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PRELIMINARY INSPECTION REPORT

Company Inspected	**NAGOR Limited** **127/129 Deerdykes View** **Westfield Industrial Estate** **Cumbernauld, Scotland** **GLASGOW G68 9HN** **UNITED KINGDOM** **Phone : +(44) 1236 780780**
Activities	☐ Non OBL Manufacturer (Responsible for marketing in Europe) ☒ OBL Manufacturer (Responsible for marketing in Europe) ☐ Medical devices Assembler ☐ European Representative ☐ Importer ☒ Distributor ☐ Sub-Contractor ☐ Other
Date of inspection	8th to 9th December 2015.
ANSM Inspector	, Accompanied by , Regulatory Affairs Section Head of the Medicines and Healthcare products Regulatory Agency (MHRA).
References	Reference of the mission : 15IPV021. Mission letter dated 10th November 2015.

CONTENTS

I. ABBREVIATIONS AND DEFINITIONS

I.1 Abbreviations

AE	Adverse Event.
AFMPS	Agence Fédérale du Médicament et des Produits de Santé (Belgium Medicines and Healthcare products Regulatory Agency).
ALCL	Anaplastic Large Cell Lymphoma.
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French national Agency for medicines and health products safety).
BI	Breast Implant.
CAPA	Corrective Action and Preventive Action.
DHR	Device History Record.
FSCA	Field Safety Corrective Action.
MDD	Council Directive 93/42/EEC applicable to medical devices (Medical Devices Directive).
MHRA	Medicines and Healthcare products Regulatory Agency.
MV	Materiovigilance.
OBL	Own Brand Labeller (Manufacturer that markets, under its own brands, medical devices coming from other manufacturers).
OEM	Original Equipment Manufacturer (Original manufacturer of medical devices).
PMS	Post-Market Survey.
PSR	Periodic Summary Report.
QMS	Quality Management System.
SAE	Serious Adverse Event (in the framework of clinical studies).

I.2 Definitions

- **Serious incident** (MDD Annex II point 3.1) :
  Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health. The Manufacturers are required to notify the competent authorities of such incidents immediately on learning of them.

- **Serious deterioration in state of health** :
  (MEDDEV 2.12-1 « *Guidelines on a Medical Devices Vigilance System* » points 3.1.2 and 5.1.1)
  - Death of a patient, user or other person ;
  - Life-threatening illness ;
  - Permanent impairment of a body function or permanent damage to a body structure ;
  - A condition necessitating medical or surgical intervention (including clinically relevant increase in the duration of a surgical procedure or a condition that requires hospitalisation or significant prolongation of existing hospitalisation) ;
  - Foetal distress, foetal death or any congenital abnormality or birth defects.

II. GENERAL INFORMATION

II.1 Presentation of the company and its activities

NAGOR Ltd is a company founded in 1979 in the Isle of Man, to distribute silicone implants for the healthcare market. It belongs today to a Holding company, called GLOBAL CONSOLIDATED AESTHETICS or *'GC AESTHETICS'*, which is headquartered in Dublin, Ireland. This Holding company also owns two other companies, called EUROSILICONE and BIOSIL Ltd. The common activity of NAGOR Ltd, BIOSIL Ltd and EUROSILICONE covers the design, development, production, marketing and distribution of implantable medical devices intended to aesthetic and reconstructive surgery : breast implants (BIs), gluteal implants, calf implants, testicular implants, tissue expanders, facial implants, breast sizers…

The legal status, activities and interfaces between these three companies can be summarized as follows :

