

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

Trials and Vigilances Inspection Department

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Réf : MV-Allergan-27042015-C3-15IPV009

FINAL INSPECTION SUMMARY REPORT

Company inspected	<p style="text-align: center;">ALLERGAN Limited Marlow International, Parkway, Marlow Blucks SL7 1YL United Kingdom</p> <p style="text-align: center;">Phone : +44 (0)1628 497247 Fax : +44 (0)1628 494956</p>								
Activities	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"><input checked="" type="checkbox"/> Non OBL Manufacturer (Responsible for marketing in Europe)</td> <td style="width: 50%; border: none;"><input type="checkbox"/> OBL Manufacturer (Responsible for marketing in Europe)</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Medical devices Assembler</td> <td style="border: none;"><input type="checkbox"/> European Representative</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Importer</td> <td style="border: none;"><input checked="" type="checkbox"/> Distributor</td> </tr> <tr> <td style="border: none;"><input type="checkbox"/> Sub-Contractor</td> <td style="border: none;"><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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Date of inspection	27 th April to 1 st May 2015								
ANSM Inspector ANSM Expert									
Summary of the main stages of the inspection	Reference of the mission : 14IPV009 Mission letters dated 15 th April 2015 Date of shipment of the preliminary inspection report : 29 th May 2015. Dates of receipt of the responses from the Company : 25 th June 2015.								

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

The findings notified by the inspector in the preliminary inspection report are recalled and summarized in this final report, preceded by a number in 'D' for the deviations and a number in 'R' for the remarks.

The assessment of the responses provided by the company is preceded by the sign « → ».

The term '*satisfactory*' means that the reported response provides evidence of the implementation of appropriate corrective and/or preventive action(s).

The term '*acceptable*' means that the reported response is appropriate in principle, but in the absence of evidence submitted, the implementation of the corrective and/or preventive action(s) could be verified during a next inspection.

The term '*noted*' means that the reported response and corrective and/or preventive action(s) need to be completed or deepened.

The term '*not satisfactory*' means that the response is not adequate to provide a solution to the reported findings.

III.1 Quality Management System (QMS)

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

→ Satisfactory response.

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">• 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' ;• ALLERGAN Materiovigilance procedures ;• Risks associated to the medical devices marketed by ALLERGAN.
Marketing and Commercial staff.	<ul style="list-style-type: none">• Risks associated to the medical devices marketed by ALLERGAN ;• Principles of identification of safety and MV cases ;• Identification of ALLERGAN MV staff to whom shall be passed on the cases communicated.
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">• 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.

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

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® 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.

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

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

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

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 the preliminary inspection 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 TRACKWISE® 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*' as '*without any delay that could not be justified*'.

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

→ Acceptable response.

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*.

➔ **Unsatisfactory response**, in the absence of transmission of the updated Complaint Processing procedure *SOP12-018* stating that the processing of each complaint and/or MV case (not limited to cancers, cancer-breast, lymphoma and ALCL cases), when the batch number or serial number of the medical device involved is known, shall include a systematic review of the *DHR*.

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).

➔ Acceptable response, considering the commitment of ALLERGAN Ltd to update its *SOP-001 Corrective and Preventive Action (CAPA)* and *SOP12-001 Field Corrective Action* procedures by 31st July 2015, so that those procedures shall incorporate the appropriate references of MEDDEV 2.12/1 and Annex II of the MDD. However, an error has been noted in the wording of the second point of R3, in the preliminary inspection report : the wording '*likely to induce substantial changes to the manufacturing processes of the devices covered (MDD Annex II item 3.1)*' must be replaced by the wording '*likely to induce substantial changes to the design and/or manufacturing processes of the devices covered (MDD Annex II item 3.4)*'.

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).

➔ Acceptable response.

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).

➔ Acceptable response.

D5 The Post Market Survey (PMS) process description in ALLERGAN Ltd Marlow documentation system, related to the 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.

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

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

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

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 the preliminary inspection 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 ¹ 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.

→ Acceptable response.

¹ 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

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

- **Unsatisfactory response** : It was already noted in the preliminary inspection report that the next audit of the subcontractor '*Professional Information*' is planned for Q3 2015, but ALLERGAN Ltd Marlow does not provide, in its response file, documents describing precisely :
- the risk-based methodology used to issue the annual audit schedules, as mentioned in its response file ;
 - how is monitored this subcontractor, within this methodology (considering that the last audit of *Professional Information* was performed in May 2009).

III.4 Management reviews

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 the preliminary inspection report).

- **Unsatisfactory response**, in the absence of :
- clear commitment that the last management review conducted on June 10th 2015 integrated the trends of the reported incidents broken down by :
 - categories of incidents ;
 - regions of occurrence of the incidents (Worldwide / Europe / local countries) ;
 - years of sales ;
 - sale volumes per year ;
 - surface (smooth or textured) of the BIs.
 - communication of the stakes, challenges and conclusions issued from this management review.

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

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.

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

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).

→ Satisfactory response.

