

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

Trials and Vigilances Inspection Department

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Réf : MV-Allergan-27042015-C1-15IPV009

**PRELIMINARY INSPECTION REPORT**

<b>Company inspected</b>	<p align="center"><b>ALLERGAN Limited</b></p> <p align="center"><b>Marlow International, Parkway, Marlow</b></p> <p align="center"><b>Blucks SL7 1YL</b></p> <p align="center"><b>United Kingdom</b></p> <p align="center">Phone : +44 (0)1628 497247 Fax : +44 (0)1628 494956</p>								
<b>Activities</b>	<table border="0"> <tr> <td><input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)</td> <td><input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)</td> </tr> <tr> <td><input type="checkbox"/> Medical devices Assembler</td> <td><input type="checkbox"/> European Representative</td> </tr> <tr> <td><input type="checkbox"/> Importer</td> <td><input checked="" type="checkbox"/> Distributor</td> </tr> <tr> <td><input type="checkbox"/> Sub-Contractor</td> <td><input type="checkbox"/> Notified Body</td> </tr> </table>	<input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)	<input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)	<input type="checkbox"/> Medical devices Assembler	<input type="checkbox"/> European Representative	<input type="checkbox"/> Importer	<input checked="" type="checkbox"/> Distributor	<input type="checkbox"/> Sub-Contractor	<input type="checkbox"/> Notified Body
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<b>Date of inspection</b>	27 <sup>th</sup> April to 1 <sup>st</sup> May 2015								
<b>ANSM Inspector</b>  <b>ANSM Expert</b>									
<b>References</b>	<p>Reference of the mission : 14IPV009</p> <p>Mission letters dated 15 April 2015</p>								

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## I. ABBREVIATIONS AND DEFINITIONS

### I.1 Abbreviations

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

### I.2 Definitions

- **Serious incident** (MDD Annex II item 3.1) :  
Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health. The Manufacturers are required to notify the competent authorities of such incidents immediately on learning of them.
- **Serious deterioration in state of health** (non exhaustive list) :  
(MEDDEV 2.12-1 « *Guidelines on a Medical Devices Vigilance System* » items 3.1.2 et 5.1.1)
  - Death of a patient, user or other person ;
  - Life-threatening illness ;
  - Permanent impairment of a body function or permanent damage to a body structure ;
  - A condition necessitating medical or surgical intervention (including clinically relevant increase in the duration of a surgical procedure or a condition that requires hospitalisation or significant prolongation of existing hospitalisation) ;
  - Foetal distress, foetal death or any congenital abnormality or birth defects.

## II. GENERAL INFORMATION

### II.1 Presentation of the company and its activities

ALLERGAN Inc. is a worldwide multi-specialty health care company whose activity covers the development, production, marketing and distribution of pharmaceuticals, biologics and medical devices throughout the world. This company was acquired by the pharmaceutical group ACTAVIS on 17 March 2015.

Regarding medical devices, the activity of ALLERGAN Inc. involves :

- 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 ;
- the distribution of needles for BOTOX™, under the name and brand of the manufacturer

ALLERGAN Inc. owns several subsidiaries and facilities worldwide, including :

- Its Headquarters, located in Irvine, California, USA, which also cover the research and development activities of the company ;
- ALLERGAN Ltd, located in Marlow, United Kingdom, which is :
  - the legal manufacturer of ALLERGAN breast implants marketed in Europe insofar this subsidiary holds the EC certification of these medical devices, issued by the French notified body LNE/G-MED ;
  - the subsidiary in charge of the centralization and management of the sales, regulatory, quality and vigilances (pharmacovigilance and materiovigilance) activities covering the Europe, Africa and Middle East (EAME) region ;
- ALLERGAN subsidiary located in Austin, Texas, USA, which is in charge of the centralization and management of the sales, regulatory, quality and vigilances (pharmacovigilance and materiovigilance) activities covering the USA-Canada region ;
- ALLERGAN Medical subsidiary located La Aurora de Heredia, Costa Rica, which carries out the production operations (component preparation and assembling, sterilization, packaging and final product release) of all the breast implants (BIs) marketed by ALLERGAN throughout the world.

ALLERGAN Inc. generates an annual global average turnover of about . Its global staff headcount is around 10.000 employees worldwide. This company markets its medical devices via a network that includes sales through distributors and direct sales to hospitals and health institutions, depending the countries and regions of sales.

A summarized presentation of ALLERGAN Inc. is attached in *Reference 1* of this report.

ALLERGAN Ltd Marlow site staff headcount is of 441 employees. Regarding its vigilances activities, this regional office :

- collects and processes all the complaints and vigilances cases provided by the other local subsidiaries throughout the EAME region, sends to them the completed processing documents associated to the above cases, including the incident reports, that these subsidiaries must then communicate to the relevant local authorities ;
- processes the complaints and vigilances with a computerized database called , into which can be joined all the documents associated to the processing of each case.

ALLERGAN Ltd Marlow markets its BIs under the brands NATRELLE™ (formerly MC GHAN™), INSPIRA™, CUI™ and BRST™. The design of those medical devices is broken down according to :

- 2 types of fillers :
  - BIs pre-filled with a silicone gel (TRUFORM™), itself broken down under 5 grades of cohesivity and the shell of which is broken down under 2 types of barrier layer (INTRASHIELD™ or DRIE™) ;
  - BIs inflatable with physiological serum (*Saline filled BIs*) ;
- 2 types of profiles : round or anatomical ;
- 3 types of surfaces : smooth, textured (BIOCELL™) or micro-textured (MICROCELL™) ;
- 5 projections : Low, Low Plus, Moderate, Full or Extra Full ;
- Variable volumes from 125 ml to 800 ml.

The raw materials used by ALLERGAN (Costa Rica site) to manufacture the shell and the silicone gel of the above concerned BIs are sourced from the sole supplier located . The shell of those BIs is made of :

- *Standard layers (5 mole % Diphenyl)* manufactured with the raw material referenced *NUSIL MED-6400* by the above supplier and *P/N 200,003* by ALLERGAN ;
- *Barrier layers (15 mole % Diphenyl)* manufactured with the raw material referenced *NUSIL MED-6600* by the above supplier and *P/N 200,004* by ALLERGAN.

A simplified table of these design configurations is attached in *Annex 2* of this report and the document stating the references of the raw materials used to manufacture the shell of the BIs pre-filled with silicone gel (*NUSIL MED-6400* and *NUSIL MED-6400*) is attached in *Reference 2* of this report.

## II.2 Regulatory certifications

Within the framework of the CE marking procedures set out in article 11 of the MDD, ALLERGAN Marlow manufacturer has chosen the Annex II (*EC Declaration of conformity, Full quality assurance system*) point 3 (*Quality system*) and point 4 (*Design examination*) of this MDD to ensure the compliance of the BIs that it is marketing in the European Union, with the essential requirements of safety and health applicable to those medical devices.