GC AESTHETICS Global staff headcount : 450 employees.		
EUROSILICONE	NAGOR Ltd	BIOSIL Ltd
Activities : • Manufacturer : Design, development, production, marketing and distribution of medical devices intended to aesthetic and reconstructive surgery : BIs, gluteal implants, calf implants, testicular implants, tissue expanders, facial implants, breast sizers… • Original Equipment Manufacturer (OEM) : Production of tissue expanders for NAGOR Ldt, which markets those medical devices as OBL manufacturer. • Own Brand Labeller (OBL) : Marketing and distribution of tissue expanders and breast sizers manufactured by BIOSIL Ltd as OEM manufacturer. • Distributor : Distribution of several medical devices under the names and brands of NAGOR Ltd manufacturer.	Activities : • Own Brand Labeller (OBL) : Marketing and distribution of : - tissue expanders manufactured by EUROSILICONE as OEM manufacturer; - BIs, calf implants, testicular implants, tissue expanders, facial implants, breast sizers manufactured by BIOSIL Ltd as OEM manufacturer. • Distributor : Distribution of breast implants (BIs), gluteal implants, calf implants, testicular implants, tissue expanders, facial implants, breast sizer under the names and brands of EUROSILICONE manufacturer.	Activities : Original Equipment Manufacturer (OEM) : Design, development and production of medical devices intended to aesthetic and reconstructive surgery : BIs, gluteal implants, calf implants, testicular implants, tissue expanders, facial implants, breast sizers… for EUROSILICONE and NAGOR Ltd.
Facilities and staff headcount : 1 single site in Apt (Vaucluse), France, covering the Head quarter, administrative, research & development and production activities. Global staff headcount : 250 employees.	Facilities and staff headcount : 1 single site in Cumbernauld, Scotland, covering the Head quarter and administrative activities. Global staff headcount : 87 employees.	Facilities and staff headcount : • 1 main site in Cumbernauld, Scotland, common with NAGOR Ltd, covering the Head quarter, administrative, research & development and production activities. Global staff headcount : 87 employees. • 1 second site in Ashby-de-la-Zouch, England, covering production activities.

NAGOR Ltd markets its medical devices in more than 50 countries Worldwide :

- directly to the customers, in the United Kingdom, French, Italian, Spanish and German markets ;
- via a channel of distributors, in the rest of the world.

The sales achieved by NAGOR Ltd, broken down by categories of medical devices, are :

- BIs : 90 % ;
- Tissue expanders : approximately 2% ;
- Testicular implants : approximately 2% ;
- Other implants (calf, facial, etc…) : approximately 6%.

This company markets roughly units of BIs per year Worldwide. The part dedicated to the french market varies from to %. Thus, NAGOR Ltd marketed in France :

- BI units in 2014 ;
- BI units in 2015.

The BIs marketed by NAGOR Ltd are sterilized either by dry heat either by Ethylene oxide. There are :

- marketed under the brands RGI™, GFX™, CoGel™, IMPLEO™, SFS™ and SFX™ ;
- designed :
  - with two types of surfaces : *smooth* for RGI™ brand, *textured* for GFX™, CoGel™ and IMPLEO™ brands.
  - with the following features :

Round BIs			
Profile	Low	High	Extra High
Textured surface High cohesive gel	IMP–MR	IMP–HR	IMP–EHR
Textured surface High performance cohesive gel	GFX–LP	GFX	GFX–EHP
Smooth surface High performance cohesive gel	RGI–D	RGI–DH	RGI–DEH
Anatomical BIs			
Projection	Low	Moderate	High
Full	CoGel–XF1	CoGel–XF2	CoGel–XF3
Moderate	CoGel–XM1	CoGel–XM2	CoGel–XM3
Low	CoGel–XL1	CoGel–XL2	CoGel–XL3

Surface	Low profile	High profile
Smooth	SFS–LP	SFS–HP
Textured	SFX–LP	SFX–HP

The raw materials used to manufacture the shell and the silicone gel of those BIs are sourced from the sole supplier named , based in . The texturing effect is achieved with *Sodium Chloride* as texturing ingredient.

NAGOR's management of complaints and vigilance activities is entirely carried out on the site of Cumbernauld (Scotland) and is therefore not subcontracted. This company processes the complaints and vigilance cases with a computerized database called QPULSE™.

A documentation concerning NAGOR Ltd's history, activity, products and sales is *referenced 1* in this inspection report.

II.2 Regulatory certification

Within the framework of the CE marking procedures set out in article 11 of the MDD, NAGOR Ltd 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 medical devices that it is marketing, with the essential requirements of safety and health applicable to those medical devices in the European Union.

II.3 Normative certification

NAGOR Ltd is certified ISO 13485.

II.4 History of the last inspection

NAGOR Ltd did not undergo a previous ANSM inspection exclusively focused on materiovigilance.