III.6 Complaints and materiovigilance (MV) management :

III.6.1 Cases issued from the unsolicited notification (out clinical studies)

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 mentioned in the preliminary inspection report) ;
 - 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 mentioned in the preliminary inspection report) ;
- TRACKWIDE database does not always :
 - clearly mention the seriousness (point 11 mentioned in the preliminary inspection report) and causality (points 20, 24 mentioned in the preliminary inspection report) 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 mentioned in the preliminary inspection report) ;
- 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 mentioned in the preliminary inspection report) ;
 - 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 mentioned in the preliminary inspection report) ;
- 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 mentioned in the preliminary inspection report) ;

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 mentioned in the preliminary inspection report) ;
- 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 mentioned in the preliminary inspection report) ;

3. Traceability of input documents, output documents and records related to intermediate investigations, such as (*points 2, 6, 9, 10, 17, 22, 25, 30 mentioned in the preliminary inspection report*) :
 - 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 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 mentioned in the preliminary inspection report*) ;
 - 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 mentioned in the preliminary inspection report*) ;
 - some *Risk assessments* performed by ALLERGAN are not consistent with the information brought in TRACKWIDE database (*point 19 mentioned in the preliminary inspection report*) ;
 - a response provided by ALLERGAN to ANSM states that ALLERGAN cannot provide all the requested information and that investigations are ongoing, whereas (*point 29 mentioned in the preliminary inspection report*) :
 - 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.

→ Acceptable response regarding D8 items 1 to 4, considering particularly that on 31st July 2015, ALLERGAN Ltd will have reviewed, corrected and documented all of the cases (thus including ALCL cases) and points referenced within *Annex 4* of the preliminary inspection report, taken into account the conclusions of the physician notifiers and anatomopathological reports, when available, in terms of causality of some cases regarding the BIs involved.

Unsatisfactory response regarding D8 item 5, in the absence of :

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

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.

→ Acceptable response. It is reminded that the periodic reviews of the complaints and vigilance data should be systematically recorded and documented, even in the cases where no problem is identified.

III.6.2 Cases issued from the solicited notification (within clinical studies)

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).

- Satisfactory response, considering that the *Breast cancer* case identified in Spain in *RANBI* clinical study has been reported to Spanish competent authority on 15th June 2015, as demonstrated in the response file provided.

III.7 Responses to ANSM requests

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 mentioned in the preliminary inspection report*) ;
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 mentioned in the preliminary inspection report*) :
 - 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.

→ Acceptable response, considering that on 31st July 2015, ALLERGAN Ltd will have :

- reviewed, corrected and documented all of the cases and points referenced within Annex 4 of the preliminary inspection report ;
- documented to ANSM the responses that remain outstanding so that, regarding D10 item 1, the incident report (*IRF*) regarding the case referenced by ALLERGAN and by ANSM (*point 23 of the preliminary inspection report*) is to be sent to ANSM by 31st July 2015.

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

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 ² 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).

→ Responses noted, regarding :

- the committed corrective actions referenced D11.1 to D11.5 in the response file provided ;
- D11 item 1 second point : the implementation of a cross-functional team reviewing the post-market data including incident rates by production year and sales year, as mentioned in page 34 of the response file provided ;
- D11 item 2 : the risk management reviews which will cover, from now on, all reported clinical hazards and failure modes, not just the common incidents, as mentioned in page 34 of the response file provided.

Regarding the committed corrective action referenced D11.5 and related to HACCP and PFMEA, it is reminded that the risk analysis of ALLERGAN BIs (in the sense of ISO 14971 standard) shall be regularly updated in order to include all the output data from HACCP and PFMEA with the risks and risk reduction measures inherent in the production.

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

² 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 :

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.

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

II. FINAL CONCLUSION

The inspection carried out from 27th April to 1st 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.

As a result of this mission :

- Some findings raised within the scope of the production and notified in the preliminary inspection report still represent a major risk regarding the MV and safety of the BIs marketed in Europe by ALLERGAN Ltd Marlow, considering that :
 - the global response to D11 Major is not satisfactory, in the absence of response related to the investigation on the 3 batches of BIs, each of them including 2 BIs involved among the cases of ALCL diagnosed worldwide on patients bearing BIs manufactured by ALLERGAN, while 1 batch represents an average of only 6 BI units ;
 - the responses to D8 item 5 and R2 Major are not satisfactory, in the absence of :
 - clear commitment that the production batch records (*DHR*) shall, from now on, systematically be reviewed and challenged in the processing of each complaint and MV case ;
 - transmission of the updated Complaint Processing procedure *SOP12-018* stating that the processing of each complaint and MV case (not limited to cancers, cancer-breast, lymphoma and ALCL cases), when the batch number or serial number of the medical device involved is known, shall include a systematic review of the *DHR*.
- The responses provided to D2 item 2, D5, R5 and R6 are also unsatisfactory.

The corrective and preventive actions proposed in response to the preliminary inspection report are not likely to reduce all the identified risks, which does not allow this company to be able to keep under control its materiovigilance activities, in compliance with the applicable regulations.

Further corrective and preventive actions should be taken as soon as possible.

Saint-Denis, 20th July 2015.

Inspecteur de l'Agence nationale de sécurité du médicament et des produits de santé