The design of these medical devices is covered by the following certifications :

BIs categories	EC Design examination Certificates
Single Lumen gel filled BIs	EC Certificate n° 15176 Rev 11 of compliance with Annex II point 4 of the MDD, issued by the French notified body LNE/G-MED, valid from 7 January 2015 till 16 December 2018.
Double Lumen gel / Saline filled BIs	EC Certificate n° 15175 Rev 3 of compliance with Annex II point 4 of the MDD, issued by the French notified body LNE/G-MED, valid from 28 November 2014 till 16 December 2018.
Saline filled BIs	EC Certificate n° 15174 Rev 4 of compliance with Annex II point 4 of the MDD, issued by the French notified body LNE/G-MED, valid from 17 February 2015 till 16 December 2018.

The last re-certification audit of Marlow site conducted by the notified body LNE/G-MED was performed on 20 and 21 April 2015. This audit focused on medical devices other than those of class III.

## II.3 Normative Certifications

ALLERGAN Ltd Marlow facility is certified ISO 13485.

#### **II.4 Background of the last materiovigilance inspection**

ALLERGAN Ltd Marlow facility has not undergone a previous inspection focused on materiovigilance by ANSM.

#### **II.5 Main changes since the last inspection**

Not applicable.

#### **II.6 Main planned changes**

Not applicable.

#### **II.7 Main events of interests regarding the inspection**

##### **Year 2006 :**

- ALLERGAN Inc. acquires INAMED Company, which markets BIs under its brand MC GHAN™.
- The production of the BIs marketed by ALLERGAN Inc. is performed by :
  - ALLERGAN facility located in Arklow, Ireland, for the European market ;
  - ALLERGAN facility located in Costa Rica, for the non European market.
- The EC certification of the above BIs intended to the European market, issued by TÜV SUD notified body, is held by ALLERGAN Arklow as the legal manufacturer.

##### **Year 2007 :**

- Transfer-Resumption of the EC certification of the BIs intended to the European market from the notified body TÜV SUD to the notified body LNE/G-MED.
- ALLERGAN facility in Arklow, Ireland, still manufactures BIs intended to the European market.
- ALLERGAN Arklow requests to its notified body the approval of ALLERGAN Costa Rica manufacturing site as a contract manufacturer for the CE marked BIs and tissue expanders in back-up, considering the closure of Arklow site planned in 2009.
- ALLERGAN Arklow supports the above request by a validation program intended to demonstrate that those medical devices shall be manufactured with the same equipments and according to the same processes between Costa Rica site and Arklow site.
- ALLERGAN facility in Costa Rica still manufactures the BIs intended to the non European market and starts to manufacture BIs for the European market, as a subcontractor of ALLERGAN Arklow site approved by the notified body LNE/G-MED .

##### **Year 2008 :**

- Transfer-Resumption of the EC certification of the BIs intended to the European market from ALLERGAN Arklow to ALLERGAN Marlow (UK) as the new legal manufacturer and holder of the certification, considering the closure of Arklow site planned in 2009.
- MC GHAN™ is rebranded NATRELLE™.

##### **April 2009 :**

- Closure of Arklow site.
- ALLERGAN Costa Rica carries out the production operations (component preparation and assembling, sterilization, packaging and final product release) of all the BIs marketed by ALLERGAN throughout the world.

## **II.8 Main materiovigilance and safety data of interests regarding the inspection**

- 19 cases of *Anaplastic Large Cells Lymphoma (ALCL)* of breast diagnosed in France since 2011 on patients with BIs, among which 17 cases concern patients with BIs of ALLERGAN brands.
- 20 BIs of ALLERGAN brands, among which at least 19 textured BIs (BIOCELL™ and MICROCELL™), are involved among the 36 BIs concerned in the ALCL cases diagnosed in France on patients with BIs.
- 195 cases of ALCL diagnosed worldwide on patients with BIs, at the dates of the inspection, among which 130 cases concern patients with BIs manufactured by ALLERGAN, including :
  - 90 cases confirmed, among which 66 cases involving BIOCELL™ textured BIs ;
  - 40 cases suspected.
- Among the aforementioned cases :
  - The majority corresponds to an implantation period of time from 5 to 9.9 years ;
  - 3 batches of BIs manufactured by ALLERGAN, each of them including 2 BIs involved in these cases, are identified.

Furthermore, the preclinical and clinical data available in the technical documentation provided by ALLERGAN to its notified body mention that :

- '(...) *One of the main advantages of surface texturing of breast implants is a reduction in the incidence of capsular contracture*'<sup>1</sup> ;
- '(...) *The greater surface area of the textured implants receives a stronger tissue response, however the textured surface of these implants has an important function in helping to reduce the rates of excessive fibrous capsular contracture (...)*'<sup>2</sup> ;
- '*Solid state tumors can form in rodents in which solid materials with an excessive surface area have been implanted for long periods of time*'<sup>2</sup>.

## **II.9 Purpose and scope of the inspection**

Pursuant to article L 5313-1 of the French Public Health Code (CSP), this inspection performed from 27<sup>th</sup> April to 1<sup>st</sup> May 2015 at ALLERGAN Ltd facility in Marlow, United Kingdom, was intended to assess the compliance of the materiovigilance activities performed by this company, as set out in article 10 and Annex II section 3.1 of the MDD, insofar ALLERGAN Ltd Marlow is the legal manufacturer and holder of the EC certification of the BIs which are marketed in Europe.

This inspection was scoped on:

- The global organization and activity of this company regarding the materiovigilance of the BIs intended to the European market, particularly in France ;
- The review of changes in components and/or manufacturing processes of the textured BIs that may have occurred since 2007, considering particularly the BIs production transfer from Arklow site to the Costa Rica site realized this same year.

## **II.10 Applicable references and guidelines**

### **Mandatory references :**

MDD, particularly :

- Article 10 and Annex II section 3.1 regarding materiovigilance ;
- Article 3 and Annex I regarding the essential requirements applicable to medical devices ;
- Article 11 regarding the CE marking procedures, particularly Annex II chosen by ALLERGAN Ltd Marlow as manufacturer for its EC Certification.

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<sup>1</sup> [Additional information requested for evaluation of design dossier DD-0001 Rev 7 for inclusion of the MC GHAN™ INSPIRA™ products. Page 13/19].

<sup>2</sup> [Biocompatibility review of gel-filled mammary implants manufactured by INAMED Corp. Ref BR-001. Rev 12. Pages 6/43 and 10/43].

## Guidelines :

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

## II.11 People met during the inspection

The list of the people met during this inspection is attached in *Annex 1* of this report.