II.5 Main changes since the last inspection

Not applicable.

II.6 Main planned changes

Not applicable.

II.7 Purpose and scope of the inspection

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

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

II.8 Applicable legal references and guidelines

Mandatory references : MDD, particularly :

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

Guidelines :

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

II.9 People attending the opening and closing meetings

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

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

Reference 1 NAGOR Ltd's history, activity, products and sales (14 pages) ;

Rererence 2 Documentation related to the upstream traceability of materials and components in the finished products (3 pages) ;

Reference 3 Documentation related to the downstream traceability of the finished products (1 page) ;

Reference 4 Extract of the French MV Case *Ref. 15.09.42* documentation, related to NAGOR BIs involved in rupture and capsular contracture Baker I, with explantation (2 pages) ;

Reference 5 Section 12 of NAGOR Ltd's Management review for year 2014, related to the Post market Survey (PMS) (24 pages).

II.11 Annexes

Annex 1 List of the people attending the inspection opening and closing meetings ;

Annex 2 Findings raised along the review of the individual complaints and MV cases conducted during the inspection.

III. OBSERVATIONS AND FINDINGS RAISED DURING THE INSPECTION

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

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

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

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

The definitions adopted for the aforementioned levels are the following :

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

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

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

III.1 Medical devices portfolio

The availability and validity of the EC certificates covering the medical devices marketed in Europe by NAGOR Ltd, as manufacturer and distributor, were checked during this inspection. The company performs a review of its medical devices portfolio every six months with regards to the validity of their EC certificates. Records that attest to this review are available.

The management of the medical devices portfolio is satisfactory.

III.2 Quality Management System (QMS)

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

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

NAGOR Ltd documentation system, particularly the procedure *QP 028-CONTROL & ARCHIVAL OF QUALITY RECORDS*, does not clearly mention the period of archiving of the medical devices technical documentation, EC declarations of conformity, EC certificates, decisions and reports from the notified body.

R1 NAGOR Ltd should complete its procedure(s) regarding the management of its documentation system, so that they clearly mention a period of archiving at least equivalent to that laid down by the European legislation in force (MDD Annex II point 6.1), regarding the medical devices technical documentation, EC declarations of conformity, EC certificates, decisions and reports from the notified body, which shall be at least :

- 15 years after the last product has been manufactured, in the case of implantable devices ;
- 5 years after the last product has been manufactured, for the other devices.

Regarding the management of the skills and habilitations of NAGOR staff, the procedure *QP 030-MANAGEMENT OF TRAINING* was reviewed during the inspection.

R2 NAGOR Ltd should complete its procedure(s) regarding the management of the skills and habilitations of its staff, so that they mention modalities of initial and periodic trainings intended to the staff involved or likely to be involved in the communications or processing of complaints and MV cases, regarding :

1. The applicable European legal references and guidelines dealing with MV (MDD, MEDDEV 2.7/3, MEDDEV 2.12/1, MEDDEV 2.12/2) ;
2. The risks associated to the medical devices marketed by NAGOR Ltd ;
3. The identification of safety and MV cases and their communication to the staff in charge of their processing.

Such modalities should include :

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

NAGOR Ltd MV management process is described in the procedure *QP 025-02-CUSTOMER COMPLAINTS : MEDICAL DEVICE VIGILANCE & FIELD SAFETY CORRECTIVE ACTION*. However, the documentation system does not mention the reporting process agreed between ANSM and NAGOR Ltd regarding the incidents related to the BIs marketed in France.

D1 The description of the MV management process, in NAGOR Ltd documentation system, is not complete (MDD Annex II point 3.2, claimed ISO 13485 standard points 4.2.1 d, 4.2.1 f) insofar the documentation system :

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

Regarding the management of the corrective and preventive actions (CAPAs/FSCAs), the following documents were reviewed during the inspection :

- Procedure *QP 022-CONTROL OF NON-CONFORMING PRODUCT* ;
- Procedure *QP 023-NON CONFORMITY REVIEW AND DISPOSITION* ;
- Procedure *QP 024-CAPA & PREVENTATIVE ACTION*.

