports, which document the *Cytotoxicity (ISO 10993-5), Systemic toxicity (ISO 10993-11), Immunotoxicity (ISO 10993-11). Mutagenicity (ISO 10993-3), Chronic toxicity (ISO 10993-3), Carcinogenicity (ISO 10993-3), Degradation products (ISO 10993-13) and Chemical characterization ISO 10993-18)* ;
• mention that most of these preclinical trials have not been conducted on the sterilized Bls 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.
2. The in vitro preclinical study on immune cells in contact with BloCELL^{TM} texture particles does not take into account the chemical characterization of these particles.

RESPONSE

Testing on sterilized finished product
As outlined in *Biocompatibility Review of Gel-Filled Mammary Implants Manufactured by Allergan*, 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:

- 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:
    - 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.

COMMITTED CORRECTIVE ACTION

D12.1

Execute Leachable and Extractables Immune Cell Activation Study, which will include, among other things, quantitation of xylene and salt residuals as well as small molecules. Furthermore, as the study will be conducted on sterile, finished devices, it will include chemical characterization of

particles.
SCHEDULE
D12.1 – 30th December 2015
ATTACHMENTS
N/A