## II.12 Referenced documents (not transmitted)

- Reference 1 Summarized presentation of ALLERGAN Inc. (18 pages).
- Reference 2 Document certifying the raw materials used to manufacture the shell of the ALLERGAN breast implants pre-filled with silicone gel (*NUSIL MED-6400* and *NUSIL MED-6600*) (1 page) ;
- Reference 3 *Process Validation Master Plan for the Gel filled shell fabrication process Ref VAL-0617* (40 pages) ;
- Reference 4 *HACCP-02037 related to Dipped shells for gel filled mammary implants-CR* (9 pages) ;
- Reference 5 *HACCP-03 related to Single lumen gel breast implants and gel filled breast implant sizers international styles* (11 pages) ;
- Reference 6 *Shell fabrication transfer quality plan Ref CR-0013* (14 pages) ;
- Reference 7 Specifications of *Silicone elastomer dispersions Ref MS024* (6 pages) ;
- Reference 8 Specifications and test method for *Water Ref TM-039* (11 pages) ;
- Reference 9 Specifications of *Xylene isomers Ref MS023* (2 pages) ;
- Reference 10 *NaCl removal process Performance qualification protocol Ref VAL1032PQ.P* (18 pages) ;
- Reference 11 *Product Performance Qualification textured round shell gel filled product at global park facility, Costa Rica Ref VAL-0674* (8 pages) ;
- Reference 12 *CPR Validation Plan Ref 10447-VP-01* (17 pages) ;
- Reference 13 *CPR Test Summary Report Ref 10447-TSR-05* (27 pages) ;
- Reference 14 *CPR Validation Summary Report Ref 10447-VSR-02* (13 pages).
- Reference 15 *ALLERGAN breast implants reports of confirmed Lymphoma-ALCL returned devices rate table* (1 page) ;
- Reference 16 List of all the clinical studies initiated since January 2006, in which ALLERGAN Ltd Marlow is sponsor and/or investigator (1 page) ;

- Reference 17 Communication from ALLERGAN Ltd Marlow to its notified body (LNE/G-MED) related to the new textured NATRACELL™ reference of BIs, first CE marked in November 2011 (1 page) ;
- Reference 18 Data collection report related to *RANBI* clinical study (14 pages) ;
- Reference 19 *RANBI* clinical study list of *AEs* (14 pages) ;
- Reference 20 *Biocompatibility review of gel filled mammary implants manufactured by ALLERGAN* (70 pages) ;
- Reference 21 *Gap analysis for biocompatibility assessment of ALLERGAN Medical breast products testing : An expert opinion* (48 pages).

### **II.13 Annexes**

- Annex 1 List of people met during the inspection.
- Annex 2 Design of the BIs marketed by ALLERGAN Ltd Marlow.
- Annex 3 Findings raised along the review of the management of the competences, skills and habilitations of ALLERGAN Ltd Marlow staff involved or likely to be involved in safety and/or MV cases.
- Annex 4 Findings raised along the review of the individual complaints and MV cases realized during the inspection, regarding the Cancers-Lymphoma-ALCL cases.

### **III. OBSERVATIONS AND FINDINGS RAISED DURING THE INSPECTION**

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

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

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

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

The definitions adopted for the aforementioned levels are the following :

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

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

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

#### **III.1 Quality Management System (QMS)**

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

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

R1 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 database, remained unanswered. ALLERGAN Ltd Marlow shall mention, in its response to this report, the provisions planned in such a situation.

D1 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	Required knowledge
Staff in charge of the management of complaints and MV.	<ul style="list-style-type: none"> <li>• MV references and guidelines (MDD, European MEDDEV 2.12/1 'Guidelines on a Medical Devices Vigilance System', European MEDDEV 2.7/3 'Clinical investigations : Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC', European MEDDEV 2.12/2 'Post market clinical follow-up studies' ;</li> <li>• ALLERGAN Materiovigilance procedures ;</li> <li>• Risks associated to the medical devices marketed by ALLERGAN.</li> </ul>
<i>Marketing and Commercial staff.</i>	<ul style="list-style-type: none"> <li>• Risks associated to the medical devices marketed by ALLERGAN ;</li> <li>• Principles of identification of safety and MV cases ;</li> <li>• Identification of ALLERGAN MV staff to whom shall be passed on the cases communicated.</li> </ul>
Reception staff in charge of directing the calls towards the staff in charge of the management of complaints and MV.	<ul style="list-style-type: none"> <li>• Risks associated to the medical devices marketed by ALLERGAN ;</li> <li>• Principles of identification of safety and MV cases ;</li> <li>• Identification of ALLERGAN MV staff to whom shall be passed on the cases communicated.</li> </ul>

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

D2 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<sup>®</sup> 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/FSCAs) 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 MV cases, during the hours of closure of Marlow site.

The reporting process of the incidents occurred in France involving BIs, agreed between ALLERGAN Ltd Marlow and ANSM regarding the notification deadlines depending on the categories of incidents i.e. individual cases prone to immediate notifications and clustered cases prone to periodic notifications via the PSR, is properly reported in ALLERGAN Vigilance Reporting procedure *DOP-054*, updated on 20 April 2015.

D3 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 I.2 of this report) immediately on learning of them (MDD 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 \_\_\_\_\_ database within 5 working days of receipt, then a risk assessment shall be performed within 5 (more) working days of complaint entry into \_\_\_\_\_ 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*' as '*without any delay that could not be justified*'.

The above *POL-003* and *SOP-026* procedures shall be updated consequently.

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 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*.

R3 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).

D4 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)

R4 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).

D5 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 mention 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 13485 standard items 7.2.3, 8.2.1, 8.4 and 8.5), 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 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.

### III.2 Organization of the staff involved or likely to be involved in MV

The verification of ALLERGAN Ltd Marlow staff organization focused on :

- the staff organization chart, especially with regard to complaints and MV management ;
- the presence of an MV correspondent or responsible person and of his deputy(ies), consistent with the aforementioned organization chart ;
- the management of the competences, skills and habilitations of all of the above staff ;
- the continuity of the MV activity.

The staff organization chart is satisfactory and thus does not raise any comment.

D6 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<sup>3</sup> 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 2.7/3 '*Clinical investigations : Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC*', European MEDDEV 2.12/2 '*Post market clinical follow-up studies*') ;
- 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 whom shall be passed on the cases communicated.

Regarding the continuity of ALLERGAN Ltd Marlow MV activity, records of presence of the MV Head and his deputy were examined over the period from July till August 2014 and the first quarter 2015. This verification does not raise any simultaneous absence of these 2 persons and is therefore satisfactory.

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<sup>3</sup> This documentation shall include :

- Periodic and nominative (personal) plans for trainings (or) familiarization (or) sensitizing ;
- The nominative (personal) records evidencing such trainings (or) familiarization (or) sensitizing and the assessment of their efficiency.