None of these documents mentions maximum deadlines for closing the CAPAs/FSCAs opened.

R3 The CAPAs/FSCAs management process described in NAGOR Ltd documentation system should be completed so that it mentions maximum deadlines for closing the CAPAs/FSCAs opened, in order to reduce the risk that some actions might remain unclosed without justification and indefinitely.

The product recall management process is described in point 7 of the procedure *QP 025-02-CUSTOMER COMPLAINTS : MEDICAL DEVICE VIGILANCE & FIELD SAFETY CORRECTIVE ACTION*.

R4 The product recall management process described in NAGOR Ltd documentation system should be completed so that it mentions a reconciliation intended to document the efficiency of the recall, with a systematic recall full balance sheet recapitulating the quantities of product units :

- produced and/or in production ;
- present in stocks or quarantined ;
- 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).

NAGOR Ltd management of the systematic review of experience gained from devices in the post-production phase is described in the procedure *QP 037-POST MARKET SURVEILLANCE*.

R5 The Post Market Surveillance (PMS) management process described in NAGOR Ltd documentation system should be completed, so that it lays down provisions and metrics related to the construction and update of a consolidated survey report regarding the BIs since their first marketing, with a presentation of :

1. The incidents outcomes broken down by :
   - Typologies of incidents (ruptures, capsular contractures, siliconomas, seromas, breast cancers, ALCL…) ;
   - Years of occurrence ;
   - Years of sales and/or implantation ;
   - Sales volumes or numbers of BIs implanted, per year (in order to assess the significance of the reported cases) ;
   - Surface (smooth or textured) of the BIs (in order to allow the inter-comparison of the Benefit/Risk ratio of the textured BIs versus smooth BIs) ;
2. An exhaustive list of the typologies of reported incidents, from the most frequent to the rarest ones ;
3. A methodology of identification of the key points, issues and stakes stemming from the aforementioned data.

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

The verification of NAGOR Ltd staff organization focused on :

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

NAGOR Ltd organization charts do not mention the name of the qualified staff to whom shall be transmitted any case of complaint or MV.

According to the discussions during the inspection, each staff member of NAGOR Ltd is informed of an e-mail address *'vigilance@nagor.com'*, in which he shall submit any case of complaint or MV brought to his knowledge. However, no track documenting the communication of this e-mail address, to each member of the company's staff, is available.

D2 NAGOR Ltd cannot demonstrate the means implemented in its the organization to ensure that each member of its staff that may have knowledge of a case of complaint or MV knows how to communicate the case to the qualified staff in charge of its processing, which might jeopardize the MV treatment and the proper reporting of serious incidents or risks of serious incidents to the concerned competent authorities with the due diligence required (MDD Annex II points 3.1 (7th dash) and 3.2 b, claimed ISO 13485 standard point 5.5), insofar :

- NAGOR Ltd organization charts do not mention the name of the qualified staff to whom shall be transmitted any case of complaint or MV ;
- No track documenting the communication of the e-mail address *'vigilance@nagor.com'*, to each member of the company's staff, is available.

Regarding the management of the competences and skills of the staff involved or likely to be involved in the communications of complaints and MV cases, NAGOR Ltd Quality Systems Manager has communicated to the Marketing and Sales staff :

- A message summarizing the NAGOR Ltd complaints and MV management procedures, but does not have acknowledgements of receipts attesting that each concerned staff has red this message and understood these procedures ;
- A presentation of the risks associated to the medical devices marketed by NAGOR Ltd, but does not have the list of the staff who attended this presentation, which does not ascertain that all this staff has been made aware to these risks.

R6 NAGOR Ltd should complete its management of the competences and skills of the staff involved or likely to be involved in the communications of complaints and MV cases (claimed ISO 13485 standard point 5.5.2 c), by keeping records attesting that all this staff is trained or made aware of :

- Its complaints and MV management procedures ;
- The risks associated to the medical devices marketed by NAGOR Ltd.

Regarding the continuity of the MV activity, NAGOR Ltd has not implemented annual schedules of presence of its qualified staff in charge of reporting the serious incidents or risks of serious incidents to the concerned competent authorities.

D3 NAGOR Ltd cannot demonstrate the continuity of its MV activity, which induces a risk that serious incidents or risks of serious incidents might not all be processed and reported with the required due diligence to the concerned competent authorities (MDD Annex II points 3.1 (7th dash) and 3.2 b), insofar this company does not keep records demonstrating the continuous presence of at least one member of its qualified staff in charge of reporting those serious incidents or risks of incidents.

III.4 Interfaces and Contracts

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

- The internal organization and interfaces of the staff involved or likely to be involved in complaints and MV cases ;
- The external organization and interfaces between NAGOR Ltd, its partners, its customers and the competent authorities.

The internal organization and interfaces of the staff involved or likely to be involved in complaints and/or MV cases does not raise any particular comment.

The verification of the external organization and interfaces focused on :

- A contract template, between NAGOR Ltd and its distributors, that is to be implemented by 2016 according to the discussions during the inspection ;
- The contract concluded between NAGOR Ltd as OBL manufacturer and its partner BIOSIL Ltd as OEM manufacturer.

The aforementioned contract template, between NAGOR Ltd and its distributors, includes provisions which cover :

- Guarantees of traceability, by the distributors, of the devices made available to the end users ;
- The implementation of the product recall process.

This template also requires the distributor to *'notify any complaint'* to the manufacturer, but does not precise deadlines of notification.

R7 Regarding the interfaces with its distributors, NAGOR Ltd is expected to :

1. Complete its contract template so that it includes provisions in terms of :
   a) Immediate notification, to the manufacturer, of any complaint and/or MV case related to the concerned medical devices ;
   b) Identification of the party who is responsible for reporting any serious incident or risk of serious incident to the concerned competent authorities.
2. Then precise, in response to this inspection report, a short date of implementation of this contract template with all distributors for 2016.

The contract concluded between NAGOR Ltd as OBL manufacturer and its partner BIOSIL Ltd as OEM manufacturer does not raise any particular comment.

III.5 Audits

Each process of NAGOR Ltd's Quality Management System (QMS) is planned to be audited once a year. The audit schedules of the years 2014 and 2015 were presented during the inspection. They mention that audits of the complaints and MV management activities were conducted in November 2014 and November 2015. The corresponding audit reports were also presented during the inspection.

The complaints and MV management activities are under the responsibility of NAGOR Ltd's Quality Department. However, the aforementioned audits were conducted by an auditor who belongs himself to this Department, which is likely to compromise the independence of the audits.

R8 NAGOR Ltd should improve its audit management by taking the necessary provisions to assure systematically the independence of the auditors regarding the audited activities (claimed ISO 13485 standard point 8.2.2).

III.6 Management reviews

NAGOR Ltd proceeds to quarterly and annual management reviews. The management review reports for years 2014 and 2015 were presented during the inspection.

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

The management reviews do not raise any particular comment.

III.7 Traceability

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

The check of the upstream traceability of materials and components focused on the lots of shell – standard layer and barrier layer – and filling gel used in the manufacture of a textured BI corresponding to the reference *IMP HR-210*, lot *201862*.

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

The documentation used in this test is *referenced 2* in this inspection report.

III.7.2 Downstream traceability of the finished products

The check of the downstream traceability of the finished products focused on the lot *201862* of BI targeted in the upstream abovementioned test. This traceability test is also satisfactory insofar it demonstrated the reconciliation between the numbers of BI units produced and BI units in stock, no BI units being marketed at the time of this test.

The documentation used in this test is *referenced 3* in this inspection report.

III.8 Complaints and materiovigilance (MV) management

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

The details of the findings raised along the review of the individual complaints and MV cases conducted during the inspection are mentioned in *Annex 2* 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 Deviation D4 below refers to.