### **III.3 Audits**

The planification of audits is performed every year. The last internal audit of ALLERGAN Ltd Marlow complaints management and MV activity was held in September 2014 and the next audit is planned for June 2015.

The internal audit report of September 2014 was presented during the inspection. This report is satisfactory insofar its scope covers the identification of safety and MV cases associated with complaints, the management of the individual MV cases and the management of the grouped MV cases within the post-market survey (*PMS*).

Regarding the outsourced activities carried out by the subcontractor '*Professional Information*' (in charge of receiving calls, including complaints, safety and MV cases, during the hours of closure of Marlow site), the last audit was performed in May 2009 and the next audit is planned for Quarter 3 of the year 2015.

- R5 ALLERGAN Ltd Marlow should tighten the frequencies of audits of his subcontractor '*Professional Information*', unless being able to justify them.

### **III.4 Management reviews**

Management reviews of all ALLERGAN Inc. sites are held every quarter of every year. The reports of the management reviews held in ALLERGAN Ltd Marlow on Q3 and Q4 of the year 2014 were presented during the inspection. These reports refer to the audits results, outcomes and trends of products non-compliances, complaints, MV cases and CAPAs/FSCAs, as well as the follow-up of the actions implemented further to the previous management reviews and global reviews of the QMS indicators.

- R6 The management reviews should develop the *PMS* data, stakes and challenges on the basis of complete and relevant indicators and metrics regarding the BIs (see D5 and D11 Major - item 1, in this report).

### **III.5 Resumption of the breast implants production by ALLERGAN Costa Rica site and review of potential production variations since then :**

As mentioned in Chapter II.7 of this report, while ALLERGAN Arklow (Ireland) facility was manufacturing the BIs for the European market, ALLERGAN Costa Rica facility started, during years 2007 and 2008, to manufacture BIs also intended to the European market, within the framework of a production transfer between these 2 sites and considering the closure of Arklow site in 2009.

In order to check the absence of significant potential production variations that may have occurred since then, the inspection attempted to verify :

1. The main data of the production transfer validation file ;
2. The Costa Rica production staff training records documenting the transfer of skills from Arklow production staff ;
3. Regarding the known key points related to the BIs shell manufacturing process, some of which are identified in the *HACCP* supporting the above validation file :
  - the equivalence of the equipments and manufacturing processes over the period 2007-2008, based on comparative reviews of :
    - a batch record of a textured BI (BIOCELL™) manufactured by Arklow site versus a batch record of a textured BI (BIOCELL™) manufactured by Costa Rica site ;
    - a batch record of a microtextured BI (MICROCELL™) manufactured by Arklow site versus a batch record of a microtextured BI (MICROCELL™) manufactured by Costa Rica site.

- The potential production variations that may have occurred since 2007 until the dates of this inspection, based on comparative reviews of textured BIs (BIOCELL™) batch records dating from :
  - 1<sup>st</sup> quarter of year 2007 ;
  - 2<sup>nd</sup> quarter of year 2007 ;
  - 3<sup>rd</sup> quarter of year 2007 ;
  - 4<sup>th</sup> quarter of year 2007 ;
  - 1<sup>st</sup> quarter of year 2008 ;
  - 2<sup>nd</sup> quarter of year 2008 ;
  - 3<sup>rd</sup> quarter of year 2008 ;
  - 4<sup>th</sup> quarter of year 2008 ;
  - 1<sup>st</sup> quarter of year 2009 ;
  - 2<sup>nd</sup> quarter of year 2009 ;
  - 4<sup>th</sup> quarter of year 2009 ;
  - Year 2010 ;
  - Year 2011 ;
  - Year 2012 ;
  - Year 2013 ;
  - Year 2014.

The following documents were provided to support those reviews :

1. *Process Validation Master Plan for the Gel filled shell fabrication process Ref VAL-0617*, attached in Reference 3 of this report ;
2. *HACCP-02037 related to Dipped shells for gel filled mammary implants-CR*, attached in Reference 4 of this report ;
3. *HACCP-03 related to Single lumen gel breast implants and gel filled breast implant sizers international styles*, attached in Reference 5 of this report ;
4. *Shell fabrication transfer quality plan Ref CR-0013*, attached in Reference 6 of this report ;
5. *Specifications of Silicone elastomer dispersions Ref MS024*, attached in Reference 7 of this report ;
6. *Specifications and test method for Water Ref TM-039*, attached in Reference 8 of this report ;
7. *Specifications of Xylene isomers Ref MS023*, attached in Reference 9 of this report ;
8. *NaCl removal process Performance qualification protocol Ref VAL1032PQ.P*, attached in Reference 10 of this report ;
9. *Product Performance Qualification textured round shell gel filled product at global park facility, Costa Rica Ref VAL-0674*, attached in Reference 11 of this report.

Those reviews focused on the following key points :

1. Raw materials :
  - 1.1 Standard dispersion (5 mole % Diphenyl) : NUSIL MED-6400 Ref. ALLERGAN P/N 200,003 ;
  - 1.2 Barrier dispersion (15 mole % Diphenyl) : NUSIL MED-6600 Ref. ALLERGAN P/N 200,004 ;
  - 1.3 Salt for texturation : Ref. ALLERGAN P/N 200,024.
2. Manufacturing process :
  - 2.1 Dispersion mixing ;
  - 2.2 Shell dipping ;
  - 2.3 Shell curing.
  - 2.4 Shell texturation :
    - Tack coat ;
    - Immersion in salt ;
    - Overcoating in std dispersion ;
    - Oven cure ;
    - Soaking in warm water ;
    - Scrubbing (to reveal the textured surface) ;
  - 2.5 Control of shell thickness ;
  - 2.6 Control of absence of salt residues (not mentioned in ALLERGAN validation file nor specifications) ;

- 2.7 Control of absence of Xylene residues (not mentioned in ALLERGAN validation file nor specifications) ;
- 2.8 Control of surface topography (not mentioned in ALLERGAN validation file nor specifications) ;
- 2.9 Patch vulcanization ;
- 2.10 Gel mixing ;
- 2.11 Gel curing.

The above 2.3, 2.9, 2.10, 2.11 keypoints and *Oven cure* related to 2.4, were not detailed in the batch records as there are driven via automated programs.

No abnormal changes, versus the shell raw materials, validated production process key points and production specifications, particularly regarding the shell texturation, were identified along the aforementioned comparative reviews of production batch records.

Those reviews indicate that 1 batch represents an average of only 6 BI units.

The training records of Costa Rica production staff identified along those reviews, to conduct properly the manufacturing operations following the closure of Arklow site, are all available.

However, the following finding is notified, as a result of these reviews.