D4 The management of the individual complaints and MV cases by NAGOR Ltd is not completely satisfactory, which compromises the proper processing and notification of the serious incidents or risks of serious incidents to the concerned competent authorities (MDD Annex II item 3.1, claimed ISO 13485 standard items 7.2.3, 8.4 a) and 8.5), insofar :

1. NAGOR Ltd does not have systematically the traceability of the batch records (DHR) reviews and of the results obtained, while processing MV cases *(Annex 2 point 1 of this inspection report)* ;
2. An incident report communicated to ANSM and related to a case of BI *rupture* and *capsular contracture* only mentions *'deflation'* and is therefore incomplete *(Annex 2 point 2 of this inspection report) ;*
3. The date of MV case initial notification, as mentioned in NAGOR registration form, does not systematically correspond to the real date of initial notification attested by the source document *(Annex 2 point 3 of this inspection report)* ;
4. NAGOR Ltd does not keep under control all its distributors, considering that :
   - One of them had knowledge of an ALCL case but did not communicate it to NAGOR Ltd *(Annex 2 point 4 of this inspection report)* ;
   - This case was reported late to the concerned competent authority.

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

Two clinical studies involving NAGOR Ldt BIs were reviewed during the inspection, regarding the MV associated with those studies.

The first is a non interventional study started in 2003, ended in 2008, which includes a 10 years follow-up of the patients.

The second is a non interventional on going study, started in July 2015 and planned to be ended in 2016, with a follow-up of 600 patients. This study concerns IMPLEO™ textured BIs and is aimed to consolidate the BIs clinical data. 127 patients are involved to date. This study is conducted in 6 investigation sites : 3 sites in UK, 1 site in Ireland, 1 site in Belgium and 1 site in Argentina.

The line listings of the serious adverse events (SAEs) raised along those studies were presented during the inspection. Only one case of explantation due to a post-operative infection occurred so far along the second study. This case was notified to the competent authority.

This chapter does not raise any particular comment.

III.9 Corrective and preventive actions (CAPAs/FSCAs) management

The management of the corrective and preventive actions (CAPAs/FSCAs) by NAGOR Ltd was checked along the review of the individual complaints and MV cases conducted during the inspection. The details of the findings raised along this review are mentioned in *Annex 2* 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 Deviation D5 below refers to.

D5 The management of the CAPAs/FSCAs by NAGOR Ltd is not completely satisfactory, which compromises the proper processing and notification of the serious incidents or risks of serious incidents to the concerned competent authorities (MDD Annex II item 3.1, claimed ISO 13485 standard items 7.2.3, 8.4 a) and 8.5), insofar NAGOR Ltd does not have the traceability of any confirmation response from a Belgian distributor, to the reminder letter sent by NAGOR Ltd and reminding the distributor duties regarding the communication of MV cases to NAGOR Ltd *(Annex 2 point 5 of this inspection report)*.

III.10 Product recall

According to the discussions during the inspection, NAGOR Ltd has never conducted a recall of products. However, the company proceeds to annual simulations of recall. The last simulation was conducted in April 2015 with GCA Brazilian subsidiary. The assessment report of this simulation was checked during the inspection and is satisfactory.

III.11 Responses to ANSM requests

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

This chapter does not raise any other particular comment.

III.12 Systematic review of experience gained from devices in the post-production phase (PMS)

A report related to NAGOR Ltd quarterly Management review concerning the 4th quarter of year 2014 (period of October-December 2014) and related to the annual Management review of year 2014 was presented during the inspection. Section 12 of this report, related to the Post market Survey (PMS), is *referenced 4* in this inspection report.

The rough PMS data available at NAGOR Ltd and presented during the inspection raise notably that :

- 4 cases of ALCL occurred Worldwide since the first marketing of NAGOR BIs, all involving textured BIs : 1 case in Australia (before 2012), 1 case in Denmark (in 2014), 1 case in UK (in 2014) and 1 case in Belgium (in 2014) ;
- Textured BIs are significantly more involved in capsular contractures than smooth BIs.

R9 NAGOR Ltd should complete its BIs post-market survey, so that the PMS reports present some written assessments and conclusions comparing the smooth BIs versus the textured BIs, regarding :

1. The incident trends broken down by typologies of incidents, particularly capsular contractures ;
2. The key points, issues and stakes stemming from the data related to ALCL cases ;
3. The global BIs Benefit/Risk ratio including the impact of the surface.

III.13 Archiving

Complaints and MV documents in paper format are stored on the site of Cumbernauld, in the office of the Quality Assurance Compliance Officer, in a cupboard which is not protected against fire hazards.