#### D7 Major

ALLERGAN Ltd Marlow, as the legal manufacturer of BIs marketed in Europe, does not take all the necessary actions to keep under control the residues that may be contained in those BIs, 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 b and 3.2 e), insofar :

1. The water temperature, during the soaking step of the BIs integrated to the texturation, is never reported in the batch records (*DHR*) ;
2. The control of the manufactured BIs is limited to a visual inspection and some control points, the results of which may impact the safety of the BIs, 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 that 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 BIs (MICROCELL™) ;
4. The control of texturing *salt residues* after the soaking step, regarding the textured BIs (BIOCELL™), 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 BIs which are Class III devices intended to be implanted for several years.

R7 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, # 1770958) ;
- the reference of the salt (that shall be 200,024) used for the texturation (batch record # 1770958).

### III.6 Complaints and materiovigilance (MV) management :

#### III.6.1 Recovery of MC GHAN sales and materiovigilance data in 2006-2007

Further to the closure of Arklow site and to the transfer of the activities of complaints and MV management on Marlow site, the inspection attempted to verify the validation of the computerized complaints and MV data recovery, embedded in ALLERGAN *Complaint Processing and Reporting System (CPR)*.

The following documents were provided to support this review :

1. *CPR Validation Plan Ref 10447-VP-01*, attached in *Reference 12* of this report ;
2. *CPR Test Summary Report Ref 10447-TSR-05*, attached in *Reference 13* of this report ;
3. *CPR Validation Summary Report Ref 10447-VSR-02*, attached in *Reference 14* of this report.

This review does not raise any particular comment.

### **III.6.2 Cases issued from the unsolicited notification (out clinical studies)**

The details of the findings raised along the review of the individual complaints and MV cases realized during the inspection are mentioned in *Annex 4* of this report. Each finding mentioned in this Annex is followed by a number in italics (*point 1, point 2, point n ...*) to which the Critical Deviation D8 below refers to.

#### **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, 8.4 and 8.5, Meddev 2.12/1 points 5.1.7 et 5.3), in terms of :

1. Assessment of the gravity and causality of the incidents regarding the BIs 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 BIs involved (*point 12*) ;
  - database does not always :
    - clearly mention the seriousness (*point 11*) and causality (*points 20, 24*) of some cases regarding the BIs involved ;
    - take into account the conclusions of the physician notifiers and anatomopathological reports, when available, in terms of causality of some cases regarding the BIs involved (*point 12*) ;
  - ALLERGAN Ltd Marlow does not always request to notifiers :
    - for returning the BIs (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 BIs involved cannot be assessed (*point 18*) ;
    - the reasons why some BIs are not returned, which compromises again the assessment of the causality of the concerned cases regarding those BIs, 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 this 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 BIs 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 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 database ;
4. Accuracy and consistency of the information brought in the cases documentation, insofar :
  - TRACKWISE<sup>®</sup> 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 TRACKWIDE 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 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.

- R8 The periodic reviews of the complaints and vigilance data should be systematically recorded and documented, in order to trace and certify their effective realization.

### **III.6.3 Cases issued from the solicited notification (within clinical studies)**

A list of all the clinical studies initiated since January 2006, in which ALLERGAN Ltd Marlow is sponsor and/or investigator, was presented during the inspection. This list is attached in *Reference 16* of this report.

This list mentions 3 clinical studies, carried out in Europe and sponsored by ALLERGAN Ltd Marlow :

- 2 studies initiated in July 2012 (date of enrollment of the first patient) which are still ongoing and concern BIs with a new sugar-based texturation called NATRACELL<sup>™</sup> :
  - the first study, called *ENTICE-001*, concerns 18 patients implanted with round NATRACELL<sup>™</sup> BIs ;
  - the second study, called *ENTICE-002*, concerns 19 patients implanted with anatomical NATRACELL<sup>™</sup> BIs.
- 1 observational and multi-centre post-market study initiated in March 2014 (date of enrollment of the first patient), called *RANBI*, performed in France, Germany, Israel, Spain and United Kingdom, which is completed and concerns 201 patients implanted with BIOCELL<sup>™</sup> textured BIs.

The new textured NATRACELL™ reference of BIs was first CE marked in November 2011, as confirmed by the document communicated by ALLERGAN Ltd Marlow to its notified body (LNE/G-MED) attached in *Reference 17* of this report.

Although covered by a CE certificate issued by the notified body over the period from November 2011 to March 2013 and according to Marlow staff statements during the inspection, the textured NATRACELL™ BIs have never been marketed for commercial reasons, particularly because ALLERGAN Ltd Marlow considers that this new texture would not be challenging enough with regard to competition.

However, ALLERGAN Ltd Marlow indicated to its notified body that the patients included in *ENTICE-001* and *ENTICE-002* studies will be followed over 5 years.

The lists of all the adverse events (AEs) occurred along *ENTICE-001*, *ENTICE-002* and *RANBI* studies have been presented during the inspection. Those lists mention :

- No serious adverse event (SAE), nor explanation in *ENTICE-001* study ;
- No SAE, but 4 explanations for not serious reasons (at the request of unsatisfied patients) in *ENTICE-002* study ;
- Several AEs and SAEs recorded for 36 patients in *RANBI* study, the most frequent SAE being *capsular contracture*.

The *RANBI* data collection report and associated list of AEs are respectively attached in *References 18 and 19* of this report. The *RANBI* list of AEs mentions cases coded '*Breast cancer*' and identified in 3 patients (CRF \_\_\_\_\_), followed with BI removal, among which :

- 2 of the 3 patients were identified in France ;
- The 3<sup>rd</sup> patient was identified in Spain.

The above 2 *Breast cancer* cases identified in France were reported to ANSM.

#### 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).

### III.7 Responses to ANSM requests

The findings mentioned in *Annex 4* of this report, related to the review of the complaints and MV cases realized during the inspection, are followed by a number in italics (*point 1, point 2, point n ...*) to which the Major Deviation D10 below refers to.

#### 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 2<sup>nd</sup> 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.

### III.8 Systematic review of experience gained from devices in the post-production phase. Post-market Survey (PMS).

The verification of the systematic review of experience gained from devices in the post-production phase focused on the measures implemented by ALLERGAN Ltd Marlow to :

- Use and challenge the MV data ;
- Assess continuously the risks and Benefit/Risk ratio related to the BIs ;
- Identify trends and *corrective and preventive actions (CAPAs)* and/or *Field Safety Corrective Actions (FSCAs)* that may be appropriate.

#### D11 Major

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 :

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 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 *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 uncovers 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 BIs, 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 BIs production, particularly in terms of residue controls (salt, Xylene, D4/D5 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 BIs, among which 130 cases concern patients bearing BIs manufactured by ALLERGAN, with 90 cases confirmed (including 66 cases involving BIOCELL™ textured BIs) and 40 cases suspected :
    - 3 batches of BIs manufactured by ALLERGAN<sup>4</sup> 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).