R10 NAGOR Ltd should secure the archiving of all the complaints and MV documents in paper format by retaining these documents in premises protected against fire hazards (claimed ISO 13485 standard points 4.2.4, 8.5.1).

IV. IDENTIFIED RISKS

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

Incomplete management of the staff involved or likely to be involved in MV.		
Findings		**Classification**
	1. In the QMS (documentation system) :	
R2	No provisions related to initial and periodic trainings of the staff involved or likely to be involved in the communications or processing of complaints and MV cases, regarding : • The applicable European legal references and guidelines dealing with MV ; • The risks associated to the medical devices marketed by NAGOR Ltd ; • The identification of safety and MV cases and their communication to the staff in charge of their processing.	Other
	2. In practice :	
D2	No demonstration of the means implemented to ensure that each member of the staff that may have knowledge of a case of complaint or MV knows how to communicate the case to the qualified staff in charge of its processing.	Other
R6	Incomplete records attesting that the staff involved or likely to be involved in the communications of complaints and MV cases is trained or made aware of : • NAGOR Ltd complaints and MV management procedures ; • The risks associated to the medical devices marketed by NAGOR Ltd.	Other
D3	No demonstration of an organization of the MV staff suitable to guarantee the continuity of the MV activity.	Other

Incomplete interfaces		
Findings		**Classification**
R7	Contract template with the distributors : • To be completed regarding : - Immediate notification, to the manufacturer, of any complaint and/or MV case related to the concerned medical devices ; - Identification of the party who is responsible for reporting any serious incident or risk of serious incident to the concerned competent authorities. • To be implemented.	Other

Efficiency of the complaints and MV management process incompletely assessed		
	Findings	**Classification**
R8	Lack of provisions to assure systematically the independence of the auditors regarding the audited activities.	Other

Management of the individual complaints and MV cases not completely satisfactory.		
	Findings	**Classification**
	1. In the QMS (documentation system) :	
D1	• No provisions related to the reporting process agreed between ANSM and NAGOR Ltd regarding the incidents involving BIs marketed in France, in terms of : - individual cases prone to immediate notification ; - clustered cases prone to periodic notification (*Periodic summary reports* and *Trend reports*). • No procedure regarding the preparation and submission of the *Periodic summary reports* to ANSM.	Other
	2. In practice :	
D4	• No systematic traceability of the batch records (DHR) reviews and of the results obtained, while processing MV cases; • Incomplete incident report communicated to ANSM ; • Date of MV case initial notification, as mentioned in NAGOR registration form, not systematically corresponding to the real date of initial notification attested by the source document ; • Lack of control of a distributor, which induced a late reporting of an ALCL case to the Belgian competent authority.	Other

Management of the corrective et preventive actions (CAPAs/FSCAs) not completely satisfactory.		
	Findings	**Classification**
D5	No traceability of any confirmation response from a Belgian distributor, to the reminder letter sent by NAGOR Ltd and reminding the distributor duties regarding the communication of MV cases to NAGOR Ltd.	Other

Incomplete review of experience gained from devices in the post-production phase (PMS).		
	Findings	**Classification**
	1. In the QMS (documentation system) :	
R5	Incomplete provisions related to the construction and update of a consolidated survey report regarding the BIs since their first marketing, with a presentation of : • The incidents outcomes broken down by typologies of incidents, years of occurrence, years of sales and/or implantation, sales volumes or numbers of BIs implanted per year, surface of the BIs ; • An exhaustive list of the typologies of incidents, from the most frequent to the rarest ones ; • A methodology of identification of the key points, issues and stakes stemming from the aforementioned data.	Other
	2. In practice :	
R9	Lack of written assessments and conclusions, in the PMS reports, comparing the smooth BIs versus the textured BIs regarding : • The incident trends broken down by typologies of incidents, particularly capsular contractures ; • The key points, issues and stakes stemming from the data related to ALCL cases ; • The global BIs Benefit/Risk ratio including the impact of the surface.	Other

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

The inspection carried out from 8th to 9th December 2015 at NAGOR Ltd site located 127/129 Deerdykes View, Westfield Industrial Estate, Cumbernauld, Scotland, allowed to collect the information related to the organization and to the activity of this company regarding materiovigilance.

This inspection raised 5 deviations and 10 remarks.

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

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

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

Saint-Denis (France), 28th December 2015.

ANSM Inspector

Annex 2 (1/2) Findings raised along the review of the individual complaints and MV cases conducted during the inspection.

Case Identification	Summary	Findings
Refs. NAGOR ► Left BI. ► Right BI.	**BIs. Rupture and capsular contracture Baker I. Explantation. France.** • 5th October 2015 : Explantation of the concerned BIs, replaced by BIs of the brand NATRELLE™ (manufacturer ALLERGAN). • 21st October 2015 : - Notification of this incident to NAGOR by mail from the patient herself. - NAGOR QS Manager requests the return of the concerned BIs. • 27th October 2015 : NAGOR communicates the initial incident report to ANSM (reporting deadline 6 days). • BIs not returned to NAGOR so far.	• Batch records (DHR) review performed by NAGOR : no non-compliance identified, but lack of traceability of this review and of the results obtained *(point 1)*. • The initial incident report communicated to ANSM only states *'deflation'* and does not mentions *rupture* and *capsular contracture* *(point 2)*.
Ref. NAGOR	**BI. ALCL case. Denmark.** • BI explanted on 24th January 2014, not returned to NAGOR because *'discarded'* (scraped). • 30th May 2014 : Notification of this incident to NAGOR by mail from its Danish distributor NORDIC MEDICAL. • Batch records (DHR) review performed by NAGOR : no non-compliance identified along this review. • 12th June 2014 : NAGOR communicates the combined incident report to the Danish competent authority (reporting deadline 13 days).	NAGOR registration form of this case mentions a date of initial notification to the 3rd June 2014, whereas the real date of notification, attested by the source document (mail from the Danish distributor), is 30th May 2014 *(point 3)*.
Ref. NAGOR	**BI. ALCL case. United Kingdom.** • 18th September 2014 : Notification of this incident to NAGOR by phone call from a hospital in UK. • 19th September 2014 : BI explantation. • 2nd October 2014 : NAGOR communicates the initial incident report to the MHRA (reporting deadline 14 days). • 7th October 2014 : NAGOR requests to the physician additional informations and the return of the concerned BI. • 14th October 2014 : The physician provides a response to NAGOR, with the filled complaint form. • BI not returned to NAGOR, despite a relaunch from NAGOR to the physician by mail of 22nd December 2014. • 18th December 2014 : NAGOR communicates the final incident report to the MHRA.	No finding raised.

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

Case Identification	Summary	Findings
Ref. NAGOR	**BI. ALCL case. Belgium.** • 8th December 2014 : BI explantation. The Belgian distributor is informed of this incident. • 11th September 2015 : - Notification of this incident to NAGOR by the Belgian competent authority (AFMPS). - AFMPS requests to NAGOR to : ❖ provide the incident report ; ❖ provide the number of ALCL cases diagnosed Worldwide on patients bearing BIs marketed by NAGOR ; ❖ justify why this incident has not been reported earlier to AFMPS while the Distributor was aware of it since December 2014. - NAGOR questions its distributor. - NAGOR provides to AFMPS its first responses. • 14th September 2015 : Response from the distributor to NAGOR. The distributor states that the physician said that he will proceed himself to the reporting of this case to the Belgian authority. But the distributor did not inform NAGOR. • 23rd September 2015 : NAGOR communicates the combined incident report requested by AFMPS. This report notably states that a review of the BI batch record (DHR) has been performed and did not raise any non-compliance. • 21st October 2015 : As action towards the distributor, NAGOR sends him a letter which reminds its duties regarding the communication of MV cases to NAGOR, including particularly references to ALCL cases. This letter requests a confirmation from the distributor. • No confirmation from the distributor.	• The Belgian distributor had knowledge of this incident since the 8th December 2014 but did not communicate it to NAGOR *(point 4)*. • As action towards the distributor, NAGOR sent him a letter which reminds its duties regarding the communication of MV cases to NAGOR, including particularly references to ALCL cases, which requests a confirmation from the distributor, but no confirmation from the distributor *(point 5)*.