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<sup>4</sup> Batch # 1267625 manufactured in 2006 in Costa Rica, involved in 2 confirmed cases ;

Batch # 1435534 manufactured in 2007 in Arklow, involved in 2 suspected cases ;

Batch # 1511957 manufactured in 2007 in Arklow, involved in 2 confirmed cases.

Those 6 cases did not occur in France.

### III.9 Biocompatibility and preclinical data :

Regarding the biocompatibility and preclinical data related to its BIs marketed in Europe, ALLERGAN Ltd Marlow presented, during the inspection :

- A first document entitled '*Biocompatibility review of gel filled mammary implants manufactured by ALLERGAN*', written in September 2013 and attached in *Reference 20* of this report;
- A second document entitled '*Gap analysis for biocompatibility assessment of ALLERGAN Medical breast products testing : An expert opinion*', written in February 2012 and attached in *Reference 21* of this report.

ALLERGAN Ltd Marlow also launched an in vitro preclinical study on immune cells in contact with BIOCELL™ texture particles.

D12 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 :

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 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.
2. The in vitro preclinical study on immune cells in contact with BIOCELL™ texture particles does not take into account the chemical characterization of these particles.

### III.10 Archiving

ALLERGAN Ltd Marlow retains no document in paper version. All the archived data are computerized. The management of the archiving does not raise any comment.

#### IV. IDENTIFIED RISKS

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

<b>Organization of the staff involved or likely to be involved in MV incomplete</b>		
<b>Findings</b>		<b>Classification</b>
D1 D6	<p>Management of the skills and habilitations of the staff involved or likely to be involved in MV :</p> <ul style="list-style-type: none"> <li>• incompletely described in the <i>QMS</i> (documentation system) ;</li> <li>• incomplete in practice.</li> </ul>	Other Other

<b>Efficiency of the global complaints, MV and PMS management processes insufficiently assessed</b>		
<b>Findings</b>		<b>Classification</b>
D2	Incomplete description of the audit scopes in the <i>QMS</i> (documentation system), regarding particularly the outsourced activities impacting the management of complaints and MV activities.	Other
R5	Unjustified frequencies of audits of the subcontractor in charge of receiving calls, including complaints, safety and MV cases, during the hours of closure of Marlow site.	Other
R6	Management reviews based on indicators that do not allow to point out all the issues and stakes arising from the MV data in the context of the <i>PMS</i> regarding the marketed BIs.	Other

<b>Lack of demonstration of complete and relevant controls of the manufactured BIs</b>		
<b>Findings</b>		<b>Classification</b>
D7	<ul style="list-style-type: none"> <li>• Water temperature, during the soaking step of the BIs integrated to the texturation, never reported in the <i>DHRs</i> ;</li> <li>• Controls, within specifications that should be implemented, neither demonstrated in the validation of the manufacturing processes, nor performed in routine production, regarding particularly : <ul style="list-style-type: none"> <li>- <i>Xylene residues</i> ;</li> <li>- <i>Surface topography</i> ;</li> <li>- <i>Salt residues</i> in the microtextured BIs (MICROCELL™) ;</li> </ul> </li> <li>• Controls and determination of the threshold of <i>Salt residues</i> in the textured BIs (BIOCELL™) supported by a validation file without demonstration of the relevance of the medical devices used as reference versus the BIs which are Class III devices intended to be implanted for several years.</li> </ul>	Major
R7	Lack of homogenous traceability of the production operations reported in all the batch records, regarding the <i>Dispersion mixing</i> step and the reference of the <i>salt</i> used for the texturation.	Other

<b>Management of the individual complaints and MV cases not satisfactory</b>		
<b>Findings</b>		<b>Classification</b>
D3	<p>1. In the <i>QMS</i> (documentation system) :</p> <ul style="list-style-type: none"> <li>• Deadlines related to the processing of complaints and MV cases, as mentioned in ALLERGAN procedures, incompatible with the European regulatory provisions related to the immediate notification of serious incidents to the concerned competent authorities ;</li> </ul>	Other
R2	<ul style="list-style-type: none"> <li>• Systematic review of the BI's <i>DHR</i>, while processing complaints and MV cases, not planned in the procedures.</li> </ul>	Major
D8	<p>2. In practice :</p> <ul style="list-style-type: none"> <li>• Unsatisfactory assessment of the gravity and causality of the incidents regarding the BIs involved ;</li> <li>• Unsatisfactory deadlines regarding case processing and notifications to ANSM ;</li> <li>• Incomplete traceability of input documents, output documents and records related to intermediate investigations ;</li> <li>• Lack of accuracy and consistency of the information brought in the documentation related to some cases ;</li> <li>• <i>DHRs</i> never reviewed nor challenged in the processing of complaints and MV cases, which excludes any assessment of the production impacts ;</li> </ul>	Critical
D9	<ul style="list-style-type: none"> <li>• 1 case of <i>breast cancer</i> identified in Spain within a clinical study, not reported to the Spanish competent authority.</li> </ul>	Critical

<b>Responses to ANSM not always satisfactory</b>		
<b>Findings</b>		<b>Classification</b>
D10	<ul style="list-style-type: none"> <li>• ANSM request sent to ALLERGAN on 2<sup>nd</sup> February 2015, for providing an incident report (<i>IRF</i>) within 60 days, remaining unanswered to date ;</li> <li>• A response provided to another ANSM request states that ALLERGAN cannot provide all the requested information and that investigations are ongoing, whereas no investigation has been conducted and the concerned case is closed by ALLERGAN.</li> </ul>	Major

<b>Systematic review of experience gained from devices in the post-production phase (PMS) not satisfactory</b>		
<b>Findings</b>		<b>Classification</b>
D5	<p>1. In the QMS (documentation system) :</p> <p>Absence of PMS methodology for the detection and analyses of trends of the recurring incidents with relevant indicators and metrics regarding the BIs, taking into account :</p> <ul style="list-style-type: none"> <li>• the regions of occurrence of the incidents (Worldwide / Europe / local countries) ;</li> <li>• 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 ;</li> <li>• the year of implantation, which does not allow to identify possible trends and drifts ;</li> <li>• 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.</li> </ul>	Other
D11	<p>2. In practice :</p> <ul style="list-style-type: none"> <li>• Missing information in the latest <i>Risk management review summary report</i> and <i>Clinical hazards list for Silicone filled implants</i>, regarding : <ul style="list-style-type: none"> <li>- metrics related to sale volumes, years of implantation and BI surfaces (smooth or textured) ;</li> <li>- cases of <i>cancer, lymphomas, ALCL</i> and other rare incidents that ALLERGAN Ltd Marlow is however aware of ;</li> </ul> </li> <li>• Absence of a completed documentation demonstrating : <ul style="list-style-type: none"> <li>- ALLERGAN Ltd Marlow analysis of the cases of <i>cancer, lymphomas and ALCL</i> involving some of its marketed BIs, of the resulting issues, challenges and stakes that may be identified ;</li> <li>- a plan mentioning the different routes of investigations, periodic reviews and actions within the scope of BIs production, regarding particularly the control of residues (<i>salt, Xylene, D4/D5 short molecules...</i>) and <i>surface topography</i>, associated with adequate specifications ;</li> </ul> </li> <li>• Incomplete risk analysis of the BIs regarding the production impacts.</li> </ul>	Major

<b>Incomplete biocompatibility and preclinical data regarding the BIs</b>		
<b>Findings</b>		<b>Classification</b>
D12	<ul style="list-style-type: none"> <li>• Absence of demonstration of biocompatibility and preclinical data : <ul style="list-style-type: none"> <li>- supported from tests conducted on finished sterilized BIs ready for sale, which does not demonstrate that the risks associated to the manufacturing processes are taken into account ;</li> <li>- consolidated with updated data regarding risks of <i>cancer, lymphomas and ALCL</i> ;</li> <li>- consolidated with the assessment of residues of <i>salts, Xylene, short molecules...</i></li> </ul> </li> <li>• In vitro preclinical study on immune cells in contact with BIOCELL™ texture particles not associated with a chemical characterization of these particles.</li> </ul>	Other

Batch recall process incompletely described in the <i>QMS</i> (documentation system)		
Findings		Classification
D4	No mention, in ALLERGAN Ltd Marlow documentation system, 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	Other

The above accumulated findings represent a major risk regarding the MV and safety of the BIs marketed in Europe by ALLERGAN Ltd Marlow, considering particularly that :

- the knowledge and control of residues that may be present in these medical devices are documented neither in the design data (D12), nor in production data (D7 Major) nor in the MV post-market (*PMS*) data (D11 Major) ;
- the BI's *DHRs* are never reviewed nor challenged while processing the complaint and MV cases (D8 Critical, R2 Major).

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

The inspection carried out from 27<sup>th</sup> April to 1<sup>st</sup> May 2015 at ALLERGAN Limited site located Marlow International, Parkway, in United Kingdom, allowed to collect the information related to the organization and to the activity of this company regarding materiovigilance.

This inspection raised :

- 12 deviations, among which 2 are critical and 3 are major ;
- 8 remarks, among which 1 is major.

The above accumulated findings represent a major risk regarding the materiovigilance and safety of the breast implants marketed in Europe by ALLERGAN Ltd Marlow, considering particularly that :

- the knowledge and control of residues that may be present in those medical devices are documented neither in the design data (D12), nor in production data (D7 Major) nor in the materiovigilance post-market (PMS) data (D11 Major) ;
- the breast implants history records are never reviewed nor challenged while processing the complaint and materiovigilance cases (D8 Critical, R2 Major).

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

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

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

Saint-Denis (France), 18<sup>th</sup> May 2015.

**ANSM Inspector**

References	Profiles	Shell	Fillers	Texturations
Single Lumen (SL)	<ul style="list-style-type: none"> <li>• Round</li> <li>• Anatomical</li> </ul>	<ul style="list-style-type: none"> <li>• Standard layers (5 mole % Diphenyl) NUSIL MED-6400 / ALLERGAN P/N 200,003</li> <li>• Barrier layers (15 mole % Diphenyl) NUSIL MED-6600 / ALLERGAN P/N 200,004</li> <li>- INTRASHIELD™</li> <li>or</li> <li>- DRIE™</li> </ul>	<ul style="list-style-type: none"> <li>• Silicone gel broken down broken down under 5 grades of cohesivity : <ul style="list-style-type: none"> <li>- Responsive Gel = TRUFORM™ Gel 1</li> <li>or</li> <li>- Soft Cohesive Gel = TRUFORM™ Gel 2</li> <li>or</li> <li>- Cohesive Gel = TRUFORM™ Gel 3</li> <li>or</li> <li>- Firm Cohesive Gel = TRUFORM™ Gel 4</li> <li>or</li> <li>- Dual Gel = TRUFORM™ Dual Gel</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Smooth</li> <li>• Textured      BIOCELL™</li> <li>• Microtextured      MICROCELL™</li> </ul>
Double Lumen (DL)	<ul style="list-style-type: none"> <li>• Round</li> <li>• Anatomical</li> </ul>		TRUFORM™ Silicone Gel + Serum $\phi$	<ul style="list-style-type: none"> <li>• Smooth</li> <li>• Textured      BIOCELL™</li> <li>• Microtextured      MICROCELL™</li> </ul>
Saline	<ul style="list-style-type: none"> <li>• Round</li> <li>• Anatomical</li> </ul>		Serum $\phi$	<ul style="list-style-type: none"> <li>• Smooth</li> <li>• Textured      BIOCELL™</li> <li>• Microtextured      MICROCELL™</li> </ul>

**Annex 3 Findings raised along the review of the management of the competences, skills and habilitations of the ALLERGAN Ltd Marlow staff involved or likely to be involved in safety and/or MV cases.**

Activities	Staff targeted on inspection, by sampling <sup>5</sup>	Required knowledge	Findings
Staff in charge of complaints management.	<ul style="list-style-type: none"> <li>• TWH</li> <li>• MPI</li> </ul>	Risks associated to the medical devices marketed by ALLERGAN.	Absence of nominative (personal) records attesting the assessment of the efficiency of such trainings (or) familiarization (or) sensitizing given to this staff.
MV Staff.	PDH	MV references and guidelines : <ul style="list-style-type: none"> <li>• MDD ;</li> <li>• European MEDDEV 2.12/1 '<i>Guidelines on a Medical Devices Vigilance System</i>' ;</li> <li>• European MEDDEV 2.7/3 '<i>Clinical investigations : Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC</i>' ;</li> <li>• European MEDDEV 2.12/2 '<i>Post market clinical follow-up studies</i>'.</li> </ul>	<ul style="list-style-type: none"> <li>• Absence of training (or) familiarization (or) sensitizing plan(s) regarding this person for MV references and guidelines.</li> <li>• Absence of nominative (personal) records evidencing :               <ul style="list-style-type: none"> <li>- such trainings (or) familiarization (or) sensitizing followed by this person ;</li> <li>- the assessment of their efficiency.</li> </ul> </li> </ul>
Reception staff in charge of directing the calls towards the staff in charge of the management of complaints and MV.	All the staff.	<ul style="list-style-type: none"> <li>• Principles of identification of safety and MV cases ;</li> <li>• Identification of ALLERGAN staff in charge of MV, to whom shall be passed on the cases communicated.</li> </ul>	<ul style="list-style-type: none"> <li>• Absence of trainings (or) familiarization (or) sensitizing plan(s) regarding this staff.</li> <li>• Absence of nominative (personal) records evidencing :               <ul style="list-style-type: none"> <li>- such trainings (or) familiarization (or) sensitizing followed by this staff ;</li> <li>- the assessment of their efficiency.</li> </ul> </li> </ul>

<sup>5</sup> Only an identification trigram is mentioned for reasons of confidentiality.

Case Identification ALLERGAN	Case Identification ANSM	Findings
		<ul style="list-style-type: none"> <li>• database mentions that this case was reported to ALLERGAN on 11 March 2015, whereas this case was reported to ALLERGAN by ANSM in June 2014 (Point 1).</li> <li>• No traceability of (Point 2) : <ul style="list-style-type: none"> <li>- the fax acknowledgement of receipt confirming the actual date of receipt of this case by ALLERGAN staff ;</li> <li>- the date when the <i>Risk assessment</i> began ;</li> <li>- the identity of the staff who led the <i>Risk assessment</i> ;</li> <li>- the conclusion of the <i>Risk assessment</i>.</li> </ul> </li> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN : <ul style="list-style-type: none"> <li>- ranks this serious case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' (Point 3) ;</li> <li>- 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).</li> </ul> </li> </ul>
		<ul style="list-style-type: none"> <li>• Case communicated to ALLERGAN on 26 September 2014 by an investigator in a clinical trial, but information request in order to assess the causality of the case versus the BI sent to the R&amp;D team only on 14 January 2015, without documented justification explaining this delay (Point 5).</li> <li>• No traceability of the response provided by the R&amp;D team to the above request and to traceability of the possible relaunch(es) sent to this team for answer (Point 6).</li> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN ranks this serious case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' (Point 7).</li> <li>• Case notified by ALLERGAN to ANSM on 20 January 2015, although this case received by ALLERGAN on 26 September 2014 shall be notified immediately (Point 8).</li> <li>• Following the above notification, ANSM asked ALLERGAN (early February 2015) for further information within 8 days, but no traceability of the response provided to ANSM and of the written exchanges which followed (Point 9).</li> </ul>

Case Identification ALLERGAN	Case Identification ANSM	Findings
		<ul style="list-style-type: none"> <li>• 13 December 2012 : The physician notifier sends to ALLERGAN by e-mail the filled <i>Request form</i> with an anatomopathological report which confirms the causality of the case versus the BI.</li> <li>• ALLERGAN mentions that a batch record review of the BI shall be performed but the field that corresponds to the batch record review in database mentions '<i>Cancelled</i>'.</li> <li>• 4 March 2013 : ALLERGAN sends a closure letter to the notifier.</li> <li>• No traceability of (Point 10) : <ul style="list-style-type: none"> <li>- the BI batch record review, with the date and conclusions of this review, if this review was really performed ;</li> <li>- any written decision and rationales of cancellation of this review, to support database indications ;</li> <li>- the closure letter to the notifier, with its actual date of shipment and its conclusions.</li> </ul> </li> <li>• The seriousness of this case is not clearly mentioned in database (Point 11).</li> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN (Point 12) : <ul style="list-style-type: none"> <li>- ranks this serious case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' ;</li> <li>- does not take into account the conclusions of the physician in terms of causality, insofar this report mentions, consistently with database indications, that '<i>causality cannot be determined by product analysis</i>' whereas the anatomopathological report confirms the causality of the case versus the BI.</li> </ul> </li> </ul>
		<ul style="list-style-type: none"> <li>• Case notified by ALLERGAN to ANSM on 3<sup>rd</sup> October 2012, although this case received by ALLERGAN on 24 August 2012 shall be notified immediately (Point 13).</li> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN ranks this serious case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' (Point 14).</li> </ul>
		<ul style="list-style-type: none"> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN ranks this serious case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' (Point 15).</li> <li>• The processing of the case concerning a patient who worn for only few months a BI not manufactured by ALLERGAN, but implanted to replace an ALLERGAN BI worn by this same patient for several years, is such that ALLERGAN excludes the causality and risk assessment related to the Allergan BI (Point 16).</li> </ul>

Case Identification ALLERGAN	Case Identification ANSM	Findings
		<ul style="list-style-type: none"> <li>• BI not returned and BI batch number not communicated, which does not allow to assess the causality of the case versus the BI.</li> <li>• ALLERGAN QA Manager France presented in her computer, during the inspection :               <ul style="list-style-type: none"> <li>- a <i>Request form</i> for additional information sent to the physician notifier on 19 December 2014 ;</li> <li>- The physician notifier response, dated 26 March 2015, after this latter has been relaunched by ALLERGAN on 24 March 2015.</li> </ul> </li> <li>• The above written exchanges (<i>Request form</i>, relaunch of the notifier and response of the notifier by mails or letters...) are not attached in database (Point 17).</li> <li>• The relaunch sent to the physician notifier does not mention any request for returning the BI (in order to proceed to its analysis and expertise) and for the identification of its batch number, so that the causality of the case versus the BI cannot be assessed (Point 18).</li> </ul>
		<ul style="list-style-type: none"> <li>• The <i>Incident Report Form (IRF)</i> issued by ALLERGAN ranks this case in the fields '<i>All other reportable incident</i>' and '<i>No threat of public health</i>' and the <i>Risk assessment</i> performed by ALLERGAN concludes that '<i>There is not an increased risk because the device has been exonerated by the physician's office or there is not complaint against the device</i>', whereas TRACKWIDE database mentions that this case corresponds to a serious incident (Point 19).</li> <li>• No clear conclusion regarding the <u>causality</u> of this case versus the BI, particularly in database (Point 20).</li> <li>• Decision of reportability made by ALLERGAN on 8 December 2014 but this case was notified by ALLERGAN to ANSM on 8 January 2015, although this case shall be notified immediately (Point 21).</li> </ul>
		<ul style="list-style-type: none"> <li>• 3<sup>rd</sup> January 2012 : Explanted BI returned to ALLERGAN for analysis and expertise, the results of which are still expected to date.</li> <li>• According to the discussions along the inspection, ALLERGAN staff received in April 2012 a document related to additional information with regard to the original notification, but no trace of this document was presented (Point 22).</li> <li>• ANSM asked ALLERGAN, on 2<sup>nd</sup> February 2015, to provide an incident report (<i>IRF</i>) within 60 days, but this request remains unanswered from ALLERGAN to date (Point 23).</li> </ul>
		<ul style="list-style-type: none"> <li>• No clear conclusion regarding the <u>causality</u> of this case versus the BI, particularly in database (Point 24).</li> <li>• 30 March 2015 : ANSM asked ALLERGAN for providing information on the BI specificity within 8 days and for providing the incident report (<i>IRF</i>) with the manufacturing date of the BI by 27 April 2015. ALLERGAN answered this request but the traceability of the response provided to ANSM has not been found during the inspection (Point 25).</li> </ul>

